

Diagnostic strategies in rheumatology

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GLOBAL LEARNING OBJECTIVES

- Differentiate the main patterns of rheumatic diseases.
- Generate short representations of clinical cases
- Use these representations as guides for a structured approach to questioning and physical examination of the patient and as a framework for final diagnosis

SPECIFIC LEARNING OUTCOMES

- Recognise the importance of case representations, summaries and clinical patterns.
- Differentiate the main patterns of rheumatic diseases based on appropriate questioning and physical examination
- Generate short summaries of clinical cases.
- Use the clinical patterns to guide questioning and reasoning by a two-step approach to diagnosis.
- Differentiate inflammatory arthritis from osteoarthritis
- Recognise atypical osteoarthritis
- Characterise the most common patterns of arthritis and their differential diagnosis
- Recognise axial spondyloarthritis and the different aspects of spondyloarthritis
- Differentiate causes of regional pain
- Recognise fibromyalgia
- Differentiate the most common connective tissue diseases and vasculitis.

1 Basis of diagnostic reasoning

Educational research has shown that the main difference in clinical diagnosis between a novice and an expert clinician lies not mainly in knowledge, but in pattern recognition of the various symptoms, signs and clinical information. This is based on the ability of the expert to shortcut the pathways of clinical reasoning, by recognising patterns and follow trains of thought, through summarised representations of the cases. The expert follows a map, the novice is building one.

Research suggests that expert clinicians have their clinical knowledge organised around 'patterns' or 'illness scripts' that are strongly connected to summary problem representations (Elstein, 2002*; Eva, 2005*). This non-analytical reasoning, guided by scripts, concepts and representations, is an essential component of expertise in diagnosis.

We can think of no better way to convey these concepts than by using Judith Bowen's paper on clinical reasoning published in the New England Journal of Medicine (Bowen, 2006*).

1.1 Patient history

'My knee hurt me so much last night, I woke up from sleep. It was fine when I went to bed. Now it's swollen. It's the worst pain I've ever had. I've had problems like this before in the same knee, once 9 months ago and once 2 years ago. It doesn't bother me between times.'

1.2 Novice resident's presentation

'My next patient is a 54-year-old white man with knee pain. It started last night. He does not report any trauma. On examination, his vital signs are normal. His knee is swollen, red and tender to touch. It hurts him a lot when I test his range of motion. He's had this problem twice before.'

1.3 Expert resident's presentation

'My next patient is a 54-year-old white male with a sudden onset of pain in his right knee that awakened him from sleep. He does not report any trauma and was essentially asymptomatic when he went to bed. He had two episodes of similar, severe pain 9 months and 2 years ago. He is pain-free between episodes. He is afebrile today. His knee is swollen, tender to touch and erythematous.'

Consider the main differences between the two presentations.

As noted by Bowen, the novice resident transformed the patient's story a little but without any particular structure. Key elements of the clinical diagnostic reasoning process are not apparent or structured.

The expert resident transformed the patient's story into a meaningful clinical problem. This can be designated as the 'problem representation' and is an important early step of the diagnostic reasoning process. This first representation guided his choice of additional questions and helped focus his clinical examination. The patient's words are translated into abstract, clinically relevant, terms. 'Last night' becomes 'acute onset', 'I've had this problem before' becomes 'recurrent'. The expert resident presented a succinct summary of findings, highlighting the defining features of the condition and the features that helped discrimination from alternative diagnoses. His description, made into one sentence, might have been this: 'Acute recurrent monoarthritis in an otherwise healthy middle-aged man'. Adequacy and precision of language are absolutely crucial for the efficacy of the process.

The summary description, which is a representation of the problem, helps to elicit the relevant information from memory and guides the subsequent diagnostic investigation. Inability to produce appropriate problem summaries and representations will result in the exploration of multiple diagnostic hypotheses. A wrong summary will lead to a wrong diagnosis.

For this reason, the reader is strongly encouraged to exercise his/her ability to scrutinise and summarise information and checking for its validity.

1.4 The two-step approach to diagnosis

As clinicians we all follow 'a map', a route of non-analytical clinical reasoning. It is important that this process is based on evidence and solid experience. Although experience is considered indispensable for designing your own 'clinical map', this chapter attempts to offer an example to assist the reader with this process.

We propose a 'two-step approach to diagnosis' (da Silva and Woolf, 2010*). The first step aims to define the generic type of pathology, or to set a main pattern. The second step is a more detailed investigation, which is adapted to each pattern and aims to differentiate between potential causes of that pattern, thus making a final differential diagnosis.

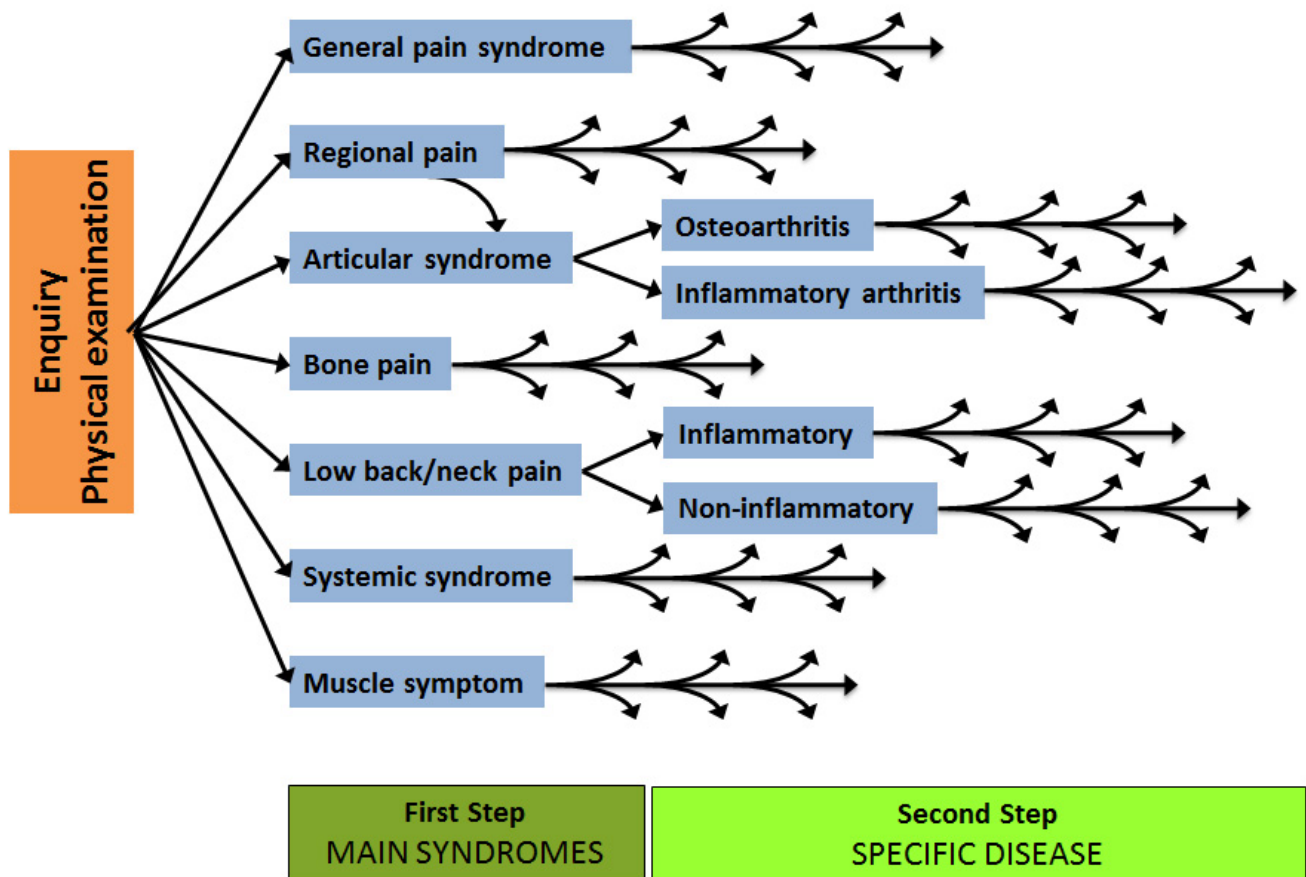
This approach allows us to identify precisely defining characteristics of each main pattern and the most important clues to differentiate between similar conditions and evaluate their severity. The main defining characteristics should guide and focus our strategic questioning and examination. The clinician should be as precise and detailed as possible in reasoning and decision-making while trying to be economical and fast in dismissing 'background noise'.

2 Main patterns

The aim of the first step is to establish the main pattern which is most representative of our patient's clinical picture (pattern recognition). Some of the main patterns are proposed below.

Figure 1 presents a short list of the nine main patterns we propose as a way of organising the first step of the diagnosis. In the following text we will explore the core characteristics of each pattern and its differentiation from others. We will leave the final steps of the clinical diagnostic pathway to the individual chapters dealing with specific conditions.

Figure 1 Main rheumatological patterns. (Reproduced and revised with permission from da Silva, *Reumatologia Prática*, 1st edn. Coimbra, Portugal: Diagnosteo Publishers, 2004.)



It is important to keep in mind that individual patterns are not mutually exclusive. The presence of one pattern does not exclude another. Rheumatic diseases are extremely variable in their presentation: different patterns may be suggested in consecutive patients with the same disease. Seronegative spondyloarthropathies, for example, may present with oligoarthritis in one case and with pure low back pain in the next. But in some other cases periarticular involvement or polyarthritis will dominate the picture, requiring completely diverse differential diagnostic investigations. Our 'map' must be flexible enough to allow for this. This will allow us to reach the right diagnosis quickly, whatever the dominant presenting symptom.

2.1 Regional pain

Regional pain syndromes are characterised by pain that affects a single musculoskeletal area (e.g., shoulder, hand or knee). In some cases several distinct regions may be simultaneously involved (e.g., polymyalgia

rheumatic, radicular pain). Questioning and examination will allow the distinction of four main origins (table 1):

Table 1 Distinctive features of regional syndromes

	Periarticular pain	Articular pain	Neurogenic pain	Referred pain
Enquiry	Only a few selective movements are painful	All joint movements are painful	Dysaesthetic; aggravated by compression of nerve or movement of the spine	Unrelated to movement; 'visceral' timing; poorly localised, may be improved by rubbing
Pain on motion	Active>passive; selected movements	Active passive; several directions	Normal; if root pain: pain on movement of the affected spine segment	Normal
Range of motion	Active movement may be limited by pain; passive movement: full	May be limited equally for both active and passive movement	Normal	Normal
Resisted active movement	Pain on specific manoeuvres	No effect	No effect	No effect
Local palpation	Tenderness over affected periarticular structure (away from joint line)	Possible tenderness over joint line, crepitus, capsular swelling, effusion, increased heat	Normal	Normal
Neurological examination	Normal	Normal	May be abnormal	Normal

- periarticular pain
- joint pain
- neurogenic pain
- referred pain.

The area affected offers an important clue: periarticular lesions are predominantly the cause of pain in the shoulders and elbows, whereas joints are more commonly the cause of pain in the forefeet and knees. The most common patterns of neurogenic pain are sciatica and carpal tunnel syndrome.

2.1.1 Periarticular pain

Periarticular pain originates in anatomical structures that are involved in joint motion but are located outside the joint capsule. Conditions affecting the capsule produce clinical features that are similar to those of intra-articular conditions.

These structures are often the site of disease, which is usually inflammatory, as a result of repeated local trauma (e.g., intensive use of the hands or shoulder) or as local manifestations of systemic synovial diseases, like rheumatoid arthritis (RA). Inflammation of the tendon and ligament insertion points (enthesopathy or enthesitis) may occur in isolation, such as after trauma, and occasionally may have no apparent cause. On the other hand, recurrent and multiple enthesopathies can be a feature of seronegative spondyloarthropathies.

A periarticular origin is especially suggested by pain that is elicited or worsened by specific movements, that involve or compress the involved structure. Other movements usually are not painful or limited (i.e., selectivity of painful movements). Although the condition might be inflammatory, the rhythm of pain tends to be ‘mechanical’—that is, made worse by movement and relieved by rest without joint stiffness.

Another clue from questioning that suggests involvement of a periarticular structure is pain that is made worse in positions that induce a compression of the structure (e.g., increased pain by lying on the affected shoulder, in rotator cuff tendonitis, or on the affected lateral thigh in trochanteric bursitis).

On clinical examination, patients with periarticular lesions will have more pain on active motion than on passive movement (make sure your patient is relaxed on passive movement to assess this clue properly). Passive movement is not limited in periarticular lesions. This is to be expected as the involved structure remains rested during passive movement. Conversely, patients with joint lesions tend to have pain of similar intensity on both active and passive movement and may show equal limitation of both.

Resisted movements involving the periarticular structure will cause intense pain. Such manoeuvres do not cause aggravation of pain when the problem is purely intra-articular. Palpation directly onto the inflamed periarticular structure will reproduce the patient’s pain, whereas with arthritis tenderness is maximal along the joint line. Swelling, heat and redness are usually not seen, except in acute inflammation of superficial bursae, subcutaneous fascia and skin.

2.1.2 Joint pain

A lesion that affects a single joint will obviously result in a regional pain syndrome. Pain is related to use of the joint but, unlike periarticular lesions, all movements tend to be painful. Physical examination will show pain in all movements, with active and passive movements being similarly affected. Joint movement is often limited due to swelling or structural damage. Resisted movements do not exacerbate the pain (as expected since the

joint is not moved by such manoeuvres). Affected joints are often tender on palpation along the joint margins (figure 2). When coarse crepitus, capsular swelling, effusion and/or deformity are also present, this makes involvement of the joint more obvious. Increased articular warmth also indicates intra-articular inflammation, but caution should be exercised to distinguish extra-articular local inflammation, such as in cellulitis overlying a joint.

Figure 2 *Elbow synovitis is an articular syndrome (note the joint line swelling) as opposed to olecranon bursitis which is a periarticular lesion.*



Joint pain will be further elaborated in section 2.4 (Articular syndrome).

2.1.3 Neurogenic pain

Neurogenic pain is caused by compression or irritation of nerve roots or peripheral nerves. Sciatica, carpal tunnel syndrome and ulnar nerve syndrome are the most common examples.

Neurogenic pain typically associates with uncomfortable sensory disturbance (dysaesthesia) with tingling and/or numbness, and is often described as ‘burning’ or ‘like an electric shock’ affecting the sensory distribution of a particular nerve or root. Pain derived from root lesions may be exacerbated by movement of the affected spine segment or by increasing intrathecal pressure through coughing or straining during defecation (or by Valsalva’s manoeuvre during patient assessment).

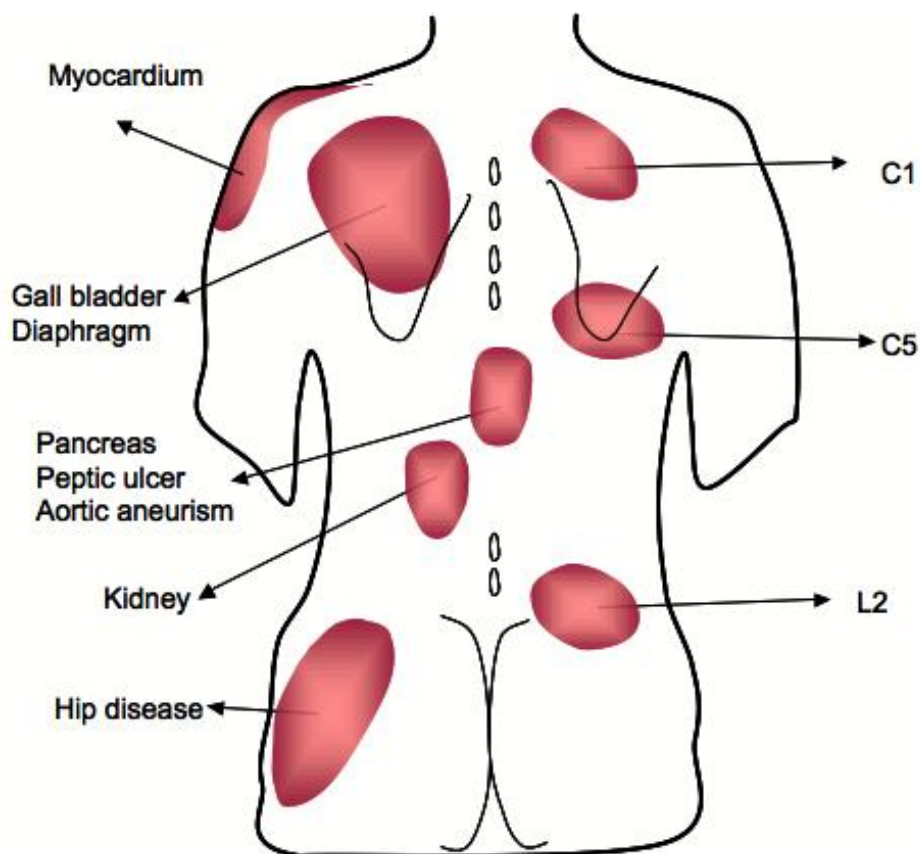
In the absence of associated pathology, regional musculoskeletal examination is normal. Guided neurological examination is the key to the diagnosis (e.g., testing sensation, muscle strength, straight leg rising, Tinel’s and Phalen’s tests, tendon reflexes, etc.). Because detailed neurological examination is not routinely performed by many doctors, the diagnosis can be easily missed if the enquiry fails to elicit the clues. It is important to keep in mind that muscle atrophy (as in carpal tunnel syndrome) and loss of pinprick sensation are late features in root lesions and nerve compressions.

2.1.4 Referred pain

Referred pain denotes symptoms felt at a distance from their anatomical origin. Axial and large proximal joints (spine, sacroiliac joints, glenohumeral joints, hips) may cause distal radiation of maximal pain, presenting with pain at some distance from the originating structure. For example, although hip pain is often felt maximally deep in the anterior groin, it may present as knee pain with no proximal discomfort. Distinguishing whether hip or knee movement exacerbates the pain is difficult in the history as many daily activities involve synchronous movement of hips and knees. Two clues may suggest referred pain. First, when asked to point to the site of maximal pain the patient often describes a very wide, ill-defined area around the anterior knee which also involves the distal thigh (unlike knee-originated articular or periarticular pain which is well-defined and smaller in area). Second, the pain may be improved by rubbing the area—unlike locally originated pain which is more often worsened by rubbing over it. Examination can decisively distinguish local and referred pain—isolated hip movement will cause the knee pain, and isolated knee movement will not.

Localised musculoskeletal pain can also be referred from internal viscera. Such pain has an uncharacteristic rhythm, being more affected by the physiology of the viscera than by joint movement, and may be accompanied by other more suggestive symptoms. Local musculoskeletal examination is normal and does not reproduce the patient's pain. Figure 3 shows the most common sites of musculoskeletal pain of visceral origin.

Figure 3 Most common sites and origins of referred pain.



2.2 Generalised pain syndrome

In this syndrome, pain affects different parts of the body diffusely and imprecisely, with little or no focus on joints.

Fibromyalgia accounts for the majority of cases of 'multiple regional pain' or 'chronic widespread pain' syndrome. Patients often use or agree with the expression 'pain all over'. Pain is often migratory and worse after, rather than during, exercise. Exposure to cold and stress are frequently recognised as aggravating factors. Commonly, other symptoms are present such as 'tension' headache (often non-throbbing, lasting hours or days, mainly bifrontal), irritable bowel syndrome, tight chest and anterior chest wall pain, low mood, and poor sleep pattern with non-restoration in the morning.

Patients with fibromyalgia may present with different patterns of dominant symptoms, which can be misleading. It is not uncommon for these patients to be misdiagnosed and treated for a variety of conditions, including RA, ankylosing spondylitis (AS), connective tissue disease, disc herniation, etc. Equally, these patients must be carefully assessed to discount co-morbid joint disease, neurological abnormalities and other possible explanations for some of their complaints. The diagnosis is purely clinical and depends on demonstration of widespread hyperalgesic tender sites (i.e., lowered pain threshold) affecting all four body quadrants.

Nevertheless, experienced clinician will keep in mind the limitations of the existing criteria for fibromyalgia. Other rheumatic and metabolic conditions may involve widespread regional pain, including RA, systemic lupus erythematosus (SLE), Sjögren's syndrome, polymyalgia rheumatica (PMR), AS, polymyositis (PM), hypothyroidism, hypoparathyroidism, polyneuropathy, and debilitating systemic diseases. However, widespread hyperalgesia of naturally occurring tender sites is not a feature of these conditions. Careful questioning and examination together with minimal investigation is usually sufficient to clarify the diagnosis and the presence of any comorbidity.

The presence of fibromyalgia in association with other rheumatic conditions is common and represents some of the most difficult clinical situations in rheumatology.

2.3 Low back and neck pain

Back and neck pain is extremely common in medical practice. Most episodes of back pain resolve within a period of 6 weeks, 90% of them after 3 weeks. Back pain of more than 6 weeks' duration requires further investigation. A vast majority of cases will escape a precise aetiological diagnosis even after meticulous investigation. This is due to the anatomic complexity of the spine, muscles, ligaments, nerves and supporting soft tissues in the area, leading to a multiplicity of potential causes. The contribution of current diagnostic methods to clinical diagnosis is limited. The correlation between even sophisticated imaging and clinical manifestations is poor. Used inappropriately, imaging can therefore complicate the clinical picture.

We know that in the vast majority of cases it will be impossible to make a precise diagnosis and treatment will be guided by general rules of pain management, exercise and risk factor control. Only a small percentage of cases involve a specific aetiology requiring special diagnostic and therapeutic action. In patients younger than 45 years, about 5% of cases of chronic low back pain are due to spondyloarthritis. Features suggestive of inflammatory back pain, such as night pain and improvement of back pain with movement but not at rest, may be indicative of spondyloarthritis. In a very few cases the underlying causes are serious—such as malignancy and infection—and require urgent investigation and specific treatment. Such diagnoses cannot be missed.

The first group, by far the most common in a community setting, is ‘common mechanical’ or ‘non-specific’ back or neck pain. Faced with subjective information and unreliable investigations, the experienced clinician will focus on clinical manifestations, pain intensity and disability, more than aetiology, while keeping a careful vigilance for any clues that may suggest a potentially different or serious cause of symptoms for each individual patient. The recommended strategy for back and neck pain is based on the search and recognition of alarm symptoms and signs that indicate a higher probability for an underlying specific cause. Important points of differentiation from common mechanical pain include: progressive pain, night predominance, lack of relationship to spinal movement, and involvement of the thoracic spine. Table 2 summarises some of the summated features that allow distinction between the main categories of back and neck pain.

Table 2 Examples of typical manifestations of different categories of back pain and important red flags

Manifestations	Causes of low back pain
Asymmetrical non-progressive pain (subacute or insidious onset), affecting limited segments of cervical or lumbar spine, worse on movement, no systemic upset	Common mechanical back and neck pain
Axial pain and stiffness with inflammatory rhythm, affecting multiple segments (often including thoracic segments), symmetrical reduction of multiple spinal movements	Spondylitis
Well-localised, progressive pain, worse at night (unrelated to position in bed), may involve thoracic spine. History of prior neoplasm is an additional warning flag)	Malignancy (predominantly metastases) or infection
Acute or subacute onset severe well-localised pain, worsened by even slight movement, often involves thoracic spine (especially with risk or evidence of osteoporosis, older age)	Osteoporotic fracture
Accompanying neurological manifestations	Neurogenic pain
Visceral symptoms, pain not clearly related to spinal movement	Referred pain

The symptoms of mechanical back and neck pain, are commonly triggered by movement and relieved by rest. In adults, most of these conditions are caused by ‘spondylosis’ (a variable combination of facet joint osteoarthritis (OA), intervertebral disc degeneration and ligamentous strain). In many other cases, particularly in young people, there is no apparent cause for the pain and it is thought to be the result of mild articular

instability and irritation of the nerves and muscle bundles, leading to painful reflex muscle contractions. That is commonly treated conservatively aiming to relieve the pain and restore function. In a few cases, the pain may be neurogenic, inflammatory, infectious, neoplastic or psychogenic in nature. The clues for such special conditions are similar to those described above. The possibility of referred pain, from the heart, lung apex and shoulder, must be kept in mind. Acute lymphadenopathy, thyroiditis and meningitis represent important non-rheumatic causes of neck pain.

2.4 Articular syndrome

Arthropathies—that is, diseases affecting the joints—are at the heart of rheumatology. Final diagnosis will involve identification of a specific disease, evaluation of its activity, accumulated damage, the impact on function and participation in daily activities, and prognosis.

As the first step we have to recognise that this is an articular syndrome. As described above, this is suggested by pain that emerges with virtually all movements of the joint as opposed to selective pain found in periarticular lesions. For peripheral joints, patients can usually locate the pain precisely over the joint(s) affected. Pain from proximal joints, as the glenohumeral, sacroiliac, spinal and hip joints may present in distal joints as a referred pain. On examination, pain has similar intensity with active and passive mobilisation and both can be limited in range, unlike in peri-articular lesions where active and passive findings are discordant. Resisted movement will not affect the pain. Palpation will typically cause pain along the margins of the joint. The presence of crepitus, capsular swelling, effusion and/or deformity further confirms the articular origin.

As the second step, four fundamental features of the articular pattern should be defined:

1. 'Inflammatory' or 'non-inflammatory' in nature of the disorder
2. The temporal pattern of the disorder; especially acute versus chronic duration
3. The spatial pattern: primarily, mono-, oligo- or polyarticular arthritis and the presence of axial involvement
4. The existence of extra-articular and/or systemic manifestations.

The most important goal is to differentiate the features of joint damage, predominantly caused by OA, from those of inflammatory joint disease although in some cases a joint may synchronously be inflamed and damaged. Enquiry and physical examination are critical in this respect.

Joint damage/OA is typically associated with 'mechanical' or 'usage-related' pain—pain that increases with repeated use of the joint, which is relieved by rest, and which is often worst towards the end of the day. Patients may describe pain that increases again after resting and this may be accompanied by 'gelling', stiffness that subsides after just a few minutes. Early morning stiffness associated with OA is usually relatively brief, and is 'worn off' in well under half an hour. Symptoms of OA often fluctuate with 'good weeks' and 'bad

weeks' and change only slowly with time. Although OA signs may be detected in many joints on examination (many being asymptomatic), OA usually causes pain in just one or a few joints at any one time.

Conversely, in active inflammatory disease, pain is worst in the morning and is relieved as they get up and start to move their joints. Morning stiffness is often prolonged, lasting for more than 30 min and sometimes for several hours. Stiffness after rest may persist for more than 5 min.

With inflammatory disease sufficient to trigger the acute phase response, the patient may additionally complain of non-specific features such as fatigability, weight loss, night sweats, low mood and irritability, or just say that they 'feel ill'. With inflammatory multi-system diseases, there may also be symptoms and signs of extra-articular manifestations (e.g., anterior uveitis, skin lesions, lung or bowel problems). Such features are not associated with OA, which is purely a condition of the joints, although age-related comorbidities (e.g., obesity, hypertension, depression) may commonly occur in older patients with OA and contribute to their participation restriction.

It is noteworthy that people with OA may suffer 'flares' of pain which may relate to minor inflammation or be biomechanically initiated. During such pain exacerbations patients may have more prolonged morning and activity stiffness. However, inflammation is not a prominent clinical feature and OA does not trigger the acute phase response. Conversely, longstanding but 'inactive' inflammatory arthritis will be associated with 'mechanical' pain reflecting joint damage caused by their inflammatory disease.

Keep in mind that the rhythm of pain can be misleading if applied to non-articular pain. Pain associated with fibromyalgia or carpal tunnel syndrome has 'inflammatory' features, such as morning predominance, although there is no underlying inflammatory process. Conversely, pain from tenosynovitis may have a mechanical rhythm.

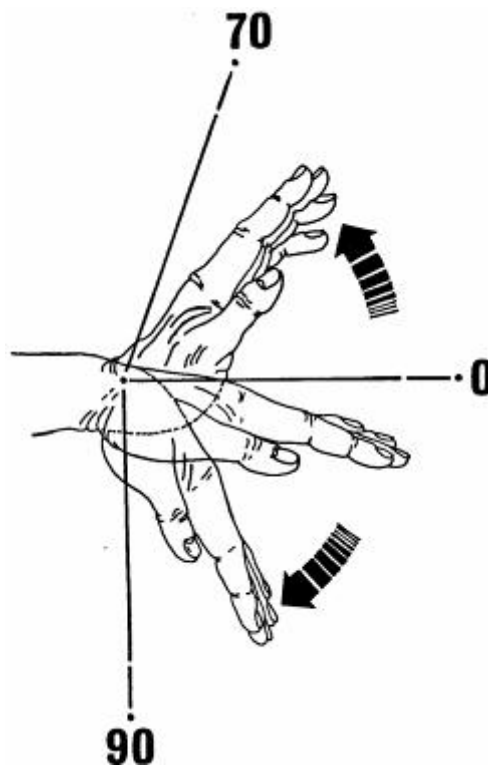
Physical examination will support joint damage/OA if there is coarse crepitus, localized joint-line tenderness and/or bony swelling (osteophyte) along the joint margin. Deformity may also be present in later stages of joint damage and OA.

In inflammatory diseases, the synovium becomes inflamed, engorged and eventually hypertrophied, and the volume of synovial fluid increases. This increase in soft tissue and fluid occurs within the limiting confines of the capsule and can increase the pressure within the joint causing pain, stiffness and restriction of movement. A joint with increased intra-articular pressure is most comfortable in the position that minimises the pressure. This position, generally mild to mid flexion, is mainly determined by the tightness of the capsule and is termed the 'loose-pack' position, in which the capsule is normally at its loosest and therefore can accommodate an increase in fluid and soft tissue. Conversely, the positions in which the capsule is naturally tight—the 'tight-pack' positions at the extremes of range of movement—are the positions that are the first to be painful when

synovitis is developing, and the first movements to become restricted. For example, glenohumeral synovitis is most comfortable with the arm adducted and internally rotated as if in a sling, and the patient will naturally adopt this attitude at rest. Conversely, the opposite movements, abduction and external rotation, are the earliest affected and most uncomfortable since these maximise intra-articular pressure.

As the inflamed joint is moved, actively or passively, through its range of movement the pain is minimal or absent in the loose pack position but increases as the joint moves into any of the tight pack positions. This uneven distribution of pain, maximal in all tight pack positions, is called 'universal stress pain'—the most sensitive sign of synovitis, occurring even before there is visible swelling or restricted movement (figure 4). Joint damage is associated with a more even spread of pain throughout the range of movement.

Figure 4 Stress pain and restriction at the wrist—there is no pain in the neutral position, but progressive pain and some restriction as the wrist moves towards full extension or full flexion.



Joint swelling due to soft tissue and fluid, of course, may also become visible and palpable clinically. Because the synovium is limited by the capsule, this swelling takes on a characteristic shape for each peripheral joint. For example, in the knee of a patient lying supine on the couch a small increase in fluid will be visible filling in the medial and lateral concavities or 'dimples' either side of the patella, allowing a 'bulge' sign to be demonstrated as the fluid is pressed transversely from one dimple to the other with the patella stabilised. A large amount of fluid within the knee will cause visible expansion of the suprapatellar pouch above and to either side of the patella, allowing demonstration of the 'balloon sign' (fluctuance). At the finger interphalangeal joints, synovium and fluid expands along the line of least resistance, appearing first as two rounded posterolateral swellings either side of the extensor tendon.

Joint inflammation may also cause increased warmth palpable over the capsular contour. Overlying redness implies an element of periarticular inflammation and this can occur with septic arthritis, gout, acute seronegative arthritis (mainly reactive and psoriatic) and some less common conditions such as palindromic rheumatism. However, even septic arthritis can be present without noticeable redness of the overlying skin, and erythema is not a feature of relatively deep joints such as the hip or shoulder. The summated features that allow distinction between joint damage and joint inflammation are shown in table 3.

Table 3 Differences between inflamed and damaged joints

	Inflamed joint	Damaged joint
Early morning stiffness	Prolonged	Brief
Inactivity stiffness	Prolonged	Brief
Increased warmth	+	–
Stress pain	Yes	No
Capsular soft tissue swelling	+	–
Effusion	+++	+ /–
Coarse crepitus	–	+++
Erythema	+ /–	–
Malalignment/deformity	–	+ /–
Instability	–	+ /–

Of course, the age of the patient, the mode of onset and distribution of affected joints, and the duration of symptoms will also influence our differential diagnosis of OA and inflammatory arthropathies. Joint conditions before the age of 40 years are likely to be inflammatory if not traumatic. Inflammatory arthritis will usually establish itself in a matter of days to weeks or months, whereas patients with OA tend to present to doctors only after years of variable but very slowly increasing pain. An acute monoarthritis on the other hand is a medical urgency and differential diagnosis mainly includes septic arthritis, crystal deposition arthritis, haemarthrosis and trauma (e.g., intra-articular fracture).

2.4.1 Patterns of inflammatory joint disease

We suggest that you always try to represent your patient's condition with as few words as possible, making a 'problem representation' in one sentence—for example, 'asymmetrical oligoarthritis, with inflammatory back pain' or 'acute arthritis with fever and rash'. This will make the final diagnosis a lot easier and reliable. Below, we describe the most common patterns we use in practice (box 1). Be critical of them, as you may find that other patterns work better for you.

Box 1 Characterisation of arthritis

- Number of joints affected
 - Monoarthritis: one single joint affected
 - Oligoarthritis: 2–4 joints affected
 - Polyarthritis: >4 joints affected
- Acute versus chronic
 - Acute: onset in hours or days
 - Sub-acute: up to 6 weeks
 - Chronic: onset over weeks (more than 6 weeks) or months
- Additive versus migratory
 - Additive: the affected joints are added progressively
 - Migratory: the inflammatory process flits from one joint to another
- Persistent versus recurrent
 - Persistent: once it has set, the arthritis persists over time (persistent ≥ 6 weeks)
 - Recurrent: episodes or crises of arthritis separated by symptom-free intervals.
- Predominantly proximal versus predominantly distal
 - Proximal: arthritis mainly affects large joints—that is, proximal to the wrist or ankle and the spine
 - Distal: the arthritis mainly affects the small joints of the hands and feet, with or without the wrist and ankle
 - Large and small joints affected—there is a mixture of joint sizes
- Symmetrical versus asymmetrical
 - Symmetrical: affects approximately the same joint groups on each side of the body
 - Asymmetrical: there is no clear relationship between the joints affected on either side of the body
- With or without inflammatory low back pain
- With or without systemic manifestations

2.4.1.1 Monoarthritis

It is useful to separate acute (onset over hours or days) from chronic monoarthritis.

2.4.1.1.1 Acute monoarthritis

The most common cause of acute inflammatory monoarthritis is crystal synovitis, although septic arthritis should always be considered because it is rapidly destructive and can be life threatening if treatment is delayed. Furthermore, crystals and sepsis can coexist in the same joint.

Crystal synovitis has the following characteristics:

- rapid onset of pain and swelling—at its worst within 6–24 h
- severe pain—often described as ‘worst ever’
- marked tenderness—often unable to bear clothes or bed sheets touching the overlying skin
- often florid synovitis with a tense effusion, adjacent soft tissue swelling and overlying erythema
- the episode is self-limiting, even without treatment, over a few days or a few weeks.

Gout is the most common cause of crystal synovitis. The first episodes often start at night and involve the first metatarsophalangeal joint, although any extremity joint (i.e., hand/wrist joints, elbows, knees, hindfoot,

midfoot, forefoot) may be involved. The attack may develop apparently spontaneously, but recognised provoking factors include local trauma to the joint and intercurrent illness or surgery. Systemic symptoms such as fever and malaise may be present.

Initial episodes of gout almost always follow a monoarticular recurrent pattern with symptom-free intervals, predominantly in the lower limbs. With time, intervals become shorter, the upper limbs also become involved, and more than one joint can be affected in each episode, occasionally leading to a polyarticular pattern.

Acute calcium pyrophosphate (CPP) crystal arthritis ('pseudo gout') presents a similar clinical picture but is mainly restricted to patients over the age of 60 years. It particularly targets the knee. Other common sites are the wrist, shoulder and ankle, although almost any joint can be affected. While a confident diagnosis of crystal synovitis may be made from the clinical characteristics, definitive diagnosis requires demonstration of sodium urate or CPP crystals in aspirated synovial fluid.

The classical presentation of septic arthritis involves the acute or subacute onset of pain, swelling and sometimes erythema in a single joint. Unlike crystal synovitis, symptoms and signs are progressive from day to day and do not plateau in the first 24 h. Systemic symptoms such as fever and malaise may be present. Note, however, that the onset may be more prolonged and inflammatory signs may be relatively mild. RA and immunocompromised status (e.g., diabetes) are risk factors, and sepsis should always be considered in a patient with RA who reports a 'flare' in just one or two adjacent joints. If the diagnosis is strongly suspected, the patient requires immediate admission and treatment for sepsis pending the results of synovial fluid and blood cultures—it is a medical emergency.

Other causes of acute monoarthritis include post-traumatic synovitis, palindromic rheumatism, reactive arthritis, psoriatic arthritis, and bacterial endocarditis. Chronic regional pain syndrome, also known as reflex sympathetic dystrophy, can pose a diagnostic challenge, but mainly involves a region rather than a single joint.

2.4.1.1.2 Chronic monoarthritis

Monoarthritis can have an indolent course, lasting from weeks to months. The main possible causes of chronic inflammatory monoarthritis include infection (*Brucella*, mycobacterium, borreliosis, others), monoarticular presentation of oligo- or polyarthritis (juvenile idiopathic arthritis, reactive arthritis, seronegative spondyloarthropathy), and a foreign body (e.g., plant thorns). Differential diagnosis must incorporate causes of non-inflammatory arthropathy, such as OA, recurrent hydarthrosis, osteonecrosis, chronic regional pain syndrome, neuropathic (Charcot's) joints and tumours, including pigmented villonodular synovitis.

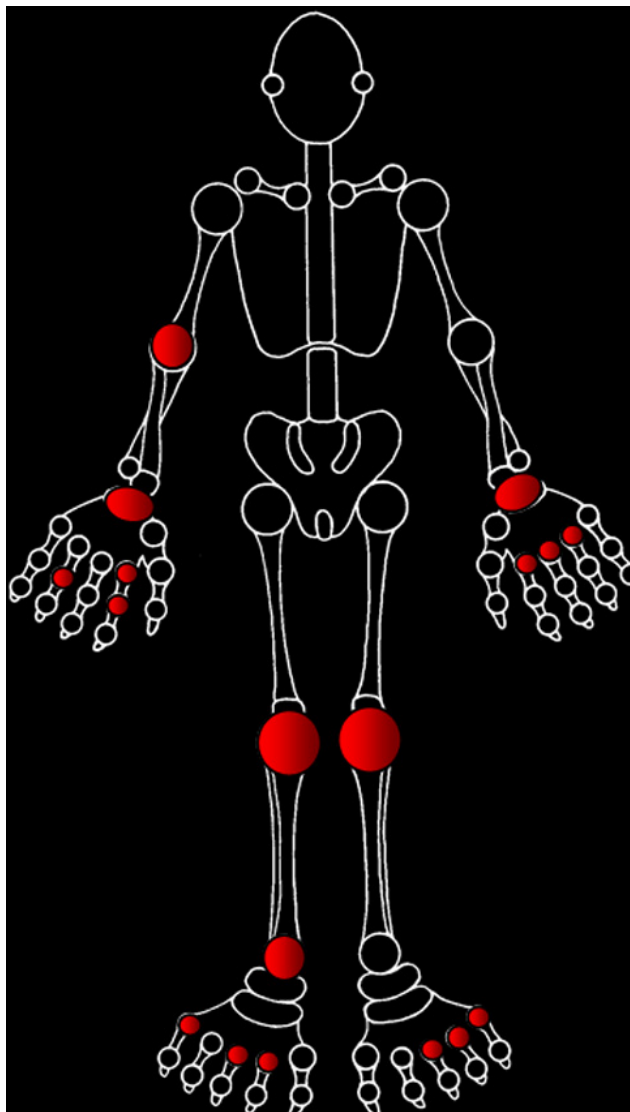
The aetiological diagnosis of chronic monoarthritis usually requires a synovial biopsy with pathological and bacteriological examination and in selective cases PCR technique. In a large number of cases, no specific cause can be identified.

2.4.1.2 Chronic symmetrical additive peripheral polyarthritis

This pattern describes joint inflammation involving, simultaneously, five or more joints (polyarthritis), for more than 6 weeks (chronic). Small joints of the hands and feet are predominantly affected, with or without the wrist, ankle and knee (peripheral), and approximately the same joints are involved on each side of the body (symmetrical). The affected joints have been added progressively (additive) over a relatively short time period (several months). There should be no inflammatory low back pain.

The most common cause for this pattern (figure 5) is RA. Onset of especially aggressive disease may be accompanied by constitutional features such as fever and lymphadenopathy. This could suggest a 'systemic syndrome', but articular manifestations dominate the clinical picture in the vast majority of patients. Other systemic manifestations may occur, but they are usually milder than the arthritis and tend to occur later in the course of disease.

Figure 5 *Chronic inflammatory polyarthritis, symmetrical, small and large joints, upper and lower limbs – the typical presentation of rheumatoid arthritis.*



This pattern of arthritis is common to other rheumatic conditions, especially other connective tissue diseases, such as SLE, primary Sjögren's syndrome, polymyositis (PM) and mixed connective tissue disease (MCTD). Psoriatic arthritis can also present with this pattern, although it tends to be more asymmetrical and involve either the distal interphalangeal or the sacroiliac joints. OA with CPP crystal deposition (CPPD) deserves consideration, especially in older patients. A pre-existing pattern of generalised OA with recurrent inflammatory episodes may suggest this condition. Chronic polyarticular gout may have a similar pattern of distribution. However, almost invariably this is preceded by a period of recurrent monoarthritis. Viral arthritis, such as is associated with parvovirus B19, HIV and hepatitis, may follow a similar pattern, but tends to have a more acute onset than RA or the connective tissue diseases.

The clinical contribution to differential diagnosis relies on careful evaluation of extra-articular manifestation. Further investigations may be useful.

2.4.1.3 Chronic asymmetrical oligo/polyarthritis

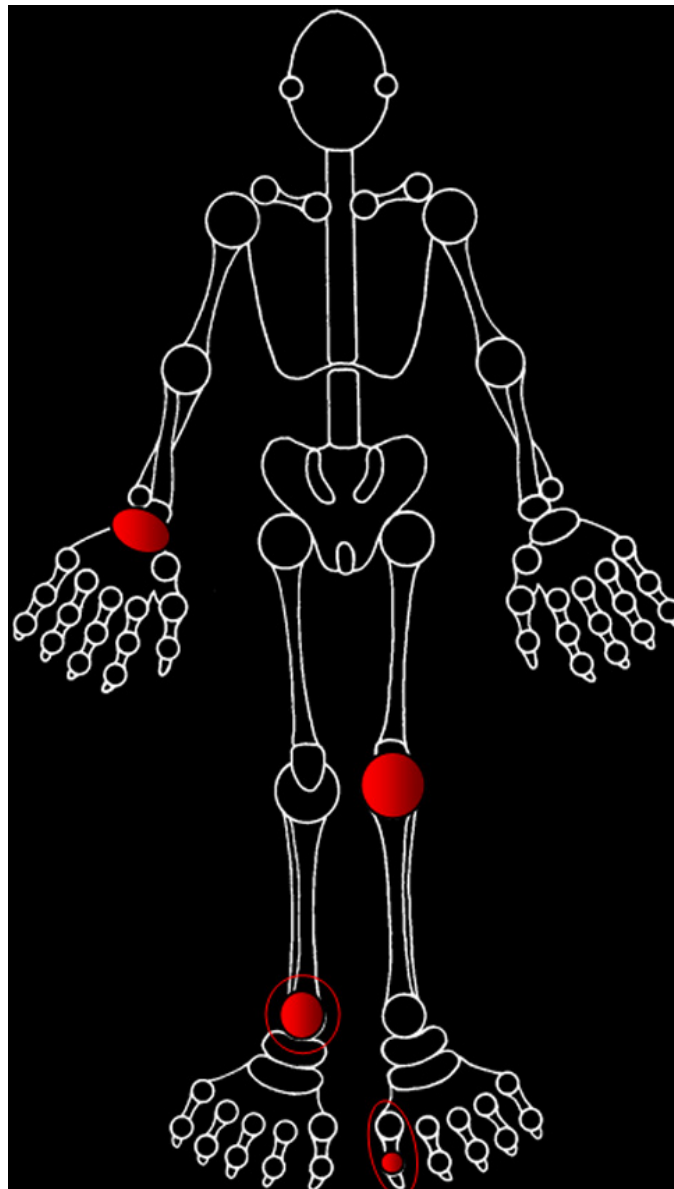
This describes an asymmetrical arthritis present for more than 6 weeks (chronic), affecting two or more proximal or distal joints (oligo/polyarthritis). Dactylitis, enthesitis or involvement of distal interphalangeal joints is a common but not mandatory feature. The combination of synovitis with adjacent periarticular inflammation (one example being dactylitis) is strongly suggestive of seronegative spondyloarthropathy.

Psoriatic arthritis is the most common cause of this pattern (figure 6). A personal or family history of psoriasis will provide support for this diagnosis. When the arthritis is limited to proximal and distal interphalangeal joints, hand OA needs to be considered as an alternative diagnosis. Although this usually has a slow development, it may evolve with acute inflammatory flares of these joints. Chronic sarcoid arthropathy may evolve with a similar pattern—the inflamed joint tends to show a nodular asymmetrical aspect as opposed to the spindle shape of psoriatic synovitis.

Other seronegative spondyloarthropathies, such as AS, may also cause this pattern of arthritis, mainly asymmetric oligoarthritis. Inflammatory back pain is expected in this condition, but may not be obvious. Reactive arthritis or arthritis associated with inflammatory bowel disease may show this pattern, but when distal joints are affected they usually adopt a symmetrical distribution.

Other causes include incipient RA, juvenile idiopathic arthritis, polyarticular gout, OA with CPPD, and Behçet's disease. Again, careful enquiry about axial and extra-articular manifestations including enthesopathy and uveitis may provide critical clues to the diagnosis.

Figure 6 Chronic inflammatory polyarthritis, asymmetrical, with synovitis plus adjacent periarticular inflammation (e.g., dactylitis)—a characteristic distribution for seronegative spondyloarthropathy.



2.4.1.4 Proximal oligoarthritis

Patients may present with inflammatory arthritis involving predominantly proximal joints. The most common causes are the seronegative spondyloarthropathies. Complete questioning and physical examination is important for differential diagnosis. The presence of inflammatory low back pain, a personal or family history of psoriasis, inflammatory bowel disease, AS, uveitis, and the occurrence of any infectious disease (infectious diarrhoea, urinary tract infection) in the weeks preceding arthritis must be explored in the enquiry.

Other causes of proximal oligoarthritis include Behçet's disease, juvenile idiopathic arthritis and incipient RA. It is not uncommon for arthritis with this pattern to defy formal classification and is better described as unclassified oligoarthritis.

Polymyalgia rheumatica is in the differential diagnosis of proximal oligoarthritis. The patient is typically an elderly person, presenting with pain and stiffness in the neck, shoulders and hip girdle due to inflammation that mainly affects the peri-articular structures (tenosynovial sheaths, bursae). Peripheral joints can be involved. Some extra-articular manifestations must be explored in questioning. Malaise, fever, fatigue, anorexia and weight loss are common features. Jaw claudication, temporal headaches and loss of vision suggest concurrent temporal arteritis.

2.4.1.5 Acute oligoarthritis or polyarthritis: febrile arthritis and arthritis with manifestations of the skin and mucous membranes

This is characterised by a rapid onset of oligo- or polyarthritis, often associated with a recent infection, fever or changes in skin and mucous membranes.

This pattern suggests the possibility of reactive arthritis. In these cases, the patient is most often a young adult man. The enquiry should explore the occurrence of a significant infection within the 2–3 weeks before the arthritis. There is a wide variety of potential causal agents, but most frequently this will be gastrointestinal, genitourinary or upper respiratory infection. Reactive arthritis is often associated with manifestations in the skin (e.g., rash, erythema, keratoderma blenorrhagica) and mucosae (conjunctivitis, urethritis, oral or genital ulceration, circinate balanitis).

The pattern of articular involvement varies. Proximal oligoarthritis is the most common, but in cases of post-streptococcal reactive arthritis or post-viral arthritis, such as parvovirus, HIV, hepatitis C and B and tropical viruses, it is often polyarticular and symmetrical.

Still's disease (in adults or children) is characterised by an acute or subacute onset of arthritis, associated with fever, evanescent skin rash, weight loss, lymphadenopathy and/or splenomegaly. SLE, dermatomyositis (DM), Behçet's disease and, occasionally, RA may present with similar features and should be considered in the differential diagnosis.

Löfgren's syndrome is a type of acute sarcoidosis that is most commonly accompanied by bilateral ankle arteritis and fever, erythema nodosum especially of the legs. A chest radiography will commonly reveal bilateral hilar lymphadenopathy.

2.4.1.6 Periodic arthritis with fever

Recurrent episodes of arthritis with fever point to the diagnosis of rare hereditary disorders with a common phenotype of lifelong, recurrent inflammatory episodes, characterised by inflammatory symptoms such as fever, abdominal pain, diarrhoea, rash, or arthralgia. Between the fever episodes, patients with most of these syndromes generally feel healthy and function normally. These syndromes include familial Mediterranean

fever, cryopyrin-associated periodic syndrome (CAPS) and others, usually starting in childhood although late onset has been described.

2.4.1.7 Polyarthrititis with systemic manifestations

This is characterised by polyarthrititis with clear manifestations or strong suggestion of compatible systemic involvement.

SLE is the most common cause but other connective tissue diseases must be considered in the face of this pattern of involvement.

Reactive arthritis and viral arthritis could present with polyarticular involvement and are associated with systemic manifestations, although these are usually of a different nature. Still's disease may deserve consideration when this pattern is present.

2.4.2 Inflammatory back pain

Inflammatory back pain is axial and symmetrical, affects multiple segments, is not relieved by rest but rather by movement, and is associated with prolonged morning stiffness. Low back pain may radiate to the buttocks and patients may describe alternating buttock pain.

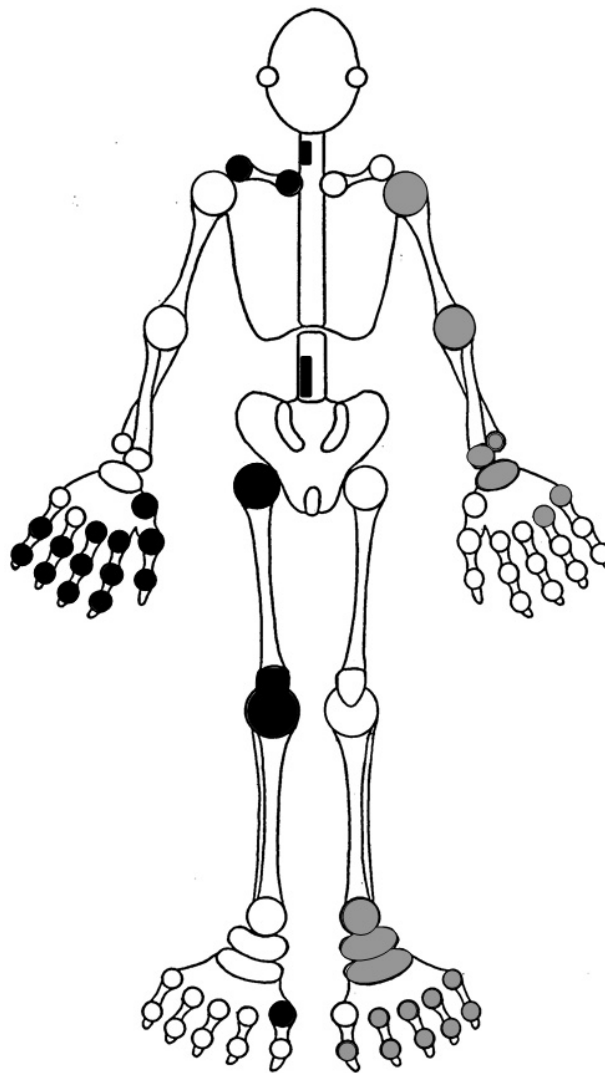
Inflammatory back pain is a typical manifestation of seronegative spondyloarthropathies: non-radiographic axial spondyloarthritis, AS, psoriatic arthritis, reactive arthritis, and spondylitis of inflammatory bowel disease. Other conditions to consider are Behçet's disease and infectious or aseptic discitis.

In seronegative spondyloarthropathy, the spine is very often affected and may or may not be accompanied by involvement of the peripheral joints. When the condition is strictly limited to the spine, non-radiographic axial spondyloarthritis or AS becomes the most probable diagnosis. If peripheral joints are also affected, the pattern of distribution and the associated manifestations are the key to the final diagnosis. Psoriasis, inflammatory bowel disease, uveitis, urethritis, conjunctivitis, venous and arterial thrombosis, and mucosal ulcerations must be explored in the history and examination.

2.4.3 Patterns of OA

OA typically develops in middle-aged or elderly people and in some joints, such as the hip or knee, symptoms may get slowly worse with time, whereas in others, such as finger interphalangeal joints, symptoms may improve. Common target sites for involvement are shown in figure 7. However, although joints such as the shoulder and elbow are not target sites for OA, the most common cause of arthritis in these joints is OA simply because of the very high prevalence of OA compared to other arthropathies.

Figure 7 Target sites for osteoarthritis are shown on the left in black; joints that are relatively spared are shown in grey on the right.



Nodal generalised OA is characterised by multiple Heberden's and Bouchard's nodes and involvement of other common target sites for OA. It predominates in middle-aged and older women and there is often a family history.

'Atypical' OA is suggested by uncommon characteristics, such as onset at a young age or an unusual joint distribution, in a patient who has usage-related pain and signs of joint damage, without inflammation. Such features should alert the clinician of the possibility of an underlying predisposing condition. Young-onset mono-articular OA (<50 years old) is most commonly a result of previous major joint injury (e.g., subchondral fracture, torn meniscus, cruciate ligament tear). However, young-onset pauci- or polyarticular arthritis that clinically, and even radiologically, appears as OA should lead to consideration of specific conditions that predispose to joint damage (box 2). Most of these have their own additional clues on enquiry and physical examination.

Box 2 Causes of ‘atypical’ osteoarthritis with young onset or atypical distribution**Mainly monoarticular:**

- Prior trauma or injury (e.g., fracture involving the articular surface, meniscectomy, instability, osteochondritis dissecans)

Mainly oligo- or polyarticular:

- Spondylo-epiphyseal and epiphyseal dysplasia (may have short stature and family history)
- Pre-existing arthritis (e.g., prior juvenile idiopathic arthritis, septic arthritis)
- Haemochromatosis (often targets hip, wrist, metacarpophalangeal joints)
- Neuropathic joint (hindfoot—diabetes; shoulder, elbow, wrist—syringomyelia; knee, spine—syphilis)
- Osteonecrosis (mainly hip, shoulder, knee, elbow)
- Endemic osteochondropathy (e.g., Kashin-Beck disease, Mselini disease)

OA itself is a risk factor for crystal deposition (CPP, basic calcium phosphates and sodium urate). Therefore, if a patient with apparent OA has an additional superimposed inflammatory component, especially with ‘flares’ of clinically overt inflammation, examination of a synovial fluid aspirate, particularly for CPP and urate, is warranted.

2.5 Bone pain conditions

Bone pain can have different presentations. One form that is important to identify is pain characterised by deep, diffuse, continuous pain, unrelated to movement and not typically confined to joints. Frequently, pain will be worse at night and disturb the patient’s sleep. These features should raise consideration of bone tumours, metabolic bone diseases or inflammation of the periosteum. Metastatic tumours are the most common neoplasms of bone, and bone is the third most common site of metastasis after the lung and liver. Pain due to a metastatic lesion may be the first symptom of the underlying malignancy. Common sites affected include the spine, the pelvis and the proximal segments of the limbs. The local examination is usually normal and does not reproduce the patient’s pain.

Another form of bone pain results from fracture. This pain may be more acute or subacute in onset, is very well localised without any radiation, and is often worse on minimal movement. Risk factors for osteoporosis and fractures include postmenopausal status, early menopause, late menarche, low body mass index (BMI), sedentary lifestyle, low dietary dairy intake, and family history of osteoporosis or fracture. Secondary causes include malabsorption, hypogonadism, hyperthyroidism, hyperparathyroidism, excess alcohol use, and prolonged glucocorticoid use.

2.6 Muscle symptoms

Myalgia is a frequent symptom of viral infections, but is also commonly associated with systemic diseases such as lupus, vasculitis and PMR. These may cause pain and muscle tenderness, but usually not weakness. However, primary muscle disease is most commonly reflected by proximal weakness and muscular atrophy.

Myopathic patients may have difficulty going up and down stairs, getting up from a low chair or combing their hair, but their handshake is firm and they can walk on tiptoe. Examination may show decreased proximal muscular power and muscle tenderness. Muscle atrophy is a later and inconsistent finding.

PM, DM and inclusion body myositis (IBM) are the most typical causes of this pattern. Arthralgia and low grade arthritis may also occur, especially when inflammation of muscle occurs as part of a connective tissue disease, such as systemic sclerosis or MCTD. Systemic complaints such as low grade fever, fatigue, weight loss and skin rashes are often present.

The differential diagnosis of adult PM/DM must include a broad array of conditions capable of affecting skeletal muscle. Hypothyroidism, sarcoidosis, and metabolic myopathies must be considered in this clinical context, as the myopathy associated with these conditions may dominate the clinical presentation. Muscle pain and stiffness of the proximal limb girdles, characteristic of PMR, may be interpreted as myopathy, but with PMR muscle weakness is not a feature.

Rheumatologists should also give special attention to commonly used drugs which can cause neuromuscular complications, including glucocorticoids, hydroxychloroquine, colchicine, cyclosporine, statins and fibrates among several others.

Non-inflammatory myopathies must also be considered and they include an enormous variety of neurological conditions, such as spinal muscle atrophies, myasthenia gravis, myotonic diseases, congenital myopathies and storage diseases.

Generalised muscle pain with 'tender points' is an integral part of fibromyalgia can lead to a subjective feeling of muscle weakness which in most cases is not confirmed on physical examination.

2.7 Systemic syndrome

Inflammatory joint diseases may be accompanied by extra-articular manifestations. Examining for extra-articular manifestations should be an integral part of the investigation. Commonly, these manifestations occur together with polyarthritis and sometimes they can dominate the clinical picture. The term 'systemic syndrome' is a term used to further explore the diagnosis. Table 4 presents the most common and relevant manifestations.

Table 4 Main systemic manifestations associated with rheumatic diseases

Main systemic manifestations associated with rheumatic diseases	Associated diseases*
<i>Constitutional manifestations</i>	
Fever	RA, SLE, DM/PM, SSc, MCTD, vasculitis, FMF and other periodic fever syndromes
Weight loss, severe fatigue	RA, SLE, DM/PM, SSc, MCTD, vasculitis
<i>Skin manifestations</i>	
Photosensitivity, alopecia	SLE, DM
Sclerodactyly, telangiectasia	SSc, MCTD, overlap syndromes
Heliotrope rash, Gottron's papules	DM
Raynaud's phenomenon	Idiopathic Raynaud's phenomenon, SSc, SLE, MCTD
Psoriasis	Psoriatic arthritis
<i>Mucosal manifestations</i>	
Oral and genital ulcers	SLE, Behçet's disease, Crohn's arthropathy, vasculitis
Dry eyes and mouth	Sjögren's syndrome, rheumatoid arthritis
Serositis	SLE, rheumatoid arthritis, MCTD, FMF
Uveitis	Reactive arthritis, ankylosing spondylitis, Behçet's disease and other vasculitis, sarcoidosis
Scleritis, episcleritis	Vasculitis, relapsing polychondritis
<i>Others</i>	
Arterial or venous thrombosis	Vasculitis, antiphospholipid antibody syndrome, Behçet's disease
Recurrent abortion	Antiphospholipid antibody syndrome
Dysphagia	SSc, MCTD, PM/DM, IBM
Dyspnoea	Several connective tissue diseases
Lower limb oedema, hypertension	SLE
Lymphadenopathy	Several connective tissue diseases
Muscular weakness	PM/DM, IBM, MCTD, SSc myositis, overlap syndromes
Convulsions, psychosis	SLE, CNS vasculitis, antiphospholipid antibody syndrome
Peripheral neuropathy	Vasculitis, primary Sjögren's syndrome, SLE, sarcoidosis, RA
ENT manifestations—sinusitis, otitis media, deafness	Vasculitis
Diarrhoea	IBD related arthropathy

*In approximate descending order of prevalence.

DM, dermatomyositis; ENT, ear, nose and throat; FMF, familial Mediterranean fever; IBD, inflammatory bowel disease; MCTD, mixed connective tissue disease; PM, polymyositis; IBM, inclusion body myositis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis

Connective tissue diseases and vasculitides are the most common causes of systemic syndrome. Their distinction is based on the predominant clinical manifestations of each disease (table 5). The clinician must, however, exercise flexibility here as overlap between different diseases is extremely common.

Table 5 Manifestations associated with the different connective tissue diseases

Manifestations	SLE	Systemic sclerosis	PM/DM	MCTD	Vasculitis
Constitutional symptoms	++	–	+	+	+++
Arthritis	+++	+	+	+++	+
Diffuse swelling of the hands	Rare	++	Rare	++	–
Photosensitivity	+++	+	+++	+	–
Cutaneous sclerosis	–	+++	–	+	–
Calcinosis	–	+++	–	–	–
Erythema	++	–	++	+	–
Vasculitic lesions	+	+	Rare	Rare	+++
Raynaud's phenomenon	+	+++	+	+++	+
Hair loss	++	++	Rare	Rare	Rare
Sicca syndrome	++	++	+	++	–
Uveitis/scleritis/episcleritis	Rare	–	–	–	++
Serositis	++	+	–	++	–
Arterial and venous thrombosis*	+	Rare	Rare	Rare	+++
Miscarriages*	+	Rare	Rare	Rare	Rare
Central nervous system	+	Rare	Rare	Rare	+
Muscular	–	+	+++	++	+
Digestive	–	++	+	++	–
Haematological	+++	–	–	++	–
Renal	+++	++†	Rare	+	++
Pulmonary	+	++	+	++	++

The number of ' + ' signs reflects the weight of the manifestation as an argument in favour of a diagnosis.

**In secondary antiphospholipid antibody syndrome.*

†Hypertensive crisis, drop in creatinine clearance.

MCTD, mixed connective tissue disease; PM/DM, polymyositis/dermatomyositis; SLE, systemic lupus erythematosus.

Vasculitis encompasses a large number of conditions with a wide range of manifestations. This is further explored in a dedicated discussion in the EULAR online course (<http://www.eular-onlinecourse.org>).

Still's disease typically presents, in both children and adults, with a systemic syndrome dominated by fever, rash, weight loss and lymphadenopathy and leucocytosis in addition to arthritis. Serositis, pneumonitis, hepatomegaly and myalgia may also be present in a complex multisystem clinical situation demanding differential diagnosis with connective tissues diseases, vasculitis, malignancy and infection, among others.

Occasionally, reactive arthritis may be dominated by extra-articular features, such as uveitis, nephritis, carditis, and gut and eye inflammation. Sarcoidosis should be especially considered in the presence of lymphadenopathy, erythema nodosum, or lung, eye or liver involvement.

Relapsing polychondritis and familial Mediterranean fever may also deserve consideration in the context of a systemic syndrome.

3 The 'optimal' enquiry and examination in rheumatology

Whether we are aware of it or not, we begin our differential diagnosis with our first question and then test out, reinforce or eliminate hypotheses as the enquiry goes on. The ideal enquiry should be 'economical' and critical.

3.1 Focus on relevant concerns

By 'economical' we mean short and focused, but still comprehensive and empathic. Relevant information should be explored, but irrelevant should be discarded.

Irrelevant information creates distraction or 'background noise'. To master this ability requires a clear view of what is the key information and what needs to be taken into account during the diagnostic process or treatment selection. Let us use an example. The sequence of involvement of joints in a polyarthritis makes no difference to the diagnosis: the interpretation of a chronic symmetrical peripheral polyarthritis is the same irrespective of whether the first joints affected are the feet or the hands, the wrists or the metacarpophalangeal joints. This detail is, therefore, irrelevant and should not be explored. We do not need to ask for the rhythm of pain in individual joints involved in polyarthritis.

However, we must do that for an associated back pain. In most cases this will be a comorbid non-specific mechanical back pain with no added significance. However, low back pain with an inflammatory pattern is a crucial clue to the interpretation of peripheral polyarthritis.

There is no absolute measure of the value of any piece of information that can be applied to every clinical setting. Be critical about the importance to any feature. Focus on the most important topics for your reasoning and make your own problem representation in one sentence.

3.2 Assess the validity of information

To make the enquiry work in an optimal way, it is crucial that you critically appraise the validity and the degree of certainty of each piece of information and be aware of the impact on your reasoning.

Your map is made of crossroads where your choice is guided by a signal or symptom. It is important to pay good attention, especially to signs that drive you in a very different direction. If you misread a signal, you are bound to choose the wrong road. Never forget to make an appropriate enquiry of systemic symptoms.

Symptoms and signs are often poorly defined and subjective and you cannot always be sure that you have read them precisely. This is an inherent problem in clinical medicine, but we suggest two methods to try to diminish these risks. One suggestion is that you discuss crucial symptoms with the patient in different ways, using variable expressions until you are certain you have understood the patient exactly. For this purpose, it is useful to summarise your interpretation and negotiate it with the patient.

You should keep an open, critical mind about signals and symptoms that are influential but not very precise. When facing such a problem, explore one direction, assuming the sign is real and reliable, and then explore the alternative directions—that is, different interpretations of that sign.

3.3 Listen to the patient

Dealing with the patient's concerns is the core to the objectives of the clinical encounter. Additionally, patient clues will feed your lateral thinking, open your eyes around 'predetermined' scripts, and keep you from disregarding relevant problems that you had not considered.

Examples are numerous and common: a patient describing pain and stiffness around the shoulders is finally given an opportunity to refer to his or her weight loss; back pain is finally related to a perforated ulcer when we listen to the patient's digestive complaints; unexplained pain is clarified when we allow ourselves to listen to hints of anxiety and distress, etc. Give the patient a couple of minutes at the start of the enquiry. This will help to focus the problem. Make sure that you hear the patient's own story but not formulations from other doctors.

Published reports have shown that specialists in ears, nose and throat interrupt their patients within 2 seconds of the start of an enquiry; there is no reason to believe that rheumatologists are any different. Crucial information may, thus, be lost.

Be vigilant about whether your strategy allows enough room for the patient's expression of all relevant information. Be sure always to end your questioning by asking the patient: 'Is there anything else troubling you that I haven't asked about?'

3.4 Examine properly

Physical examination will play a major role in clarifying the diagnosis. Examination is extremely important to determine the anatomical origin of the pain (articular, periarticular, muscular, neurogenic, etc.) and the nature of the disease (degenerative, inflammatory, entrapment). Once you have finished the enquiry, you will have a

natural tendency to approach the physical examination with a biased tendency to confirm expectations. If, before the examination, you are 'convinced' that your patient has fibromyalgia, you may put slightly more pressure on the tender points, ignore doubtful signs of joint swelling or forget to explore the sacroiliac joints.

Careful musculoskeletal examination can be performed in a short time and can be easily combined with an adequate general examination. Although this examination is not technically demanding, it must be done with appropriate care and detail. Pain on movement of the ankles can be arthritis or Achilles tendonitis, for example; tenderness due to anserine bursitis may be wrongly taken as indicating arthritis; pronator syndrome will never be diagnosed without the proper examination techniques; trochanteric bursitis can closely mimic sciatica, etc.

3.5 Summarise the data

We suggest that you try to define each symptom or syndrome with as few words as possible. Be aware of the exact meaning and implication of each word, on others and on yourself. Once you 'decide' or say that a patient has 'arthritis', you allow yourself and others to exclude muscle pain or periarticular lesions from consideration. Being aware of what it takes to say that a patient has arthritis; you may consider using the word arthralgia, or arthropathy to refer to less defined conditions. This exercise will help you to scrutinize the validity for each piece of data you use. Using specific terms when possible will enhance the precision of your communication with others and of your own reasoning process.

By summarising the data you focus on what is relevant, diminish 'background noise', and enhance the efficiency of your reasoning. Most nuances are not crucial for diagnosis: there is, for example, a certain temperature profile which is more typical of Still's disease, but you should think of this hypothesis in any patient with fever, arthritis and lymphadenopathy. Nuances that are 'really' important should be part of your summarised description, anyway.

In the clinical exploration the doctor must have a split mind: one part is interacting and keeping empathy with the patient, while the other is checking the map, the quality and relevance of signs, and to direct the diagnostic journey.

4 Role of laboratory tests in rheumatology

Laboratory tests have limited usefulness in the diagnosis of most rheumatic conditions. Their influence varies according to the clinical picture and they should be chosen to clarify a clinically supported hypothesis. Ordering a battery of laboratory tests will often introduce information noise and cost rather than clarify the diagnosis.

The ability of a test to classify subjects correctly as having or not having a given disease depends on sensitivity and specificity.

Sensitivity is the proportion of true positives (i.e., true patients) who are correctly identified as such and is, therefore, equal to 1 minus the false-negative rate. Specificity is the proportion of true negatives (i.e., non-patients) who are correctly identified as such and is, therefore, equal to 1 minus the false-positive rate.

Specificity is profoundly affected by the population used to establish it—that is, the number and medical conditions of the control population. For example, the prevalence of rheumatoid factor in the general healthy population increases with age and is associated with a variety of non-rheumatic conditions (such as endocarditis and tuberculosis) and rheumatic diseases such as Sjögren's syndrome and SLE. The calculated specificity in any given study will be increased by exclusion of the confounding conditions from the control group and decreased by the inclusion of older people or patients with SLE. Ideally, we would have accurate numbers reflecting the clinical context of each individual patient, but that is, obviously, impossible.

Taken lightly, sensitivity and specificity can be easily overvalued in practice. The clinician needs to consider the limitations of these numbers. Let us consider, for example, antinuclear antibodies (ANA) and the diagnosis of SLE.

It is certainly remarkable that ANA can be found in over 95% of patients with SLE. A negative ANA test certainly makes the diagnosis of SLE very unlikely. A positive test supports the diagnosis, but the impact will depend on the clinical situation. Positive ANA are also found in about 5% of the general population, with the incidence rising with increasing age. However, SLE is a rare disease, affecting about 1 in 2000 of the population. This makes SLE a relatively rare cause of positive ANA. If all people with musculoskeletal symptoms were 'blindly' screened for ANA (about 20% of the total population), 100 in 2000 of the population would be found to have ANA, while only one would have SLE. Therefore most people with a positive ANA test do not have SLE or any other rheumatic condition. Similar limitations, obviously, apply to other tests.

Adequate weighing up of sensitivity and specificity can be helped by stating to oneself the complementary message: rheumatoid factor is present in 80% of patients with RA (sensitivity), therefore 20% of patients with RA do not have rheumatoid factor.

The impact of test results on the probability of the diagnosis is better supported by consideration of the pre-test probability and the likelihood ratio. A positive test could increase the likelihood of the diagnosis, on the contrary, a negative result could 'rule out' a suspected disease. This and other aspects of weighing up evidence and laboratory results are explored in more depth in another chapter, dedicated to the critical appraisal of evidence.

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Summary points

- **Willing or not, nearly all practising clinicians follow trains of thought and use ‘maps’ of clinical reasoning.**
- **Reflect on your practice, take lessons from your own experiences and incorporate them into your own ‘mind map’.**
- **Focus on the typical characteristics of each condition and on the crucial aspects that differentiate it. Give attention to indicators of prognosis, activity and progress.**
- **Never forget the decisive role of enquiry and examination in diagnostic process.**
- **Balance the need to guide your patient through the enquiry and his/her freedom to express their concerns.**
- **Always be critical about the clarity, validity, accuracy, sensitivity and specificity of the clinical and laboratory data you use.**
- **Be aware of the importance of words as ‘guides of thought’ and exercise the use of clinical descriptors that are as accurate and precise as possible.**
- **Make a problem representation in one sentence.**
- **Consider the ‘mind map’ we offer in this chapter as a mere example, waiting to be adapted and continually revised by you, in a search for the map that works best for you and your patients.**

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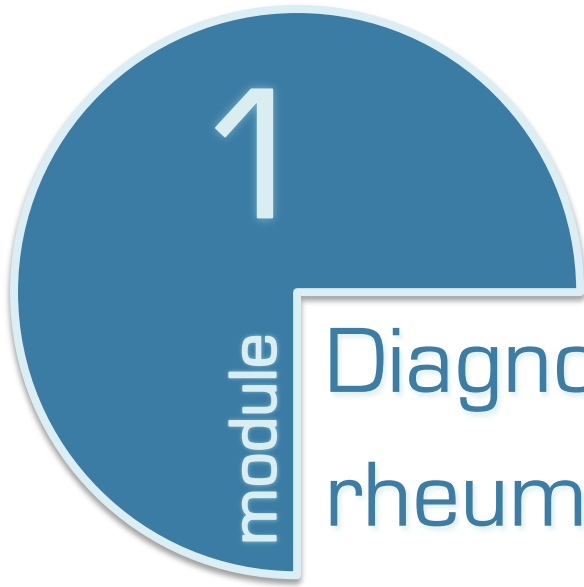
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EULAR on-line course on Rheumatic Diseases

Diagnostic strategies in rheumatology

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IN-DEPTH DISCUSSION I

Vasculitis: diagnostic strategy

A 45-year-old man is admitted to your department.

His history is:

I'm visiting you because of a rash on my legs which I noticed just yesterday. I have been unwell for about 3 weeks. I have pain all over, and I have also felt sweaty at night and have lost 2 or 3 kg. I don't feel right and am very tired.

Clinical examination and laboratory results show a palpable rash on his legs (See Figure). His blood pressure is 195/100 mmHg, temperature 37.8°C, and diffusely tender muscles. Urine dipstick shows 1+ of protein. Lab reveals mild normocytic and normochromic, anaemia and a CRP of 85 mg/L (normal <5 mg/L).



Try to formulate a one-sentence representation defining the case in abstract terms

The one-sentence representation can be as follows:

A 45-year-old Caucasian male with a systemic syndrome consisting of B-symptoms for 3 weeks and a non-itching palpable purpuric rash suggestive of leukocytoclastic vasculitis. He has hypertension and proteinuria which might point to possible involvement of his kidneys.

Could it be an Infectious disease?

Yes – it could be – the relatively short duration of symptoms and low-grade fever might point to an infectious process such as parvovirus B19, HCV, HBV or SBE. A vasculitic rash and an increased CRP could be a manifestation of these diseases as could kidney involvement. Serological studies and cultures should be performed.

In addition to ruling out infection, how should we classify this cluster of symptoms? Answer: a systemic clinical picture for which the DD includes vasculitis, SLE, PM/DM, MCTD/pSS

Could this patient have a vasculitis? Why?

Yes, the patient might have a vasculitis. He has constitutional symptoms and signs of systemic disease with kidney involvement. The vasculitis rash further strengthens this possibility although it is not mandatory.

DIAGNOSTIC APPROACH

Step one: When to suspect vasculitis?

Vasculitis is an inflammation of blood vessel walls. It is a highly heterogeneous group and can affect vessels of all sizes in any organ. The clinical picture of vasculitis can vary from a benign loco-regionally restricted processes to systemic necrotising vasculitis leading to life-threatening conditions.

The presenting symptoms (Table 1) varies. They include such constitutional symptoms as fatigue, weight loss, night sweats and low grade fever (the B-symptoms) and also more specific symptoms derived from tissue and organ ischemia, such as claudication, angina, stroke, cutaneous ischemia and mesenteric ischemia depending on the vessels involved. Several organs may be affected. Ischemia is especially suggestive when it affects a

young person without atherosclerosis. Also multiple organ dysfunctions in a systemically ill patient should raise the possibility of vasculitis.

You have to suspect vasculitis when a patient presents with:

- Unexplained systemic illness
- Symptoms of organ system ischaemia
- Nephritic syndrome

Table 1. When should we suspect vasculitis? This shows the most common manifestations, remember that most manifestations can be seen in any kind of vasculitis

General clinical feature	Signs or presenting disorders	Type of vasculitis
Constitutional symptoms	Low grade fever, fatigue, malaise, anorexia, weight loss	GCA, GPA, MPA, eGPA, PAN, less commonly other vasculitis.
Polymyalgia rheumatica	Proximal muscle pain with morning stiffness	GCA
Myalgias	Diffuse	PAN , GPA, MPA, eGPA
Non-destructive oligoarthritis	Joint swelling, warmth, painful range of motion, migratory	PAN, MPA, eGPA, GPA, hypersensitive vasculitis
Skin lesions	Livedo reticularis, necrotic lesions, ulcers, nodules, digital tip infarcts	Any medium-vessel vasculitis
	Palpable purpura, urticaria-like	Any small-vessel vasculitis
ENT symptoms	Sinusitis, otitis, hearing loss	GPA, eGPA, MPA
Cranial symptoms	Headache	GCA, TAK, GPA
Multiple mononeuropathy (mononeuritis multiplex)	Injury to two or more separate peripheral nerves (e.g. drop foot, wrist drop)	PAN, eGPA and GPA MPA,

Renal involvement	Renal artery involvement	PAN, TAK
	Glomerulonephritis	MPA, GPA, cryoglobulinaemia, Henoch-Schönlein purpura
Gastrointestinal involvement	Abdominal pain, nausea, diarrhoea, bleeding	GPA, eGPA, PAN, Henoch-Schönlein purpura
Cardiovascular involvement	Hypertension	Any type of vasculitis
Ocular involvement	Visual disturbance	GCA, TAK, GPA
	Scleritis, episcleritis, uveitis	Behçet's disease, GPA
Pulmonary involvement	Asthma	eGPA
	Infiltrates	GPA, eGPA

GPA Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis); eGPA Eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome); MPA Microscopic polyangiitis; GCA Giant cell arthritis; TAK Takayasu's arteritis.

In this In-depth discussion, we have now given you the first step of your two step approach to diagnose vasculitis: when to suspect vasculitis.

Now reaching step two you have to be aware that several other conditions can mimic vasculitis or initiate a secondary vasculitis. These conditions need to be considered and excluded before you finally decide on the specific type of primary vasculitis.

Think about diagnostic groups that might mimic vasculitis

Mimics of vasculitis:

- Infections
- Embolic disorders
- Malignancy
- Drugs

Consider diagnostic groups that can cause secondary vasculitis

Conditions that may cause secondary vasculitis

- Infections
- Drugs
- Malignancy
- Connective tissue diseases

These lists pose an important practical dilemma: immediate onset of immunosuppressive treatment might be lifesaving in primary vasculitis – but it could also be fatal in cases of an infectious disease.

A structured diagnostic approach is indispensable.

Step two: The diagnostic strategy

Having considered the possibility of primary vasculitis we suggest you try to answer the following questions in succession:

Is this a condition that could mimic the presentation of vasculitis?

Is this a secondary vasculitis?

How do I confirm the diagnosis of vasculitis and what is the extent of the disease?

What specific type of vasculitis is this? Is this a large-vessel, medium-vessel or small-vessel vasculitis?

Consider mimics of vasculitis

Vasculitis mimics should be excluded first.

- Infections
- Embolic disorders
- Malignancy
- Drugs

In particular, infections deserve careful attention, as they are major mimics of vasculitis and would be aggravated by medication aimed to suppress vascular inflammation. Infective endocarditis should always be considered. It is known to mimic vasculitis. Although the endocardium is the primary site of infection, it often results in multisystem manifestations, involving several organs. Bacteraemia and peripheral embolic events are common. Circulating immune complexes may lead to immune responses most often affecting the skin, the kidney and the central nervous system.

Differential diagnosis is not always simple.

Think about the clinical and laboratory findings you will expect to find in both a vasculitis and an infection

Table 2. Clinical and laboratory similarities between infection and vasculitis

Clinical findings:

- B-symptoms (fatigue, weight-loss, fever)
- myalgia
- arthralgia

Laboratory findings:

- normocytic normochromic anaemia
- lymphocytosis
- thrombocytosis
- elevated ESR
- raised CRP

Like infections, other conditions can mimic vasculitis. Mimics of vasculitis lead to ischemia and systemic signs and symptoms, but are caused by other physiological mechanisms. They are frequently entitled pseudo-vasculitis or vasculitis-like syndromes.

An embolism from an atrial myxoma or cholesterol emboli from an atheroma are examples of embolic diseases that can mimic vasculitis.

Thrombotic disorders such as antiphospholipid syndrome, thrombotic thrombocytopenic purpura and sickle cell disease can cause thrombosis and thus mimic vasculitis. Amyloid angiopathy and fibromuscular dysplasia are non-inflammatory vessel wall disorders causing ischaemic organ damage. Some conditions like end-stage renal failure and hyperparathyroidism can be associated with a livedo reticularis-like rash which can be mistaken as a sign of vasculitis.

Drugs can induce vasoconstriction and ischaemia. These include ergots, cocaine and phenylpropanolamine. Some drugs can cause coagulopathy and in this way mimic the vasculitis e.g. Warfarin.

Malignancy will often have B-symptoms and basic laboratory findings such as normocytic normochromic anaemia, lymphocytosis, thrombocytosis, elevated ESR and raised CRP. Radiological findings of multi nodular lung shadows due to metastasis can suggest GPA.

Consider secondary vasculitis

Secondary vasculitis includes the same diagnostic headings as the mimics, but in addition, several of the connective tissue diseases need to be considered.

- Infections
- Drugs
- Malignancy
- Connective tissue diseases

Consider infections which cause secondary vasculitis

Infections

Many infections can result in secondary vasculitis; the majority are viral.

Hepatitis B and C, Parvovirus B19, Human immunodeficiency virus (HIV), Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) are examples of viral conditions which are known to cause secondary vasculitis. Hepatitis C has a special association to secondary vasculitis. Cryoglobulins can be found in many of the primary or secondary vasculitis.

Infections with *Salmonella*, *Streptococcus pneumoniae*, *Clostridium septicum*, *Chlamydia pneumoniae* and *Mycobacterium tuberculosis* can also result in vasculitis. Even parasites (e.g. *Ascaris*) and fungi (e.g. *Aspergillus*) have been associated with secondary vasculitis.

Many clues suggest the hypotheses that infections may be the cause of true primary vasculitis, but we will leave this discussion to the modules on vasculitis.

Drugs

Drugs from almost every pharmacological class have been mentioned as the cause of secondary vasculitis. Some have been shown in large clinical trials; others just in case reports. Hydralazine, propylthiouracil, minocycline and related agents are well described ANCA-associated drugs, while leukotriene inhibitors, sulfasalazine, D-penicillamine, ciprofloxacin, phenytoin, clozapine, allopurinol and several others are suspected of causing secondary vasculitis without ANCA association. Intoxication (drug abuse) with cocaine, morphine and others can also result in secondary vasculitis.

The clinical presentations are highly variable, from small vessel hypersensitivity vasculitis and leukocytoclastic vasculitis to conditions resembling granulomatosis with polyangiitis (GPA), polyarteritis nodosa (PAN) and eosinophilic granulomatosis with polyangiitis (eGPA). However, cutaneous manifestations, such as palpable purpura and maculopapular rash, are the most common manifestations of drug induced vasculitis. The lesions more frequently affect the lower part of the legs and are almost always synchronous with respect to the time of onset and rate of progression, as opposed to primary vasculitis where lesions occur at different times and progress independently.

Musculoskeletal symptoms are common and involvement of the kidneys, liver, CNS and other organs can occur.

Diagnosing a drug induced vasculitis might be very difficult. A comprehensive drug history should be obtained for all patients with vasculitic manifestations.

Malignant diseases such as solid tumours, myeloproliferative and lymphoproliferative disorders can be associated with secondary vasculitis.

Connective tissue diseases, especially rheumatoid arthritis (RA), SLE and primary Sjögren's syndrome are known to cause secondary vasculitis. An important clue is that the vasculitis usually appears late in the disease, which makes the diagnosis easier.

Inflammatory bowel diseases can also originate secondary vasculitis.

Confirming the diagnosis of vasculitis and assessing the extent of the disease

We have now discussed different diseases that mimic vasculitis or result in a secondary vasculitis looking at many similarities, but how do we exclude the mimics and secondary vasculitis from the primary vasculitis? And how do we separate isolated cutaneous manifestations from multisystem involvement?

Let us revert to our initial case:

A 45-year-old Caucasian male with a 3-week history of B-symptoms and a non-itching rash on the lower part of the legs looking like a leukocytoclastic vasculitis. He has possible involvement of his kidney and CRP is raised at 85 mg/l.

How will you continue the assessment of this patient?

The secret to the diagnosis is to systematically ask and look for symptoms or signs of the skin, muscle, nervous system or vital organ impairment pointing to local ischemia, arterial and venous thrombosis, arterial hypertension, bloody nose discharge, sight loss, mononeuropathy, pulmonary infiltration. Be aware that what might look like an isolated cutaneous vasculitis can be complicated by life threatening internal organ involvement and the need for immediate aggressive systemic treatment.

In the early stage of vasculitis, the diagnosis is especially difficult while late manifestations are often more specific.

Our patient could have a mimic of vasculitis, secondary vasculitis as well as primary vasculitis. In order to get closer to the diagnosis, you first have to exclude mimics and secondary vasculitis:

- Expand the history taken
 - Travel history
 - Drug history
- Full clinical examination
- Urine protein: creatinine ratio and urine microscopy

- Chest x-ray
- Basic blood screening (complete blood cell count, liver enzymes, CRP, ESR, creatinine)
- Electrocardiogram

Laboratory testing is only occasionally helpful in classifying vasculitis, but it is most important in excluding other diseases and determining organ involvement. Here you have to have all the former conditions in mind and undertake laboratory testing based on the history and clinical examination.

You may consider:

- Blood cultures
- Hepatitis B and C screening, CMV and Parvovirus B19
- HIV test
- Relevant testing for bacteria, fungi or parasites
- Serological tests
 - ANA, anti-double stranded DNA, rheumatoid factor, glomerular basement membrane antibody, creatine phosphokinase, complement factors (C3, C4)
 - ANCA (PR3/MPO)
 - Antiphospholipid antibodies
 - Lupus anticoagulant
 - Cryoglobulins
- Echocardiogram

Consider which basic tests you will need to explore organ involvement in vasculitis?

A detailed history and physical examination together with a chest x-ray, urine examination for protein and microscopy and basic laboratory tests will, for most patients without primary vasculitis, be sufficient to exclude systemic involvement.

Consider how you can confirm the diagnosis of primary vasculitis, once you have excluded mimics and secondary vasculitis

Confirming the diagnosis of primary vasculitis

The diagnosis of vasculitis is based on a combination of clinical, serologic, histological and angiographic parameters.

Histological confirmation of vasculitis should be sought in most cases by undertaking a tissue biopsy. The site of biopsy is guided by clinical manifestations and by the likelihood of the results affecting treatment decisions. If there is an indication of kidney involvement (proteinuria), kidney biopsy will be preferred. Other favoured sites are skin, temporal artery, muscle, nasal mucosa, lung, sural nerve and testis. Although pathological proof of vasculitis should be looked for, it is not mandatory for the final diagnosis. In the context of a clinical picture suggestive of GCA, a negative temporal artery biopsy does not rule out GCA. Likewise, a full blown picture of ANCA associated vasculitis does not necessarily require pathological confirmation.

In patients with large or medium vessel vasculitis there is commonly great difficulties verifying the biopsy and an angiography, computed tomography angiography (CTA), magnetic resonance angiography (MRA) or even positron emission tomography scan (PET scan) should be considered. For example, gastrointestinal tract vasculitis or renal artery involvement may show in anCTA. CTA can reveal characteristic images, such as multiple microaneurysms in patients with polyarteritis nodosa (PAN). MRA of the thoracic aorta may show stenosis, occlusion or aneurysm formation in patients with large vessel vasculitis such as Takayasu's arteritis.

Which specific type of vasculitis is this?

A in depth approach to this question is better served by the modules on vasculitis. Here, we will just give a short introduction.

Knowledge of the aetiology and pathogenesis of vasculitis is still limited. The group is very heterogeneous and there is considerable clinical overlap in their manifestations. Several attempts to classify have been tried. One of the most accepted is the Chapel Hill classification from 2012. It builds on microscopic findings, but also considers the size of vessels involved, and immunological markers (e.g. ANCA in GPA) and immunohistological findings (e.g. IgA-dominant immune deposit in Henoch-Schönlein purpura). Many other manifestations help with diagnosing the type of vasculitis such as demographic associations, clinical features and histological findings (Table 3).

Table 3. Clinical symptoms, demographic associations and size of vessels involved

Clinical symptoms	Age	Sex ratio (M:F)	Ethnic origin	Type of vasculitis	Vessel size
Arm or leg claudication, decreased pulses, subclavian/aortic bruit	15-40	1:9	Asian > others	Takayasu's arteritis	Large
Headache, jaw claudication, shoulder girdle/hip pain, diplopia	>50	1:3	Caucasian >> others	Giant cell arteritis	Large
Weight loss, livedo reticularis, mono/poly neuropathy, hypertension	40-60	2:1	Any	Polyarteritis nodosa	Medium
Fever, conjunctivitis, cervical lymphadenopathy, mucositis, polymorphous exanthema	1-5	1.5:1	Asian > white > others	Kawasaki's disease	Medium
Sinusitis, oral ulcers, otitis media, haemoptysis, active urinary sediment	30-50	1:1	Any	GPA	Small
Asthma, atopic history, mono/poly neuropathy, pulmonary infiltrates, eosinophilia	40-60	2:1	Any	eGPA	Small
Palpable purpura, abdominal pain, bloody diarrhoea	5-20	1:1	Any	Henoch-Schönlein purpura	Small
Oral and genital ulcers, folliculitis, uveitis, thrombophlebitis	20-35	1:1	Middle Eastern > others	Behçet's syndrome	Small
Palpable purpura, maculopapular rash	30-50	1:1	Any	Leukocytoclastic vasculitis	Small

GPA Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis); eGPA Eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome)

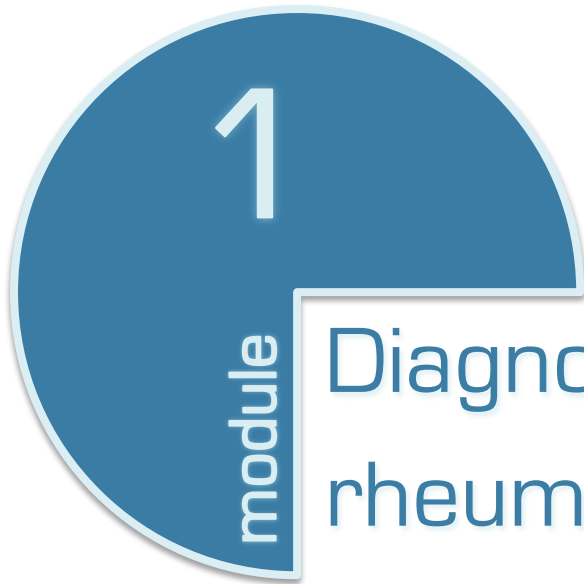
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EULAR on-line course on Rheumatic Diseases

Diagnostic strategies in rheumatology

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IN-DEPTH DISCUSSION II

Idiopathic inflammatory myopathy (IIM)

Clinical case:

The patient, a 56-year old female, is a married bank accountant. She is a non-smoker and reports of no previous health problems.

Her history is:

“During the last three months it has become increasingly difficult to walk up the stairs to my apartment on the 3rd floor. I have increasing problems combing my hair and occasionally I have found it difficult to swallow certain types of food, particularly larger chunks of meat and a dry bread. I have noticed some sort of rash on my elbows and knees and when I go for a walk I oft get a feeling of breathlessness.”

Clinical examination:

A middle aged woman, normal weight. No obvious muscular atrophy. She has a violet erythema and papules on the dorsal side of metacarpal and interphalangeal joints and skin changes on the extensor side of the elbows and knees joint that resemble psoriasis plaque. Her hands are marked by dryness and scaling and hyperkeratosis most apparent of the thumbs and rash and dryness on the eyelids.

Her blood pressure is 132/84 mmHg, temperature 37.0°C. Lung auscultation reveals low sounding crackles over the basal parts. Muscle strength evaluation is abnormal. She has problems elevating her arms over head and has problems rising from sitting position. Her finger grip strength is normal.

Blood tests:

Hgb 10.8 g/dL, creatinine 65, albumin 37, ASAT 450, creatinine kinase 3,500, ESR 69 mm/h, C-reactive protein 12 mg/L.

Try to formulate a one-sentence representation defining the case in abstract terms.

56-year female who, over the last three months has developed progressive and symmetrical weakness in proximal muscle groups, respiratory symptoms and findings, and skin abnormalities consisting of Gottron's sign and papules, heliotrope rash and mechanic hands.

DIAGNOSTIC APPROACH

Step one: Is the diagnosis of idiopathic inflammatory myositis suspected?

Do the clinical symptoms, signs correlate to the diagnosis of idiopathic inflammatory myositis (IIM)?

In table 1 symptoms and signs of myositis are reviewed. Confer to the clinical case.

Table 1. Symptoms and signs of myositis

- **Reduced muscle strength**

- proximal, distal or both?
- symmetric or asymmetric?
- Time of involvement?
- Muscle atrophy?

- **Dysphagia**

Problems initiating swallowing and/or aspirations.

- **Skin involvement**

- Gottron's changes, shawl sign, heliotrope rash, mechanical hands, periungual erythema, erythroderma?
- Calcinosis cutis?

- **Other extra muscular involvement**

- From joints: arthritis?
- From lungs: interstitial lung disease?
- From the heart: myocardial affection?

Which investigations would you do
1) to confer the diagnosis of myositis, 2) to classify the myositis
3) and chart the severity of the myositis

In table 2 the most common investigations are reviewed.

Table 2. Investigations in myositis

- **Blood tests:**
 - **Haematological status, inflammation markers (ESR and CRP)**
 - **Markers of muscle damage; increased levels of Creatinine kinase (CK) and myoglobin** are the most specific muscle markers. Levels of Lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and aldolase may also be increased, but less muscle specific.
 - **Serologic tests** including antinuclear antibodies (ANA), antibodies against extractable nuclear antigens (anti-Ro/SSA, anti-La/SSB, anti-Sm and anti-RNP), and “myositis specific or associated” antibodies (e.g. anti-histidyl-t-RNA synthase (anti-Jo-1), anti-PL12, PL7, OJ, EJ in addition to anti-Mi-2, SAE, NXP-2, TIF1γ, anti-MDA5, anti-HMGCR and anti-SRP)
- **Electromyography (EMG)** is a diagnostic procedure to assess muscles and motor neurons.
- **Muscle imaging, most commonly by Magnetic Resonance Imaging (MRI)** Can be used to guide muscle biopsy site.
- **Standardized assessment of muscle function and strength by manual muscle tests** as a standardized tool of evaluation and follow-up.
- **Muscle biopsy to confirm the clinical diagnosis and to classify the muscle inflammation**
- **Assessment of swallowing function by dynamic X-ray, often supplemented with gastroscopy and/or manometry.**
- **Investigations of lungs** if there is a suspect of interstitial lung disease
 - **high resolution CT scan (HRCT)**
 - **Pulmonary function tests**
 - **Echocardiography and/or MRI of heart**
- **Other**
 - **Nailfold Capillaroscopy** is a non-invasive method to evaluate vascular dysfunction.

What would be the most likely diagnosis?

Table 3. The clinical spectrum of idiopathic inflammatory myopathy (IIM)

- Polymyositis (PM)
- Dermatomyositis (DM)
- Juvenile dermatomyositis (jDM)
- Necrotising myopathy
- Inclusion body myositis (IBM)
- Amyopathic/hypomyopathic dermatomyositis
- Myositis in overlap syndromes
- Paraneoplastic myopathy

The clinical spectrum of idiopathic inflammatory myositis is listed (table 3).

Patients with polymyositis (PM), dermatomyositis (DM) and necrotising myopathy will typically develop symmetrical and proximal muscle weakness over a period of weeks to few months. Patients with inclusion body myositis (IBM) are typically older than the PM/DM patients (mean age at onset 65-70 years) and will often have a slow progressive weakness that may be asymmetric at least initially and affects both proximal and distal muscle groups. In addition, their creatinine kinase (CK) values are usually lower than the values in patients with PM, DM or necrotising myopathy.

Proximal oesophageal affection does not clinically distinguish between the IIMs. By performing dynamic x-ray barium swallow study patients with IBM, in contrast to patients with the other IIMs, often have cricopharyngeal dysfunction or spasm. In select cases this cricopharyngeal muscle dysfunction can be treated with selective myotomy, oesophageal dilatation and/or Botox injections.

Dermatological manifestations of dermatomyositis can in some cases be mixed with psoriasis, but skin biopsy could separate. Our patient had skin changes typical for dermatomyositis. The combination of prototypical skin changes, progressive symmetric proximal muscle weakness and high CK is highly suspect of DM.

DIAGNOSTIC APPROACH

Step two: The diagnostic strategy

Having considered the possibility of idiopathic inflammatory myositis (IIM)

We suggest you try to answer the following questions in succession:

Is this a condition that could mimic the presentation of IIM?

How do I confirm the diagnosis IMM and what is the extent of the disease?

The case would probably have been more difficult to resolve if the skin changes were absent. There are several important differential diagnoses to consider in patients with muscle weakness and/or high muscle enzymes (table 4).

Most of the metabolic myopathies and muscle dystrophies are diagnosed at an early age, but in some cases, the clinical picture can evolve later in life. It is therefore important to retrieve information about relatives with muscle diseases.

A thorough review of current and earlier medication, alcohol use and illicit drug abuse is important. Screening for endocrine myopathy (by assessment of thyroid and adrenal hormone levels) and electrolyte disorders.

It is important to evaluate the patient for systemic autoimmune disease as mentioned (table 4).

Table 4. Disorders that mimics idiopathic inflammatory myositis (IIM)

- **Metabolic myopathies**
 - **Disorders of the glycogen metabolism**
 - McArdle's disease
 - Lysosomal acid maltase deficiency (GSD II)
 - Etc.
 - **Disorders of the lipid metabolism**
 - Carnitine deficiency syndromes: Primary systemic or muscle carnitine deficiencies and secondary carnitine deficiencies
 - Fatty acid transport disorders: Carnitine - palmitoyltransferase 1A deficiency / - acylcarnitine translocase deficiency / - palmitoyltransferase 2 deficiency
 - Myoadenylate deaminase (MADA) deficiency, a disorder of purine metabolism.
 - Lipin-1 deficiency
 - Multiple acyl-CoA dehydrogenase deficiency (MADD)
 - **Mitochondrial myopathies:** a dysfunction in the mitochondria that affect the aerobic metabolism.
- **Muscle dystrophies** is a group of several different muscle disorders that also can involve other organ

systems by abnormal genes that interfere with the production of muscle proteins.

- **Facioscapulohumeral muscular dystrophies (FSHD)**
 - **Becker and Duchenne muscular dystrophies (BMD and DMD)**
 - **Limb-girdle muscular dystrophy (LGMD)**
 - Calpainopathies by mutations in the calpain-3 gene.
 - Dysferlinopathies by mutations dysferlin gene
 - Sarcoglycanopathies
 - Laminopathies
 - Caveolinopathies are caused by mutations in the caveolin 3 gene
 - **Emery-Dreifuss muscular dystrophy (EDMD)**, also known as humeroperoneal muscular dystrophy
 - **Myotonic dystrophy type 1 (DM1) and type 2 (DM2)** are autosomal dominant, multisystem disorders.
- **Endocrine myopathies**
- Hypothyroid or hyperthyroid myopathies
 - Cushing syndrome or Addison's disease related myopathies
 - Myopathies associated with hyperaldosteronism.
 - Hyperparathyroid myopathies
 - Hyperaldosteronism
- **Electrolyte disorders:** Hypo-/hyperkalaemia, hypo-/hypercalcemia, hypo-/hypernatremia.
- **Drug induced myopathy** that either causes a direct myotoxicity or secondary immunologically mediated myopathy or both.
- Statin myopathy. Statins can cause both a toxic and an immunologically mediated myopathy with symptoms from myalgia, to myopathy, myositis and necrotising myopathy that can be associated with anti-HMG-CoA reductase antibodies.
 - Corticosteroid myopathy
 - Colchicine myopathy
 - Hydroxychloroquine/chloroquine myopathy with typical histological changes with myeloid and curvilinear bodies.
 - Zidovudine myopathy
 - Alcohol myopathy with both acute and chronic forms that are associated with longstanding alcoholism.
 - Cocaine myopathy can lead to massive and life-threatening rhabdomyolysis
 - Interferon alpha
 - D-penicillamine
 - Etc.
- **Neuromuscular diseases**
- *Anterior horn lesions* as seen in motor neuron diseases like amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA) and poliomyelitis.
 - *Secondary to peripheral nerve lesions* as in polyneuropathies or mononeuropathies /mononeuritis multiplex.
 - *Involvement of neuromuscular junction* as in myasthenia gravis or Lambert-Eaton syndrome.
- **Myopathy of systemic rheumatic disease**
- Autoimmune diseases – Systemic sclerosis (SSc) with myositis overlap. Mixed connective tissue disease (MCTD). Also primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE).
 - Vasculitis with muscle involvement as part of systemic vasculitis.

- Other systemic disease as – sarcoidosis
- **Infectious myositis**
 - **Pyomyositis** is a purulent infection of skeletal muscle.
 - **Myopathies associated with viral infections** can be caused by: HIV, Coxsackie virus, Epstein-Bar virus, Hepatitis B and C, Influenza A and B, Varicella zoster virus, Cytomegalovirus etc.
 - **Parasitic myopathies** can be caused by: toxoplasma gondii, Trypanosoma cruzi, Schistosoma, Microsporidia etc.
 - **Helminthic myopathies** can be caused by: e.g. Trichinella, Echinococcus.

Paraneoplastic myopathy

How do I confirm the diagnosis IMM and what is the extent of the disease?

The most widely used diagnostic criteria for DM and PM in clinical research is the Peter and Bohan criteria presented in 1975. There are five items in the criteria, each giving one point. Based on the total score, PM and DM is divided into; 'definite', 'probable' and 'possible' cases. The disadvantage of the Peter and Bohan criteria is that they may allow patients with diseases that mimic myositis to be classified as having an inflammatory myopathy. In addition, IBM may also be misclassified as polymyositis. The New European-American IIM classification criteria are in development, and are expected to be launched by the end of 2016.

The Peter and Bohan criteria antedated the discovery of myositis specific autoantibodies (MSA). This is a major drawback as the MSA have proven to be very valuable as diagnostic and prognostic tools in myositis. For example; necrotising myopathy is associated with the presence of anti-HMGCR and anti-SRP antibodies. The anti-synthetase antibodies (anti-Jo-1, PL12, PL7, OJ, EJ, HA, KS Zo) are associated with interstitial lung disease (ILD). Anti-MDA5 antibodies are rare and are associated with necrotizing dermatomyositis with severe ILD. Anti-Mi-2 antibodies are associated with DM. Anti-NXP-2 and anti-TIF1y antibodies are associated with cancer in adult patients (table 1 and further the chapter for inflammatory myositis).

Are there “red flags” or alarming aspects concerning our patient.

Name two aspects that would concern you regarding the patient.

1.

The major concern is that the patient has symptoms and findings suspect of myositis-associated interstitial lung disease (ILD).

High resolution CT thorax was performed and showed finding consistent with ILD. Pulmonary function test revealed restrictive lung disease with FVC 78%, FEV1 79% and DLCO 75% of expected values.

Serologic test showed a high titre of anti-histidyl-t-RNA synthase (anti-Jo-1) antibodies, consistent with anti-synthetase syndrome that can coincide with dermatomyositis.

Several studies have shown that ILD is a major determinant of mortality and morbidity in myositis.

#2

Adult-onset dermatomyositis carries an increased risk of malignancy, but this is not the case in juvenile onset dermatomyositis. Increased risk has been confirmed in several population-based studies, with standardized incidence ratios of cancer ranging from 2.0 to 6.0. The association between cancer and inflammatory myopathies has been extensively reported in dermatomyositis (DM), but in lesser degree in polymyositis (PM). Inclusion body myositis (IBM) have shown conflicting results regarding cancer risk. The patients are generally older and recent studies have not confirmed an increased risk of cancer compared with age matched background population. Amyopathic dermatomyositis is reported to have a similar risk as DM and necrotizing myopathy is reported to be associated with cancer.

In Western countries, common malignancies associated with DM include; ovarian, lung, pancreatic, gastric, and colorectal cancers, while among patients from Southeast Asia, DM is seen strongly associated with nasopharyngeal carcinoma. Cancer is most commonly recognized within 2 years of the diagnosis. The risk factors for underlying malignancy in myositis include; older age of onset, resistance to treatment, severe cutaneous involvement with ulcerations, leukocytoclastic vasculitis and severe and therapy resistant muscle disease. Paraneoplastic myopathy has been associated with anti-NXP-2 (anti-p140) and anti-TIF1γ (anti-p155, anti-p155/140) antibodies. Screening for underlying malignancy is mandatory in patients above the age of 40 with new diagnosis of inflammatory myositis. Currently, there is no consensus on how extensive such

screening work-up should be. A careful history, a complete physical examination, appropriate laboratory tests and age-appropriate cancer screening are indicated. Any abnormalities detected that may signal the presence of an occult cancer should be further

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2

module

EULAR on-line course on Rheumatic Diseases

Early arthritis: diagnosis and management

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LEARNING OUTCOMES

- ➔ Discuss the term early arthritis and its significance
- ➔ Describe and evaluate the measures used in the diagnosis of early arthritis (clinical, radiological and laboratory)
- ➔ Describe and discuss the prognostic factors in early arthritis
- ➔ Outline and evaluate the treatment modalities (pharmacological and non-pharmacological) available for the management of early arthritis
- ➔ Discuss the aims of treatment and the outcome measures used to evaluate treatment efficacy

1 Introduction

Rheumatoid arthritis (RA) is the most common and serious inflammatory arthritis. Untreated it results in joint destruction, functional impairment and increased mortality. The outcome of the disease, however, has improved considerably in recent years with early diagnosis, the availability of effective treatments and the recognition that early intensive treatment strategies result in better outcomes. Recently, the treat-to-target strategy study in recent-onset RA has been demonstrated that treatment targeted to low disease activity determines long-term outcomes after 10 years. Drug-free remission, prevention of functional deterioration and clinically relevant radiographic joint damage, and normalized survival, comparable with survival of the background general population, are realistic outcomes (Markusse et al, 2016).

In practice, patients with inflammatory arthritis should be seen and recognized early and treated at the earliest opportunity. Clinicians must differentiate the early features of RA (an inflammatory arthritis that has the potential to become progressive and destructive) from those arthritis that will remit spontaneously, and from diseases that may present with similar clinical features of arthritis - for example, systemic lupus erythematosus (SLE) and Sjögren's syndrome. Decision about the best therapeutic strategy and adapting the therapy to an individual patient are required. The goal of treatment is early suppression of inflammation and ideally, establishing remission as early as possible in order to prevent joint damage, disability and the long-term complications of the disease. The hope for the future is that interventions will be so timely, individual and effective that drug-free remission with resolution of symptoms of arthritis and normalized function status is achieved. Nowadays this outcome is increasingly achievable, indicating that RA-chronicity can be influenced (Ajeganova et al, 2016).

This chapter will provide some background and an approach to the diagnosis and treatment of early arthritis. Other reviews on the topic: Combe et al, 2009; Finckh, 2009; Raza and Filer, 2009*; Hoes et al, 2010; Klareskog et al, 2010*; Scott et al, 2010; Breedveld, 2011; de Vries et al, 2011; Dekkers et al, 2016.

2 Background

2.1 The rationale for early management

Although definitions vary, remission implies a state without damaging and disabling. Spontaneous remission without treatment is rare in RA (Wolfe and Hawley, 1985; Eberhardt and Fex, 1998). In most untreated patients, the disease persists and results in joint damage, functional decline and premature mortality. However, several studies have reported that drug (DMARD)-free sustained remission can be achieved in approximately 10-15% of the patients with early RA (Wolfe and Hawley, 1985; van der Woude et al, 2009; van der Woude et al, 2012).

The joint damage and loss of function in RA occur early in the disease process. Radiographic outcome studies have shown that 70% of patients with recent-onset RA develop bony erosions within the first 3 years (van der Heijde et al, 1995). Importantly, already within 3 months of disease onset, 25% of patients have erosions evident on X-ray examination (Nell et al, 2004). More sensitive imaging techniques such as magnetic resonance imaging (MRI) and musculoskeletal ultrasonography (MSUS) have confirmed evidence of damage within weeks of onset of symptoms (McGonagle et al, 1999; Wakefield et al, 2000). The MSUS detects at least 1.4-fold more patients with erosions than X-ray examinations (Funck-Brentano et al, 2009), and the prevalence of bone erosions detected by MSUS is reported in as many as 60% of early RA-patients (Tămas et al, 2014).

The presence of early radiographic erosions predicts the future progress of joint damage. The bone erosions seen on MSUS are correlated with later development of X-ray erosions (McQueen et al, 2001), and baseline and early changes in MRI measures predict later X-ray and MRI progression (Baker et al, 2014). Of note, persistent MRI bone marrow oedema, but not persistent MRI synovitis, is strongly associated with erosive progression, independently of local synovitis (Nieuwenhuis et al, 2016).

However, the role of MSUS and MRI imaging techniques in diagnosis of early arthritis, assessment of disease activity and therapy choice in clinical practice is so far unclear. Thus, adding information on the presence of MRI detected bone marrow oedema and erosions increases sensitivity but considerably decreases specificity of 2010 EULAR/ACR criteria for RA, and does not improve the accuracy and discriminative ability of the criteria (Nieuwenhuis et al, 2015). MSUS-guided assessment of disease activity on the top of clinical examination did not result in better clinical and MRI outcomes than DAS-guided assessment, though MSUS-driven therapy led to more intensive treatment (Dale et al, 2016).

Several studies have shown that a delay in treatment commencement is associated with poorer outcomes. In a meta-analysis of 12 studies in patients with RA and symptom duration of <2 years, an average 9-month delay with starting disease-modifying antirheumatic drugs (DMARDs) significantly increased subsequent radiographic progression (Finckh et al, 2006). In an early arthritis cohort, the first assessment by a rheumatologist of patients with symptom duration ≥ 12 weeks was associated with a 1.3-times higher rate of joint destruction over 6 years and a hazard ratio of 1.87 for not achieving DMARD-free remission, as compared with assessment in <12 weeks after symptom onset (van der Linden et al, 2010). A recent meta-analysis of 18 cohort studies and randomised controlled trials has confirmed that that prolonged symptom duration is associated with radiographic progression and a lower chance for DMARD-free sustained remission (van Nies et al, 2014). Although we have learned last years about the importance of early initiating of DMARDs, the referral of the persons with suspected inflammatory arthritis should be also early. The assessment by a rheumatologist is however delayed by about 18 weeks in patients having RA or spondyloarthritis, and only 31% of the RA patients are assessed in <12 weeks of symptom onset (van der Linden et al, 2010).

As most patients with RA will have persistent disease, as joint damage occurs early and as it is expected that therapy delay results in worse outcomes, RA should be diagnosed and treated early. The question remains 'how early is early'?

2.2 Window of opportunity

The crucial therapeutic goal is to delay and prevent, where possible, progression of undifferentiated arthritis or very early RA. The concept of a 'window-of-opportunity' suggests that there is a limited period early in the course of the disease when the disease process can be altered or maybe even reversed with a complete return to normality. The start of treatment with DMARDs during this period may have a much greater effect in halting disease progression and make a real difference in the outcome of the patient than treatment at a later stage (Cush, 2007). It is expected that implementation of the new EULAR/ACR criteria for RA diagnosis can help to identify early RA patients and thence to start therapy as soon as possible in order to reach remission and prevent damage.

The cut offs between 'early' and 'established' RA have progressively decreased over the past decades. Previously, the cut-off <5 years after symptom onset was used to define an early disease. By the 1990s, symptom duration of <12–24 months was considered early. This duration was chosen because by 2 years up to 70% of patients treated conventionally may have erosive disease. Currently, 'early RA' is defined as disease duration less than 1 year. It is suggested that very early RA - that is, within the first 12 weeks of symptom onset - may present an immunopathologically distinct disease phase compared with later RA-disease (Raza et al, 2005). Thus, the early RA period is divided into 'very early RA' with disease duration < 3 months and 'late early RA' with the duration of symptoms from 3 to 12 months.

The treatment studies have evaluated the concept of very early window of opportunity. A non-blinded study of a single dose of glucocorticoid in 63 patients with mild early inflammatory arthritis of median duration of 20 weeks found that the strongest predictor of disease remission at 6 months was a symptom duration of <12 weeks at the time of treatment (Green et al, 1999). Clinical and radiographic outcomes were significantly better in 20 patients with RA who started DMARDs 3 months after disease onset (very early) compared with 20 patients who started therapy after a median of 12 months' (early) (Nell et al, 2004). In this study, a significant difference in the DAS28 improvement in favour of the very early treatment group was evident already after 3 months of DMARD therapy, and remission was achieved in 50% in the very early group compared with only 15% in the early group. The importance of early treatment has been also demonstrated in the randomized controlled trial of 417 patients with early RA treated with methotrexate (MTX) +/- etanercept. In this study, the patients with symptom duration of <4 months achieved significantly better disease control with a 40% increase rate of remission, lower disease activity scores and more likely did not have radiographic progression compared to the patients who started treatment >4 months to 2 years (Emery et al, 2012). A recent analysis in

two cohorts which included 1271 early RA patients followed for 5 years has convincingly shown that the shape of the associations between symptom duration at treatment initiation and persistence of RA defined as drug-free remission is not linear, suggesting the presence of a confined period in which RA is more susceptible to treatment, and this favourable period was discriminated at 15-20 weeks of symptom duration (van Nies et al, 2015).

Inflammatory arthritis may begin much earlier than it is now could be detected. It is proposed that the development of RA includes several distinct phases, which might or might not occur as a disease continuum, from pre-clinical asymptomatic to clinically evident phase of undifferentiated arthritis (UA) and RA. The auto-antigens triggered by innate, environment, lifestyle and stochastic stimuli can lead to formation of non-matured autoantibodies. In the genetically susceptible persons, in the phase just before arthritis development, the autoantibody response matures as reflected by increasing titers and extensive isotypes and affinity spreading (Hensvold et al, 2015; Dekkers et al, 2016). It is not known whether persons during this phase already experience arthralgia.

Several serological abnormalities have been shown to present years before the onset of clinical arthritis, such as presence of rheumatoid factor (RF) and antibodies to citrullinated peptide (ACPA) (Rantapää-Dahlqvist et al, 2003) and raised levels of high sensitivity C-reactive protein (CRP) (Nielen et al, 2004). Structural changes have been detected by MSUS and arthroscopy in joints without clinical synovitis in patients with early RA (Conaghan et al, 2004). A study in 150 patients with clinically suspect (inflammatory) arthralgia followed for ≥ 6 months have demonstrated that age, localization of initial symptoms in small and large joints (compared with small joints only), C-reactive protein level, ACPA-positivity and subclinical MRI inflammation associates with further development of clinical arthritis. ACPA-positivity and MRI inflammation were most strongly associated with arthritis development (hazard ratios of about 5 to 6). In this study, subclinical MRI inflammation preceded clinical arthritis with a few months, and only 6% of persons developed RA in absence of MRI inflammation (van Steenbergen et al, 2015).

2.3 The challenges of early disease

The first few weeks or months of symptoms, therefore, represent an important therapeutic window in patients with very early synovitis who will develop RA. However, treating patients within this phase presents several challenges:

1. Assessing patients with inflammatory arthritis early;
2. Predicting which patients with early synovitis will develop RA and thus require treatment;
3. Determining how such patients should be treated.

As there is no single diagnostic test, a combination of clinical features and laboratory tests is used to make the diagnosis of RA. The 1987 American College of Rheumatology (ACR) classification criteria had previously been used to define RA. However, as these criteria were developed in patient populations with longstanding definite disease, they do not perform well for the diagnosis of recent-onset RA. In a systematic review of literature published between 1988 and 2006, the 1987 ACR criteria when applied in early RA have sensitivity ranging from 40 to 90% and specificity from 50 to 90% (Banal et al, 2009). The 1987 ACR criteria have poor sensitivity in early RA disease i.e. patients with RA may not fulfil these criteria. Because of relatively low specificity, other arthritis such as post-viral arthropathies and spondyloarthropathies may satisfy the ACR criteria.

The poor performance of 1987 criteria in early RA coincided with a shift in the focus in RA from 'established' to 'early disease', growing evidence that time to treat is a key driver of outcomes, the advent of ACPA test and an explosion of targeted biologic therapies. A collaborative initiative between ACR and EULAR to define RA at an early stage led to the development of new classification criteria for RA (Aletaha et al, 2010*). The emphasis of the 2010 ACR/EULAR RA classification criteria is on identifying patients with a short duration of symptoms and poor prognosis who will benefit from early diagnosis and early initiation of DMARD therapy. These criteria were meant to be applied to patients newly presenting with undifferentiated inflammatory synovitis and incorporate factors that best discriminate between those patients who are and those who are not at high risk for persistent and/or erosive disease. The criteria were satisfied in 87-97% of the patients where physicians initiated methotrexate (not meant to be used for diagnostic purposes).

According to the new 2010 ACR/EULAR criteria, classification as 'definite RA' is based on the clinical evidence of synovitis (i.e. swelling) in at least one joint and absence of an alternative diagnosis better explaining the synovitis (for example, SLE, psoriatic arthritis and gout). Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. The distal interphalangeal joints, the first metatarsophalangeal joint, and the first carpometacarpal joint are excluded as these joints are typically involved in osteoarthritis. Synovitis should not be better explained by another diagnosis - for example, SLE, psoriatic arthritis and gout. Classification as 'definite RA' is then based on achieving a total score of ≥ 6 out of possible 10 from individual scores in four domains (table 1): (A) number and site of involved joints (score range 0–5); (B) serological abnormality (range 0–3); (C) raised acute phase response (range 0–1) and (D) symptom duration (range 0–1) (table 1). These criteria do not include features typical of late RA-disease, i.e. symmetry, rheumatoid nodules and radiographic changes. There is no longer requirement of >6 weeks of symptom duration. The criterion of morning stiffness has been omitted and the serologic marker of ACPA is included. Patients with typical history of long-standing RA-disease, including those whose disease is inactive, patients with erosive disease with RA-type erosions on X-ray can be classified as RA even if they do not fulfil the criteria.

Table 1 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA)

A. Joint involvement	
1 Large joint	0
2–10 Large joints	1
1–3 Small joints (with or without involvement of large joints)	2
4–10 Small joints (with or without involvement of large joints)	3
>10 Joints (at least one small joint)	5
B. Serology (at least one test result is needed for classification)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
C. Acute phase reactants (at least one test result is needed for classification)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1
D. Duration of symptoms	
<6 Weeks	0
≥6 Weeks	1

Score-based algorithm: add score of categories A–D. A score of $\geq 6/10$ is needed for a definite classification of 'definite RA'.

High positive RF or ACPA is defined as >3 times upper limit of normal (ULN).

ACPA, antibodies to citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

In an internationally 'Stop-Arthritis-Very-Early' trial with ≤ 16 weeks of symptom duration, which included patients with a variety of diseases diagnosed during follow-up, has been shown that the predictive and discriminative abilities of the 2010 ACR/EULAR classification criteria were satisfactory and substantially better than that of the 'old' 1987 ACR criteria (Biliavska et al, 2013). The performance of the 2010 ACR/EULAR classification criteria has been tested in patients with early arthritis ≤ 12 months in the Rotterdam Early Arthritis Cohort (REAC) (Alves et al, 2011). In this study using the cut-point of 6 to start treatment 30% of persistent patients would not be treated, whereas 30% of the non-persistent patients would have been treated. Similar results have been reported in others studies (de Hair et al, 2012). Over diagnosis is of concern with the new RA criteria, and more patients whose disease eventually resolved without requiring DMARD are classified at baseline as RA according to the 2010 criteria than with the 1987 criteria, 8% vs 2% (Cader et al, 2011).

As rheumatologists see patients earlier in the course of disease, it has also become clear that a proportion of patients who present with an inflammatory arthritis may have an UA—a form of arthritis that does not fulfil classification criteria for a more definitive diagnosis. The outcome of these patients varies and the diagnosis may change in the first years of follow-up. Some patients will progress to RA, some to other rheumatic diseases, and some patients will continue to have undifferentiated disease or enter into remission (figure 1).

Estimates from the Leiden early arthritis clinic suggest that of all patients presenting with UA, 30% will remit, 30% will develop RA (based on the 1987 ACR criteria) and up to 20% remain undifferentiated (Verpoort et al, 2004).

Figure 1 Natural history of inflammatory arthritis



The key problem facing clinicians seeing patients with UA or early arthritis, therefore, is differentiating patients with self-limiting disease from those at risk of developing persistent inflammatory and erosive arthritis. This differentiation allows: 1) start of appropriate treatment for patients whose arthritic disease would progress and 2) avoidance of unnecessary treatment for those whose disease would resolve.

3 An approach to early arthritis

The following principles guide management strategies:

- Early recognition and treatment of patients with arthritis results in better long-term clinical outcomes.
- Regular monitoring of disease activity and treating to target (Smolen et al, 2010*), aiming for remission, improves outcomes.

The following steps have been suggested as an approach to the evaluation and treatment of patients with early arthritis (Combe et al, 2007*):

- Recognise the presence of inflammatory arthritis.
- Exclude diseases other than RA or UA that present as an early inflammatory arthritis (eg, SLE, psoriatic arthritis or other spondyloarthropathies).
- Estimate the risk of developing persistent or erosive irreversible arthritis in patients with RA or UA using a combination of clinical features, laboratory tests and imaging techniques.
- Institute treatment and monitor disease activity, escalating treatment as required in order to achieve a favourable outcome.

Although the golden standard is the determination whether arthritis i.e. synovitis is clinically present, it is now recognized that clinically suspect arthralgia (CSA) may constitute a pre-clinical phase of RA and is the earliest moment to clinically recognize arthralgia of the small joints that may progress to RA over time according to the clinical judgement of the rheumatologists (van Steenberg et al, 2015). In this study, out of 1558 patients with arthralgia presented to the rheumatology outpatient clinic, 102 patients had CSA (6.5%) according to the judgment of the treating rheumatologist at the first visit before any laboratory results were known. The main reason provided by the rheumatologists to consider the arthralgia as clinically suspect were joint pain that was worst in the early morning and improved with movement during the day, the presence of morning stiffness for ≥ 60 min, and a positive family history for RA. Subclinical inflammation as measured by MRI (present in 44% of patients with CSA), autoantibodies and elevated CRP were predictive factors (see above 2.2) for development of arthritis.

Clinical evaluation remains the cornerstone for evaluating early arthritis: determining whether arthritis is present or not, differentiating between inflammatory or non-inflammatory disease and determining the aetiology of the arthropathy. Articular symptoms may be the presenting manifestation of many infectious, inflammatory or malignant conditions. The clinical features may also provide clues to identifying those at risk of developing persistent erosive disease (table 1).

A thorough history should be documented, detailing the distribution of the symptomatic joints, duration of symptoms and early morning stiffness (EMS), response to non-steroidal anti-inflammatory drugs (NSAIDs), any prodromal illness and associated symptoms. Family history is important for RA, psoriasis and other autoimmune diseases. Personal and past medical histories, including smoking history, should also be noted. A comprehensive examination of all systems should be performed.

Laboratory investigations and imaging are ancillary measures for the diagnosis and prognosis of patients presenting with early arthritis. It is important, to be aware of their limitations when interpreting the results (eg, avoid false reassurance that disease is absent when test results are normal). Imaging techniques are potentially helpful in this setting.

4 Identification of inflammatory joint disease

The clinical finding of joint swelling not caused by trauma or bony swelling should suggest a diagnosis of early arthritis, especially if at least two joints are affected and/or EMS lasts for ≥ 30 min. Hand or foot involvement is common in inflammatory arthropathies and is suggested by a positive metacarpophalangeal (MCP) (figure 2) or metatarsophalangeal 'squeeze test'. Early referral recommendations for newly diagnosed RA have been derived from prospective clinical investigations of prognostic factors, early arthritis cohorts and the consensus of the expert panel: ≥ 3 swollen joints, metatarsophalangeal/metacarpophalangeal involvement, and morning stiffness of ≥ 30 minutes (Emery et al, 2002). Of note, all symptoms and findings together should be taken into

account as there is no single test to identify early RA. Thus, a recent study has documented that a positive squeeze test is associated with local joint inflammation but the sensitivity of the test is low, indicating a high percentage of swollen joints with a negative squeeze test. When the squeeze test is used on its own, it is insufficient to detect early arthritis (van den Bosch et al, 2015). The diagnostic value of morning stiffness has been newly investigated in 5,202 arthralgia and arthritis patients. It has been shown that morning stiffness ≥ 60 min in arthralgia and early arthritis patients is associated with arthritis and RA respectively, which supports incorporation of morning stiffness in the diagnostic process (van Nies et al, 2015).

Figure 2 Metacarpophalangeal squeeze test: lateral compression of the forefoot



All new patients with symptoms of an inflammatory arthritis should be referred to a rheumatologist during the early phase of the disease, ideally within 6 weeks of symptom onset (Hyrich, 2008). As a proportion of patients who will develop severe persistent inflammatory arthritis have normal/negative examination results at symptom onset, they should be referred to the rheumatologist regardless of blood test results or radiographic findings. If tests are done in primary care, referral should not be delayed while waiting for results.

5 Identification of a definitive cause of an inflammatory arthropathy

5.1 Clinical features

While joint symptoms predominate early in RA, extra-articular manifestations of RA (nodules, keratoconjunctivitis sicca, etc.) are seldom present early in the disease. In other forms of polyarthritis, extra-articular manifestations may be present early and may precede the onset of synovitis, providing clinical clues to the diagnosis. This is particularly true for SLE (malar rash (figure 3), serositis), reactive arthritis (urethritis, conjunctivitis), psoriatic arthritis (psoriasis (figure 4), nail pitting or other nail changes) and sarcoidosis (lung involvement, fever) (Dao and Cush, 2006) (table 2).

Figure 3 Malar rash in a patient with systemic lupus erythematosus.



Figure 4 Psoriatic plaques.



Table 2 Differentiating diseases that present as an early arthritis

Arthritis	Personal history	Typical pattern of joint involvement	Joints affected	Associated features	Laboratory tests
UA (non-progressive)	F > M	Insidious, oligoarthritis	PIP, MCP, wrist, MTP, knee, ankle		↑CRP/ESR, may be normal
Rheumatoid arthritis	F > M; At any age, peak 30–55years	Insidious, progressive, symmetrical	PIP, MCP, wrist, MTP, knee, ankle	Early morning stiffness	↑CRP/ESR, may be normal RF+, CCP+
Spondyloarthropathy	Psoriasis, Urethritis or cervicitis, IBD. Family history of psoriasis or IBD	Persistent, asymmetrical, oligoarticular	DIP, PIP, knee, feet, spine	Psoriasis, nail pitting, uveitis, enthesitis, dactylitis	ESR/CRP may be normal More severe course in HLA-B27+
Systemic lupus erythematosus	F > M, young	Polyarticular, symmetrical, tend to be migratory, usually non-erosive	PIP, knee	Rash, serositis	Anaemia, ↑ESR CRP usually normal proteinuria, ANA+, dsDNA+
Dermatomyositis	F > M peak 40-60 years	Symmetrical non-deforming non-erosive	MCP, PIP, wrist, ankles	Proximal muscle weakness, dysphonia/dysphagia 'Mechanic's hands', erythema, eruptions, pruritus Pulmonary involvement	Muscle enzymes elevated Jo-1, myositis-specific autoantibodies Electromyography
Scleroderma	F > M	Acute or occasionally insidious, symmetrical or asymmetrical	MCP, PIP Tendon friction rubs (diffuse disease)	Hardening and tightening of the skin Raynaud	CRP/ESR may be normal ANA+, Scl70+, ACA+
Sjögren's syndrome	F > M		Intermittent symmetrical non-erosive polyarthritis of mainly small joints Recurrent monoarthritis or oligoarthritis	Dry mouth and eyes, fatigue Systemic manifestations Rheumatoid arthritis	ANA+ SSA+ SSB+ RF+ in 50-80% Hypergamma-globulinaemia

			Usually mild synovitis		
Polymyalgia rheumatica (PMR)	F ≥ M Caucasian >50 years, mostly >60 years		Hip and shoulder girdle PIP, wrist, knee occasionally	Widespread myalgia, fatigue, fever Prolonged morning stiffness	Anaemia, ↑ ESR/CRP Seronegative
RS3PE	M > F >50 years, peak >70 years	Acute	Acute bilateral pitting oedema of the back of the hands and/or feet Symmetrical polyarthritis, synovitis, tenosynovitis	No underlying systemic disease	CRP/ESR elevated RF negative HLA-B27 may be positive Can be paraneoplastic
Rubella	Rubella epidemic and no previous vaccination Recent (2–3 weeks) rubella vaccination	Acute oligoarthritis or polyarthritis, symmetrical	PIP, MCP, wrists, knee	Rash, lymphadenopathy, fever	Rubella serology (IgM) Virus isolation from nasopharynx or joint tissue
Parvovirus B19	F > M often a contact with a small child with Viral Infection	Acute	Symmetrical self-limiting predominantly MTP, PIP	Rash, malaise, ev myocarditis, myositis, hepatitis	Serology for Parvovirus PCR B19 DNA
Epstein-Barr virus			Monoarthritis knee polyarthralgia		Serology for EBV
Alpha viruses: Chikungunya virus CHIKV (sporadic epidemics globally), Ross River virus (Australia) Barmah Forest virus (Australia) O'nyong nyong virus Mayaro virus Sindbis virus Karelian fever (West Russia) Ockelbo virus (Sweden)	Mosquito-borne RNA viruses in endemic areas (Asia and Africa) Travel to endemic areas	Acute polyarthritis	Feet, ankle, fingers, wrists	Rash, fever, tendinitis and periarticular involvement	Serology for alpha viruses

Pogosta virus (Finland)					
Hepatitis viruses (HBV, HCV)	Hepatitis risk factors	Acute polyarthritis	Oligo- or polyarthritis PIP, MCP, wrist, knee, ankles	Fever Jaundice	↑ESR/CRP, ↑LFTs Hepatitis B and C serology
Retroviruses HIV		Reactive arthritis	Acute asymmetric oligo- or polyarticular, lower limb joints		Serology HIV-1 and HIV-2 RF, ANA, antiphospholipid antibodies may be present
		Undifferentiated spondyloarthritis	low back pain shoulders and ankles		
		HIV-arthritis	mono- of polyarticular knee and ankles		
Reactive arthritis					
Post-streptococcal	Peaks 8-15 and 20-40 years		Acute-onset, persistent or recurrent, symmetric or asymmetric Affecting any small and large joints and axial skeleton	Fever, myalgia common	ESR/CRP modestly elevated
Bacteria: Urinary bacteria: Chlamydia trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum, E.coli	antecedent pharyngitis/ tonsillitis by group A streptococci (GAS)	Common symptoms involving the urethra, conjunctiva, and joints	Asymmetric monoarthritis or oligoarthritis of lower limbs		20-25% positive HLA-B27
Enteric bacteria: Salmonella, Shigella, Campylobacter, Yersinia, Clostridium difficile, Giardia lamblia, Tropheryma whipplei	Antecedent enteric or urogenital infection		Sacroiliitis, back pain, enthesitis, rash, ocular inflammation		↑ESR/CRP Serology, microscopy, Serology, PCR rRNA culture
Lyme disease Borrelia burgdorferi infection	Tick-borne	Intermittent or chronic	Mono- or oligoarthritis, particularly of knees	Erythema migrans, systemic features, ECG disturbances,	Serology

				neurological abnormalities	
Sarcoidosis	F > M	Acute symmetrical Chronic uncommon	Knees, ankles Periarticular involvement	Fever, erythema nodosum and hilar lymphadenopathy (Löffler syndrome)	↑ESR/CRP X-ray lungs bilateral hilar lymphadenopathy
Septic arthritis (non-gonococcal)	Peak incidence in elderly Immuno-compromised state Joint prostheses	Acute, monoarticular, often extremely painful (beware may be polyarticular)	Knee—most common, hip, shoulder, ankle, wrist	Systemic symptoms common	Commonest cause <i>Staphylococcus aureus</i> Synovial fluid is Gram stain positive in 50% and culture positive in 90%
Gonococcal	F > M, young, sexually active	Acute oligoarthritis or polyarthritis	Wrist, knee	Fever, rash, skin blisters/pustules, tenosynovitis	↑ESR/CRP, ↑WBC Synovial fluid Gram stain positive in 25% and culture positive in 50% of cases
Osteoarthritis (OA)	F > M, men with knee or hip involvement ↑Age	Progressive oligoarthritis or polyarticular asymmetrical or symmetrical, bony swelling	DIP, PIP, CMC1, knee, hip, MTP, spine		Normal laboratory tests
Gout	Men, postmenopausal women Diuretic use (especially in elderly)	Sudden onset, severe pain with attacks, oligoarticular early, polyarticular later	MTP, toes, ankle, knees	Tophi	Synovial fluid—urate crystals ↑Uric acid level (normal levels in 40% of acute attacks) RF+ in low titre may be present
Hemochromatosis	M > F 40-60 years	Insidious Symmetric and progressive	Mainly small joints of the hands - MCP II-III Occasionally knees, hips, and shoulders Mild swelling and stiffness	Scin pigmentation, spoon nails, hepatomegaly, liver cirrhosis, diabetes mellitus, hypogonadism, amenorrhea, heart failure Degenerative-like changes in the joints not commonly involved in OA as	Serum ferritin↑ Transferrin saturation↑ ↑LFTs <i>HFE</i> mutations C282Y, H63D

MCP, wrists, elbows,
shoulders

ACA, anticentromere antibody; ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; CMC1, first carpometacarpal joint; CRP, C-reactive protein; DIP, distal interphalangeal joint; ESR, erythrocyte sedimentation rate; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; LFT, liver function test; M, male; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor; UA, undifferentiated arthritis; WBC, white blood cells; RS3PE, Remitting Seronegative Symmetrical Synovitis with Pitting Oedema.

5.2 Investigations

Most cases of suspected inflammatory arthritis will warrant a complete blood count, inflammatory markers and basic serological tests, including RF, ACPA and antinuclear antibodies, renal and liver function tests and a urine analysis.

The need for more specific tests may be directed by the clinical presentation, including tests for uric acid, cultures where infection is suspected, serology for infections - for example, Lyme disease and virology—for example, hepatitis B, C or B19 parvovirus (IgM antibodies), and specific autoantibodies and genetic markers. If crystal arthropathy or infection is suspected, an aspirate of a joint effusion will be of value in making a definitive diagnosis. Findings on X-ray examinations may further assist in making the diagnosis of a specific arthropathy—for example, the presence of cartilage calcification in calcium pyrophosphate dihydrate deposition disease (figure 5), large asymmetrical erosions with periosteal reaction and late development of ‘pencil in cup’ deformities in psoriatic arthritis, joint space narrowing with sclerosis and hook-like osteophytes of MCP2 and 3 in hereditary haemochromatosis, large asymmetrical erosions with sclerotic rims in gout and space narrowing with subchondral sclerosis and osteophyte formation sparing MCP joints in osteoarthritis.

Figure 5 Calcification of the triangular fibrocartilage of the wrist in calcium pyrophosphate dihydrate deposition disease (CPPD).



6 Prediction of outcome of undifferentiated and early RA

After excluding other diseases and making a diagnosis of probable RA or UA, the third step is to determine which patients are at risk of developing persistent and/or erosive arthritis. This prognostic assessment is important for guiding optimum treatment strategies. Predictors of persistence and disease progression include demographic, genetic, clinical, serological and radiological factors (Landewé, 2007).

6.1 Assessment of disease persistence

The frequent spontaneous remission of synovitis in patients with early arthritis (especially those with symptoms of <3 months' duration) means that a therapeutic approach, which targets all patients with very early synovitis, will expose many patients to unnecessary and potentially toxic treatments. The ability to distinguish resolving disease from synovitis that persists and will develop to RA is thus essential. Female gender, cigarette smoking, duration of symptoms, the tender and swollen joint count, hand involvement, the level of acute phase response, presence of RF and ACPA, and fulfilment of the 1987 ACR diagnostic criteria for RA (sensitivity 88%; specificity 73%) are factors associated with disease persistence (box 1).

Box 1 Candidate predictors of disease persistence in early arthritis

- Female gender
- Duration of symptoms (more than 12 weeks)
- High tender and swollen joint count
- Hand involvement
- Cigarette smoking
- Raised acute phase response
- Positive RF
- Positive ACPA
- Erosions on X-ray examination

ACPA, antibodies to citrullinated peptide; RF, rheumatoid factor.

An alternative approach is to differentiate the patients with arthritis that more likely to enter spontaneous early remission. Sero negativity for RF and fewer active joints at baseline in early RA have been suggested as markers of a favourable outcome (Eberhardt and Fex, 1998).

6.2 Assessment of disease severity

In clinical practice, treatment of early RA should be started as soon as the diagnosis of RA is made, treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patients, and treatment should be and adjusted according to the disease activity and other factors such as progression of structural damage, comorbidities and safety concerns.

Many of the factors predicting disease persistence are also markers of disease severity. Joint damage and functional disability are the two most common outcome measures of disease severity.

The most reliable prognostic factors of radiological joint damage are a high acute phase response, the presence and titre of RF and ACPA, the HLA-DRB1*0401 allele subtype and early erosions. Factors that have been found to predict future disability include a baseline Health Assessment Questionnaire (HAQ) score, Ritchie index, erythrocyte sedimentation rate (ESR) and CRP, and presence of erosions. Female gender, older

age, the number of damaged joints, RF positivity and the presence of nodules (although usually a later finding in RA) at baseline are other documented factors (box 2).

Box 2 Candidate predictors of disease severity in early arthritis

- Female gender*
- High tender* and swollen joint† count
- High HAQ score*
- Raised acute phase reactants*†
- Positive RF†
- Positive ACPA†
- Shared epitope†
- Erosive disease*†

**Predictors of functional disability; †predictors of joint damage.*

ACPA, antibodies to citrullinated peptide; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor.

6.3 Individual factors predicting persistence and disease severity

6.3.1 Symptom duration

Several studies have shown longer symptom duration at first visit to be a predictor of disease persistence (Tunn and Bacon, 1993; Schumacher, 2004). In a study by Green et al, 63 patients with mild untreated early inflammatory arthritis were given a single dose of glucocorticoids at presentation. At 6 months, 49 patients (78%) had persistent inflammatory joint disease and 14 (22%) had clinical disease remission. The strongest predictor of persistence was disease duration of >12 weeks (Green et al, 1999). With disease of ≤12 weeks, the chance of remission was increased 5-fold. The 1987 ACR classification criteria for RA were found to be less helpful in predicting persistence in those with shorter disease duration; of those fulfilling the ACR criteria at presentation, 53% with disease duration of ≤12 weeks had persistent disease 6 months later compared with 94% who presented with symptoms >12 weeks.

A further study examined the use of intra-articular glucocorticoid injections in patients with early oligoarthritis (Green et al, 2001). At least 50% of patients in this study had complete response at 2 weeks and the presence or absence of synovitis at 2 weeks predicted response at 12 and 26 weeks. Failure to respond by 2 weeks indicated a high likelihood of further persistent disease and the need for DMARD therapy.

As discussed earlier, symptom duration is also an important predictor of disease severity, with better clinical and radiographic outcomes seen in patients with shorter symptom duration at the first visit to the rheumatologist (Emery et al, 2012; van der Linden et al, 2010).

6.3.2 Early morning stiffness

EMS is an early symptom of an inflammatory arthritis. It is, however, a complex symptom and may be difficult for patients to distinguish from pain and functional limitation. It has been used as a clinical marker of disease

persistence (Visser et al, 2002; van der Helm-van et al, 2007). During the first phase development of the 2010 ACR/EULAR RA classification criteria, EMS—using the traditional cut-off point of 1 h—was not found to be predictive of starting methotrexate in patients with early inflammatory arthritis and was therefore subsequently not included in the final classification criteria (Funovits et al, 2010). This notion has been challenged during subsequent investigations that in the large dataset demonstrated that in patients with arthralgia morning stiffness ≥ 60 min was associated with arthritis, and in the group of patients with early arthritis duration of morning stiffness ≥ 30 min discriminated patients with RA (van Nies et al, 2015).

6.3.3 Joint involvement

In a cohort of 121 patients with early arthritis followed up for a median duration of 5 years, those with polyarticular disease and hand involvement were more likely to have persistent disease (Schumacher et al, 2004). These findings have been confirmed by several other studies (Machold et al, 2002; Sokka et al, 2003). Persistent joint inflammation leads to joint destruction.

6.3.4 Functional disability

Functional disability as measured by the Stanford HAQ disability index is one of the most reliable predictors of disease outcomes in early arthritis (Pincus and Callahan, 1985). A high baseline HAQ is an important risk factor for the development of future functional disability and predictive of both all-cause and cardiovascular mortality in patients with early disease. Analysis of data from a primary care-based inception cohort of patients with recent-onset polyarthritis found that the 1-year HAQ score was a better predictor of subsequent outcome than the baseline HAQ score (Wiles et al, 2000). The baseline HAQ score has been shown to be predictive of quality of life and work disability (Combe et al, 2003; Eberhardt et al, 2007) in patients with early RA.

6.3.5 The acute phase response

A rise in the level of acute phase reactants, such as the ESR and CRP, provides a surrogate measure of inflammation. The combination of ESR and CRP yields useful information that is often not apparent when only a single test is used.

6.3.6 Rheumatoid factor

Historically, RF has been one of the most consistent markers of disease persistence and progression of radiographic damage in patients with inflammatory arthritis (Wolfe et al, 1993; Bukhari et al, 2002; Machold et al, 2007). Further, RF at a high titre was found to be a predictor of disability (Harrison et al, 2000).

6.3.7 Anti-cyclic citrullinated peptide antibodies

Research into autoantibodies other than RF in serum samples of patients with RA led to the discovery of antiperinuclear factor in the 1960s and anti-keratin antibodies in the 1970s. Subsequent studies showed that these antibodies recognised a similar antigen, citrulline. This non-standard amino acid is generated by the post-translational modification of arginine residues by the enzyme peptidylarginine deiminase. Several tests have been developed to identify the antibodies to citrullinated peptides/proteins (ACPA). The assay using the second-generation cyclic citrullinated peptide as an artificial autoantigen (CCP2) is the most commonly used test in clinical practice.

ACPA are present early in the disease course and can precede onset of symptoms by up to 10 years, particularly in the 2 years before symptom onset (Rantapää-Dahlqvist et al, 2003; Berglin et al, 2004). ACPA represents an independent risk factor for developing RA in patients with undifferentiated arthritis or arthralgia. In early UA, 93% of patients who were ACPA (CCP2) positive at baseline were diagnosed with RA at 3 years. Conversely, only 25% ACPA-negative patients had a diagnosis of RA at follow-up (van Gaalen et al, 2004). In patients with arthralgia but without clinical synovitis, an expanded ACPA repertoire recognizing different citrullinated peptides and higher anti-CCP levels (were associated with a higher risk of developing inflammatory arthritis (van de Stadt et al, 2011).

A review of data has shown that ACPA has a similar sensitivity to RF in cohorts with early RA (41–63% vs 41–66%), but a greater specificity (91–100% vs 87–97%). The positive predictive value for ACPA in UA was 78–96% in the cohorts with early RA, and the negative predictive value 62–96% (Aggarwal et al, 2009).

The presence of ACPA has also been shown to independently associate with baseline and long-term disease severity in patients with inflammatory polyarthritis (Farragher et al, 2010) and of radiographic damage and radiographic progression in patients with RA (Meyer et al, 2003). One study has shown a direct association between ACPA, osteoclastogenesis and serum markers for osteoclast-mediated bone resorption in patients with RA (Harre et al, 2010). ACPA titres have also been related to disease severity (Berglin et al, 2006) but measuring ACPA titres has not been proved to be of value in monitoring treatment outcomes. A subanalysis of the CARDERA (Combination Anti-Rheumatic Drugs in Early RA) trial has evaluated the usage of ACPA in guiding treatment decisions. In this study patients who were ACPA-positive had less radiographic progression when treated with combination DMARD therapy or when treatment included an initial high dose of oral glucocorticoids. ACPA-negative patients, as expected, had minimal radiographic progression irrespective of treatment (Seegobin et al, 2014).

However, the recent subanalysis of the Dutch dynamic treatment strategy study, the BeST-trial, pointed out that treatment of all patients with early and active RA should focus on rapid relief of symptoms, and there is no reason to weigh the initial treatment choice based on the presence of autoantibodies. In this analysis,

ACPA-negative and RF-negative patients also benefited from initial combination therapy, with a better functional ability at 3 and 6 months follow-up compared to patients treated with initial methotrexate monotherapy (Akdemir et al, 2016).

6.3.8 Other autoantibodies and immune markers

Despite the diagnostic value of ACPA and RF, the disease in a proportion of patients with inflammatory arthritis will still be classified as seronegative RA. Research has led to the finding of several other autoantibodies, antibodies to carbamylated antigens (anti-CarP) are ones of these new autoantibodies (Trouw and Mahler, 2012). These autoantibodies recognise carbamylated but no citrullinated protein antigens. IgG anti-CarP and IgA anti-CarP antibodies have been described in 16% and 30% of ACPA-negative individuals with inflammatory arthritis, respectively (Shi et al, 2011). Anti-CarP antibodies have been found in both ACPA-negative and ACPA-positive patients with RA and also in preclinical phase of the RA-disease. In patients positive for CarP and negative for ACPA, more severe erosive course of disease has been reported (Shi et al, 2011). Already in the pre-symptomatic ACPA-negative individuals the presence of anti-CarP antibodies has been shown to associate with RA development (Brink et al, 2015). In the recent analysis in early RA, anti-CarP antibodies were associated with more radiographic progression in the ACPA-positive/RF-negative, ACPA-negative/RF-positive and ACPA-positive/RF-positive patients, but with known ACPA and RF status the anti-CarP antibodies did not improve correct classification of patients with progressive joint damage disease (Ajeganova et al, 2016).

In addition to autoantibodies, levels of cytokines and chemokines, including interleukin (IL)-1 α , IL-1 β , IL-6, IL-10 and tumour necrosis factor α (TNF α), have been found to be elevated in the preclinical period of RA development, with increasing numbers of cytokines/chemokines predictive of decreased time to diagnosis (Deane et al, 2010).

6.3.9 Genetic markers

The shared epitope (SE), a group of HLA-DRB1 alleles that share a similar amino acid sequence, is strongly associated with RA. Among the different HLA-DRB1 alleles examined, HLA-DRB1*401 and DRB1*0404 have been consistently associated with radiographic erosions in different ethnic groups. This association appears to be dose dependent as patients with two RA-associated alleles (DRB1*04 or DRB1*01) have more radiographic erosions and more joint replacement than patients with non-disease-associated alleles (Weyand et al, 1992). Studies have shown that individuals who were homozygous for HLA-DRB1*0404 were four times more likely to develop erosions than those who were SE negative (Harrison et al, 1999; Goronzy et al, 2004).

Since ACPA tests have been included in multivariate analyses, however, HLA-DRB1 genes have no longer been shown to be independent predictive factors of severity in RA. In most populations, their effect is accounted for

by the presence of ACPA. (Further discussion on the association with the SE and smoking and the development of ACPA can be found in chapter 9, Rheumatoid Arthritis: Pathogenesis and Clinical Features.)

A number of other genetic polymorphisms have been studied in patients with early RA. We refer for an in-depth discussion to the chapter on genetics in this EULAR Textbook.

Although discovery of specific genetic risk factors (in particular, SE) has been essential in our understanding of RA pathogenesis, testing for these markers is not recommended in routine clinical practice.

6.3.10 Smoking

Smoking is the most recognised environmental risk factor for the development of RA. There is also a strong association between smoking and increased occurrence of extra-articular manifestations, including rheumatoid nodules, in early seropositive RA.

Studies have gained insights into the potential role of smoking in the pathogenesis of RA. It has been shown to increase the risk of developing ACPA. In the presence of HLA-DRB1 SE alleles, this risk is further increased—up to 20 times in homozygotes as compared with SE-negative non-smokers in ACPA-positive persons (Klareskog et al, 2006; Klareskog et al, 2007). It suggests that smoking in a genetically predisposed individual triggers apoptosis and protein citrullination, followed by an anti-citrulline-specific immune response. Former smokers are also at an increased risk for RA up to 20 years after stopping smoking, with a gradually decreasing risk over time (Heliovaara et al, 1993).

Outcomes of studies assessing the effect of smoking on disease severity vary, however. Several cross-sectional studies have demonstrated significant associations between smoking and more radiographic damage progression (Saag et al, 1997; Masdottir et al, 2000), while other studies, including a large observational study of 2004 patients with RA (Finckh et al, 2007), have found no difference in rates of radiographic progression between current or previous smokers and non-smokers (Harrison et al, 2001; Forslind et al, 2004). The large multi-centre study indicated that effect of smoking on joint damage is mediated via ACPA and that smoking is not an independent risk factor for radiological progression in RA (de Rooy et al, 2014). In the population-based early RA cohort, current cigarette smokers have been shown to respond less likely to methotrexate and TNF inhibitors (Saevarsdottir et al, 2011). The decreased chance of response associated with current smoking was observed for a good response and remission according to the EULAR criteria, and for the DAS28 scores and the joint counts at follow-up. In this study, the influence of smoking did not differ significantly between ACPA-positive and ACPA-negative patients.

6.3.11 Imaging

6.3.11.1 Conventional radiographs

X-ray examinations are the conventional imaging modality. Radiographic erosions have a high specificity in discriminating between self-limiting and persistent arthritis (Visser et al, 2002). Early radiographic changes are also predictive of disease progression. In a cohort of 518 patients with UA the presence of two or more erosive joints at baseline showed a positive predictive value for RA development of 53% and for persistent disease of 68% (Thabet et al, 2009). Patients with erosions that did not develop RA were less often ACPA-positive, RF-positive and had lower CRP/ESR and number of swollen joints compared to those who developed RA. Feet erosions were equally predictive compared to erosions at hands in this study.

Radiographic examination should include assessment of the hands and feet as erosions often start in the feet and in about 14–18% of cases are only detected in the feet (figure 6) (Fex et al, 1996). In general, anteroposterior views are used. Other views—for example, lateral or oblique views, may be requested if clinically indicated.

Figure 6 Conventional radiograph of the foot showing erosions of the fifth metatarsal head.



Radiographic damage at baseline is also the best predictive factor of poor structural outcome. Irrespective of the scoring systems (eg, van der Heijde Sharp score (SHS) and Larsen score) used, the initial radiographic score consistently predicts future radiographic damage (Jansen et al, 2001).

Joint erosions and joint space narrowing seen on X-ray examinations, however, are generally late findings. Newer imaging modalities have been shown to provide additional diagnostic information at an earlier stage.

6.3.11.2 Magnetic resonance imaging

Magnetic resonance imaging (MRI) can assess all structures of the inflamed joint. It is more sensitive than clinical examination and radiography for the detection of synovitis and erosions in early RA. There is also evidence that MRI findings (synovitis, bone oedema and bone erosions) may predict subsequent radiographic progression. Changes resembling mild synovitis or small bone erosions, however, are occasionally found in the joints of healthy subjects. The newly published review of the literature on 31 MRI studies assessed the occurrence of MRI features in symptom-free persons (Mangnus et al, 2015). The MRI erosions were present in 33-52% of symptom-free persons, synovitis in 27% and bone oedema in 0-16%. The prevalence of MRI-detected erosions was shown to increase with age. Higher costs, longer examination times and lower availability are some disadvantages of MRI compared with conventional radiographs. The role of MRI of joints in clinical practice is to be established.

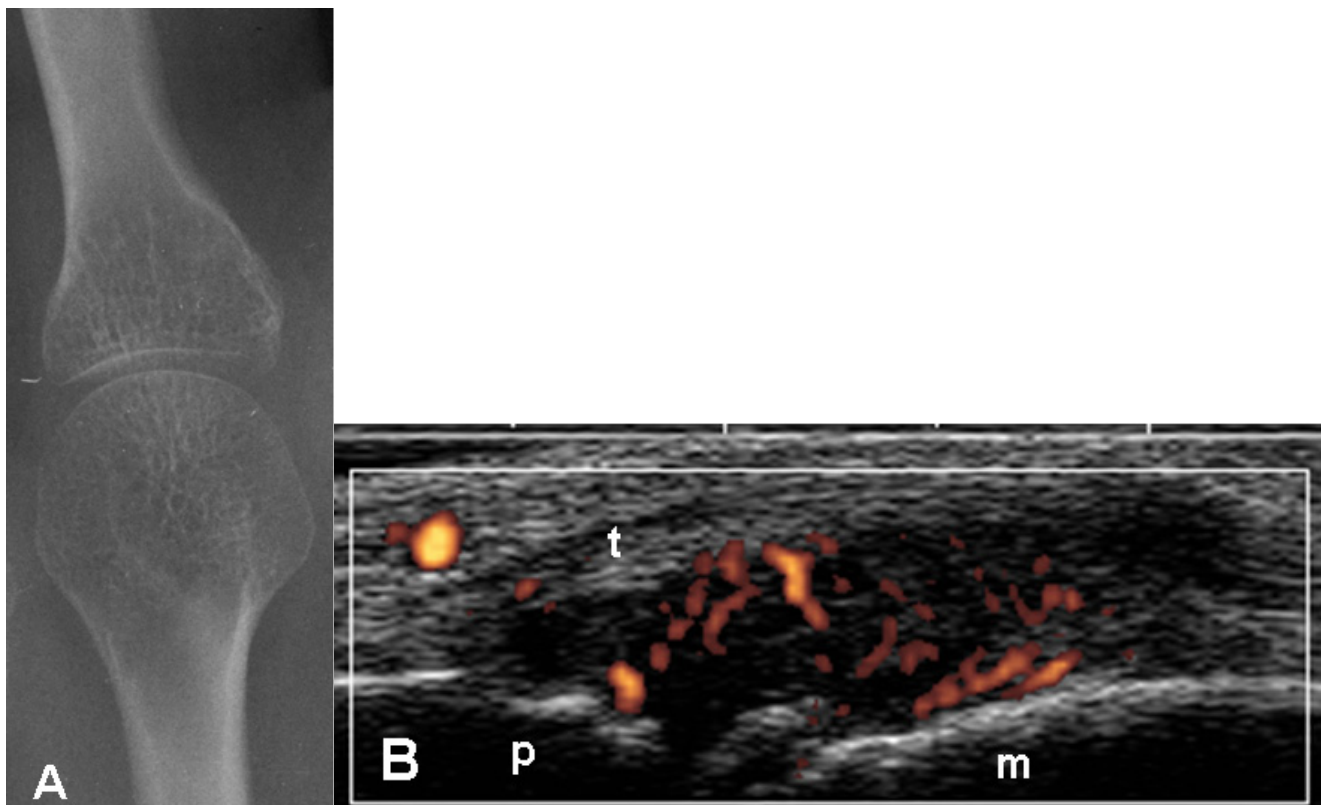
6.3.11.3 Musculoskeletal ultrasonography

The use of MSUS for the management of patients with early arthritis has increased over the years. It is useful for detecting synovitis in small joints of the hands and feet with greater sensitivity than clinical examination. It is also more sensitive for visualising synovitis and bone erosions in the finger joints than conventional X-ray examinations (figure 7). The advantages of US are that it is relatively inexpensive, non-invasive and allows assessment of many joints. The main disadvantage is its dependency on the skills of the operator and problems with reproducibility.

In patients without clinical synovitis, the role of ultrasound is not clear. One of the studies encouragingly reported prediction of development of inflammatory arthritis in patients with seropositive new-onset arthralgia, based on MSUS findings (grey scale, power Doppler signal and erosions) (Rakieh et al, 2015; Nam et al, 2016). However, it should be noted that MSUS findings are quite common in healthy persons and were reported in 88% of healthy persons without joint symptoms (Padovano et al, 2015). It is of importance to interpret MSUS imaging cautiously and always in the context of clinical situation. In patients with RA, MSUS findings in active both large and small joints reflect synovial histological scores, DAS28 and CRP (Abe et al, 2016).

So far it is not proved that including ultrasound examination leads to better outcomes for patients with early RA (Dale et al, 2016; D'Agostino et al, 2016). The level of agreement and impact on treatment decision-making of adding MSUS to clinical assessment of disease activity in early RA patients has been assessed in the TSERA study (Targeting Synovitis in Early Rheumatoid Arthritis study) (Dale et al, 2014). MSUS power Doppler was performed in 14 joints on patients with low disease activity ($\text{DAS28} < 3.2$) and with moderate disease activity ($3.2 \leq \text{DAS28} < 5.1$) without clinically swollen joints. Data from 414 paired DAS28 and MSUS assessments were pooled to determine the level of agreement between each method. MSUS identified persistent disease activity in a quarter of patients with low disease activity or clinical remission; on the other hand, MSUS confirmed active disease only in one-third of patients with moderate disease activity. In 29% of assessments MSUS findings contradicted the DAS28 and led to modified therapeutic decisions. The authors conclude that compared to the DAS28, global RA disease activity assessment using a limited MSUS joint set provided additional disease activity information and led to altered treatment decisions in a significant minority of occasions. In the real-life cohort of patients with RA followed for 3-5 years, 'the silent radiographic progression' in an individual joint without any clinical activity in any other joint has been reported to be very rare, 5.8% of the patients, suggesting that remission assessed clinically is a marker of structural stability (Gärtner et al, 2016).

Figure 7 Imaging of the second metacarpophalangeal joint of a patient with rheumatoid arthritis. (A) Conventional radiography shows juxta-articular osteoporosis. (B) Ultrasonographic examination, in the longitudinal dorsal scan, shows proliferative synovitis with marked intra-articular power Doppler signal. m, metacarpal bone; p, proximal phalanx; t, extensor tendon.



Mostly, MSUS imaging is currently used for disease monitoring as a part of clinical investigation. Whether combination of clinical, serological and imaging (ultrasound) findings could potentially help for more precise treatment decisions in individual patients with early arthritis is to be defined.

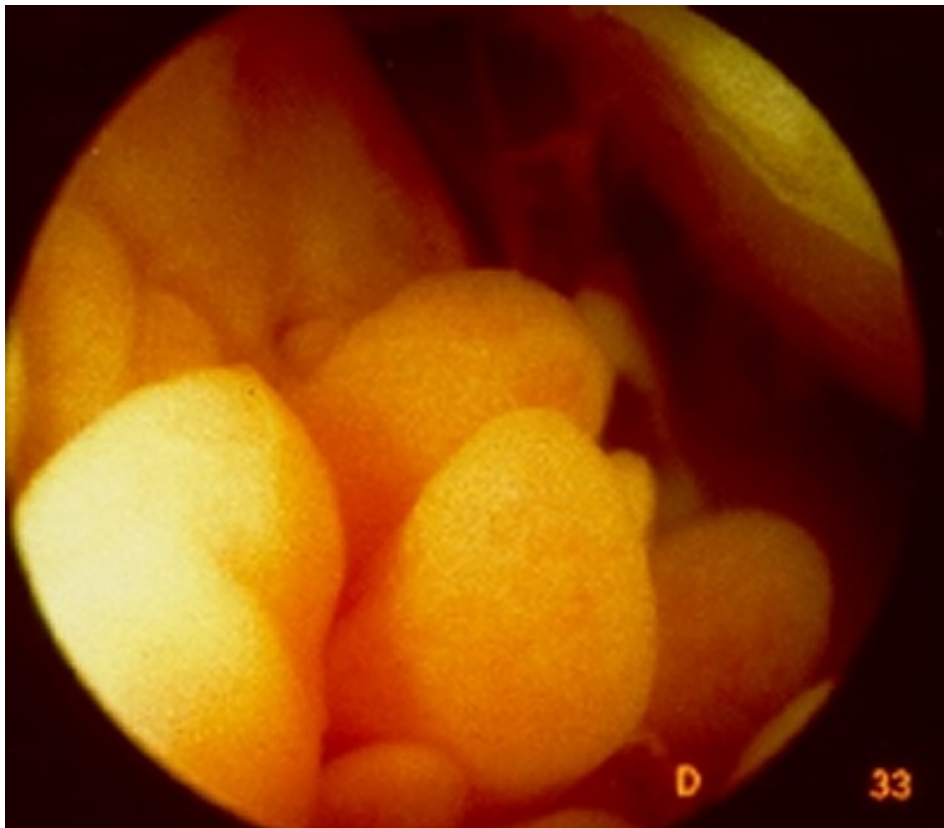
6.3.12 Hand bone densitometry

With newer treatments for RA, erosion progression is lower, requiring more sensitive measures to assess treatment outcomes. In RA, bone loss, particularly in the hands, takes place early in the disease process. Measuring hand bone loss may therefore be useful for diagnosis and as a marker of disease activity. Dual energy X-ray absorptiometry (DEXA) measures bone density with high precision, making it sufficiently sensitive to detect even small changes in bone mass. Studies in RA assessing bone mineral density (BMD) have shown a good correlation between BMD loss in the spine (Gough et al, 1994) and hand (Devlin et al, 1996) with disease activity. DEXA has been found to be a more sensitive tool than radiology for measuring disease-related bone damage. Of 58 patients with early RA of <12 months' duration, 50% showed significant individual BMD hand bone loss after 24 weeks compared with only 22% showing the smallest detectable radiographic progress evaluated by SHS method at 48 weeks (Haugeberg et al, 2007). In early arthritis patients without baseline erosions, early metacarpal BMD loss after 4 months is reported as the main predictor of radiological progression after 1 year (Wevers-de Boer et al, 2015). Change in BMD hand bone loss at one year is correlated significantly and inversely with the change in SHS at two, five and eight years, and only change in SHS during the first year and the presence of ACPA has been reported as independent predictors of long-term progressive joint damage in early RA (Forslind et al, 2012).

6.3.13 Histology

Studies using arthroscopy have confirmed imaging findings of subclinical synovitis examining asymptomatic joints of newly diagnosed RA. Distinct macroscopic vascular patterns have been seen in early RA and psoriatic arthritis (figure 8). Comparison of histopathological features of synovial tissue in early RA and non-RA synovitis has shown subtle differences in histological features, cytokine and protease expression patterns, as well as apoptosis. An analysis of synovial biopsies of 95 patients with early arthritis showed that the higher scores for the number of CD38+ plasma cells and CD22+ B cells were the best markers for distinguishing between patients with and without RA. The number of CD68+ macrophages in the synovial tissue of patients with RA was also increased (Kraan et al, 1999). Thus far, however, the clinical value of the histopathological characteristics of synovial tissue in early arthritis has not yet been proved (Hitchon and el-Gabalawy, 2003). Widespread use of synovial biopsies in the clinical setting is also limited by its invasiveness.

Figure 8 Arthroscopy showing rheumatoid synovitis. Hypertrophic, rounded, polypoid-like villi with an opaque, ill-defined background due to congestion and oedema.



6.3.14 Biomarkers of joint destruction

Molecular markers that reflect synovial, bone and cartilage turnover have been studied as potential tools for early identification of patients with RA at high risk of rapid disease progression (Landewé, 2007). These include urinary glucosyl-galactosyl-pyridinoline, a marker of destruction of the synovium, and C-terminal crosslinking telopeptides of type I and type II collagen (CTX-I and CTX-II), markers of bone and cartilage destruction. High baseline levels of CTX-I and CTX-II have been shown to (weakly) associate with radiographic progression.

Raised levels of matrix metalloproteinases, enzymes involved in the degradation of articular cartilage in RA, have been found in tissue, synovial fluid and the systemic circulation of patients with RA. Several studies have shown a correlation between increased matrix metalloproteinase levels and progression of joint damage.

The osteoprotegerin:nuclear factor (NF) kappaB ligand (OPG:RANKL) ratio may be another marker of joint destruction, with low levels predictive of more rapid progression. Osteoclasts play a key role in the mechanism of joint destruction in RA. RANKL and its receptor RANK are central to the stimulation of osteoclast formation and activation, and the soluble receptor-like molecule OPG is a natural inhibitor of RANKL. Bone resorption is regulated by the balance between RANKL and OPG.

High levels of calprotectin (myeloid-related protein 8/14, expressed in granulocytes and monocytes) in plasma/serum and/or synovial fluid have been shown to predict erosive joint damage progression and therapeutic responses (Abildtrup et al, 2015).

However, analysis of cartilage and bone biomarkers is not more useful than current predictors of clinical and radiographic outcomes in RA—for example, ACPA and the presence of early radiographic damage. In daily clinical practice, the role of these biomarkers is not demonstrated.

6.4 Phases up to the development of RA

Research at the very earliest stages of RA has led to the formation of a ‘Study Group for Risk Factors for RA’ (Gerlag et al, 2012*). The group has published recommended terminology to define the specific phases up to the development of RA in order to phenotype/characterize these phases and to standardize further research in the field (box 3). These phenotypes include certain genetic profiles (eg, SE), environmental factors (eg, smoking) and autoantibodies (eg, RF and ACPA) - known risk factors for the development of RA.

Box 3 Recommendation for terminology to be used to define specific phases up to the development of rheumatoid arthritis (RA)

In prospective studies individuals would be described as having:

1. Genetic risk factors for RA
2. Environmental risk factors for RA
3. Systemic autoimmunity associated with RA
4. Symptoms without clinical arthritis
5. Unclassified arthritis
6. RA

The term ‘arthritis’ is used to denote clinically apparent soft tissue swelling or fluid (not bony overgrowth alone).

(a) to (e) can be combined—for example, an individual may have (a)+(b), or (a)+(b)+(c) or (a)+(b)+(d), etc. The prefix ‘pre-RA with:’ can be used before any/any combination of (a) to (e) but only to describe retrospectively a phase an individual was in once it is known that they have developed RA.

Reproduced from Gerlag et al, Ann Rheum Dis 2012;71:638–41.

6.5 Predictors of persistence and disease severity: practical points

In practice, the clinical features and investigations listed in boxes 1 and 2 may be used to identify patients with early inflammatory arthritis who are at risk of a persistent and more severe disease course. X-ray of hands and feet is the mainstay imaging modality, although the use of MSUS, MRI and DEXA is coming to the fore. Non-HLA genetic markers, histology and biochemical markers remain more research-based tools rather than investigations for day-to-day patient care.

Development of the 2010 ACR/EULAR classification criteria has been an important step forward, setting a new benchmark for the early identification of patients with RA - aiming to start effective treatment as early as diagnosis is made, thus preventing the adverse sequelae of the disease. Currently great efforts are being made

with focus on identification of clinical, serological, genetic factors, MSUS and MRI imaging features aiming to predict the development of inflammatory arthritis in individuals at risk (van de Stadt et al, 2012; Rakieh et al, 2014, van Steenbergen et al, 2015).

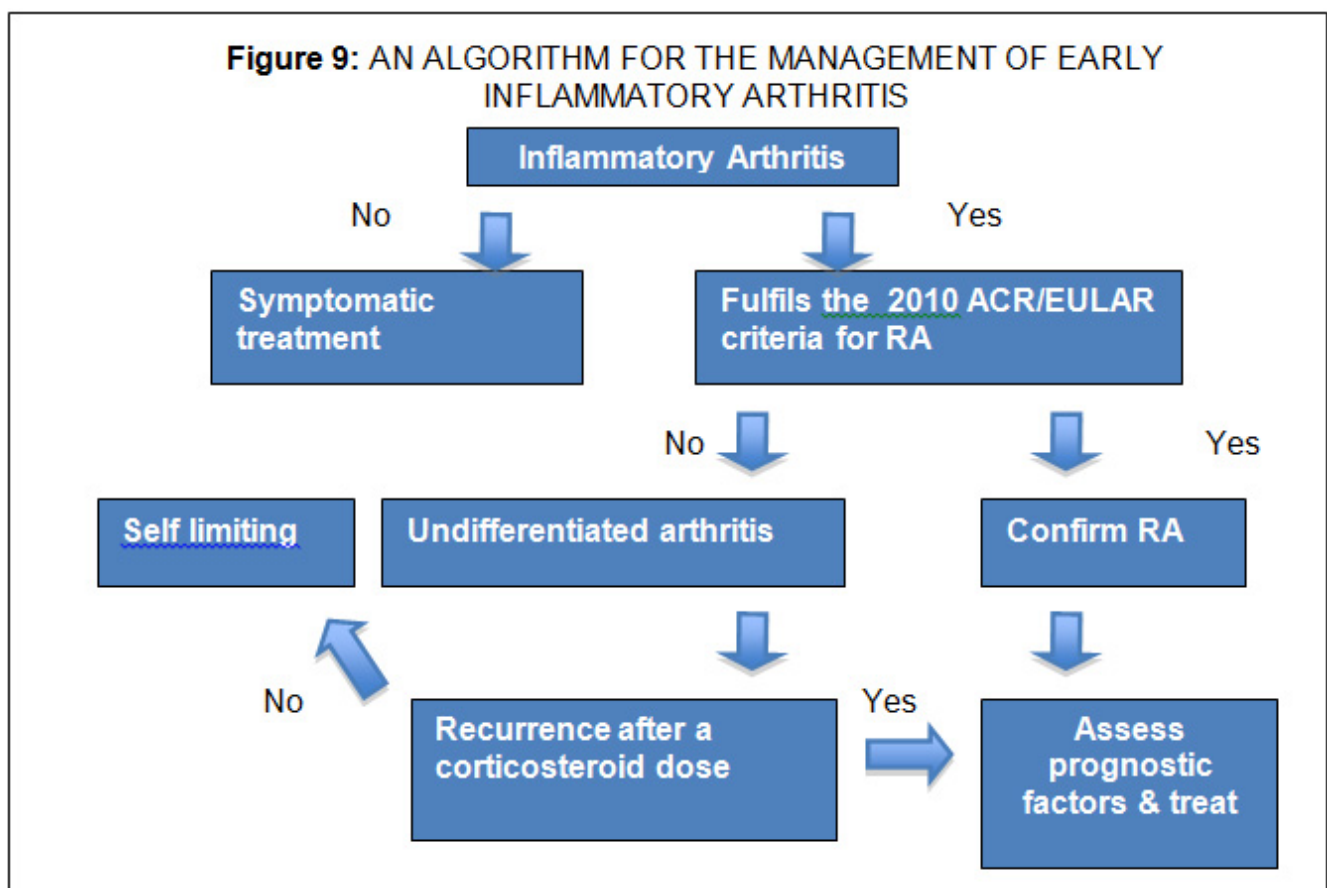
7 Treatment

Patients with early arthritis will require a combination of pharmacological and non-pharmacological treatment.

- The first principle of pharmacological treatment for early arthritis is early effective intervention.
- The second principle is treating to target - T2T (Smolen et al, 2010*) to achieve 'tight control' of disease activity. In practice, this means monitoring of disease activity and adjusting/adapting treatment as long as the target of predefined disease activity (ideally remission) has not been reached.

A suggested algorithm for the management of early arthritis is shown in figure 9.

Figure 9 An algorithm for the management of early inflammatory arthritis.



7.1 Non-pharmacological treatment and lifestyle measures

As discussed earlier in this review, smoking increases the risk of developing RA, affects progression of the disease and is associated with more joint damage progression, extra-articular manifestations and may reduce

the efficacy of anti-rheumatic therapies. Obesity in patients with early RA is associated with higher disease activity and HAQ score, more pain, worse general health, lower chance for sustained remission and higher prevalence of comorbidities (Ajeganova et al, 2013).

Though it is currently unclear whether smoking cessation and weight reduction may improve RA outcomes, apart from lowering cardiovascular risks, both factors do have an effect on response to treatment and various disease outcome measures, which justify efforts aimed at cessation of smoking and weight reduction in obese patients. Regular physical activity may also benefit patients with RA. Several non-pharmaceutical interventions—such as dynamic exercises, occupational therapy and hydrotherapy—have shown beneficial symptom-relieving effects in established RA. These are recommended as adjuncts to pharmaceutical interventions in patients with early arthritis.

7.2 Patient education

As part of the management of any chronic disease, patients should be provided with information about the disease and its treatment. Education programs may be used as adjunctive measures, aimed at coping with pain and disability and the maintenance of work ability.

Patients with an inflammatory arthritis who do not meet criteria for a specific diagnosis and do not have poor prognostic factors are much more likely to do well. About 15-50% of patients with very early undifferentiated arthritis, often those with arthritis after a transient viral infection, may be found in spontaneous remission at follow-up. Although patients may feel disappointed when a specific diagnosis is lacking, they may be reassured of a better outcome.

7.3 Pharmacological treatment

7.3.1 Symptomatic treatment

Analgesics may be required for pain management in early RA. These are often used in combination with treatments to control the inflammatory process. Both classical non-selective cyclooxygenase (COX) inhibitors and COX 2-selective non-steroidal anti-inflammatory drugs (NSAIDs) are more effective than analgesics in relief of signs and symptoms of active RA disease. At full dosages all NSAIDs are potentially equally effective; however, there is a great variation in tolerance and response to a particular NSAID. The major effect of NSAID is to reduce acute inflammation thereby decreasing pain and improving function. All of NSAIDs also have mild to moderate analgesic properties independent of their anti-inflammatory effect. NSAIDs could be considered in symptomatic patients after evaluation of gastrointestinal, renal and cardiovascular risk (further discussion may be found in chapter 10, Rheumatoid Arthritis: Treatment). It is important to note that these drugs alone do not change the course of RA-disease and do not prevent joint destruction.

7.3.2 Glucocorticoids

Glucocorticoids (GCs) have anti-inflammatory and immunosuppressive effects and are widely used for the treatment of RA (Gorter et al, 2010).

An approach for patients who present with very early undifferentiated inflammatory arthritis (<12 weeks of symptoms) is a single dose of GCs administered by either intramuscular or intraarticular injection for rapid improvement of symptoms with following assessment to evaluate persistency of synovitis or its resolution (Green et al, 2001).

Two randomised placebo-controlled studies have also investigated the benefits of a limited course of intramuscular (IM) steroids in patients with early UA. The STeroids In Very Early Arthritis' (STIVEA) trial (Verstappen et al, 2010) aimed to determine whether treatment of recent-onset inflammatory polyarthritis with three weekly injections of IM GCs could suppress evolution to RA. In this trial, 265 patients with 4–11 weeks of symptoms, ≥ 2 tender and swollen joints and hand involvement were enrolled and randomised to receive three weekly doses of methylprednisolone 80 mg IM or placebo. At 6 months, 76% of the placebo group and 61% of the steroid group had either started or been referred for DMARD therapy (OR = 2.11, $p = 0.015$). At 12 months, the arthritis had resolved in 20% of patients in the glucocorticoid arm compared with 10% in the placebo arm. However, in the Stop Arthritis Very Early (SAVE) study (Machold et al, 2010), a single dose of IM methylprednisolone 120 mg was not effective. As expected, significantly more patients with polyarthritis than with oligoarthritis received DMARDs in this study (OR = 2.84, $p < 0.0001$). The use of a single injection and longer symptom duration (≤ 16 weeks) at inclusion may have resulted in the fact that delay in development of RA was not found. However, at this point, the use of IM steroids in some patients with very early inflammatory polyarthritis is supposed to postpone the initiation of DMARD therapy.

Several randomized controlled trials and systematic reviews (Gotzsche et al, 2004; Gorter et al, 2010; Gaujoux-Viala et al, 2014) have provided good evidence for the beneficial effects of GCs in early RA. Studies have also shown that GCs in combination with DMARDs retard the progression of erosive disease (Boers et al, 1997; van Everdingen et al, 2002; Korpela et al, 2004; Kirwan et al, 2007; Gorter et al, 2010; Nam et al, 2014b). GCs have also been effectively used as part of tight control treatment strategy studies (Goekoop-Ruiterman et al, 2005; Bakker et al, 2012; de Jong et al, 2014; Heimans et al, 2014; Nam et al, 2014b) (a concept which will be discussed later in this module). According to the current recommendations, GCs in low-to-moderately high doses added to synthetic DMARD provide benefit as initial short-term treatment strategy, but should be tapered as rapidly as clinically feasible (Smolen et al, 2014*).

Concerns are often raised about possible side effects of glucocorticoids. Evidence suggests that side effects depend on the dose used and the disease being treated. A review of the published reports and safety data from RCTs in RA suggests that adverse effects associated with GCs treatment are modest and often not

statistically different from those of placebo (Da Silva et al, 2006). The side effects known to occur in other diseases treated with higher doses of glucocorticoids, such as cardiovascular risk, lipid abnormalities and osteoporosis, may not occur when low-dose GCs are used to treat RA. The EULAR recommendations on the use of GCs in rheumatic diseases effectively and with acceptable safety have been newly published (Strehl et al, 2016). The level of harm of GCs depends on both dose and patient-specific parameters. At dosages between >5 and ≤ 10 mg/day, patient-specific characteristics (protective factors such as a healthy lifestyle, inflammatory control and risk factors) determine the actual and future risk of harm.

7.3.3 Conventional synthetic disease-modifying antirheumatic drugs

Early treatment with disease-modifying drugs (DMARDs) is one of the key principles in the treatment of early arthritis (Gaujoux-Viala et al, 2010). Patients with inflammatory arthritis at risk of developing persistent and/or erosive arthritis should start treatment with DMARDs as early as possible.

There is good evidence that patients with recent-onset polyarthritis who receive earlier DMARD treatment have better outcomes for radiographic progression and function than those in whom DMARD treatment is delayed by a few months (Nell et al, 2004). Disease duration at the time of conventional synthetic DMARD initiation was shown to be the main predictor of response to treatment in the meta-analysis of 14 RCTs by Anderson et al. The best response was seen in those who had had symptoms for <1 year at the start of treatment (Anderson et al, 2000). Another meta-analysis of 12 studies examined the effect of early conventional synthetic DMARD therapy on the long-term radiographic progression in patients with early RA (<2 years at presentation). Six were open-label extensions of RCTs in which placebo patients later started conventional synthetic DMARD therapy and six were observational cohort studies. The average delay between early and late treatment was 9 months. After a median of 3 years of observation, those patients who had received early treatment had 33% less radiological progression than those with delayed treatment (Finckh et al, 2006).

Conventional synthetic DMARDs have an effect on the disease process within weeks to months. Methotrexate, sulfasalazine and leflunomide are commonly used DMARDs, which have been shown to improve clinical outcomes and delay radiological progression. (Details of these drugs can be found in chapter 10, Rheumatoid Arthritis: Treatment.) Of the conventional synthetic DMARDs, methotrexate (MTX) is considered the anchor drug and is generally used first in patients at risk of developing persistent disease or erosive disease because of its favourable long-term safety profile, clinical and radiological efficacy, and its beneficial properties in treatment combinations with biological DMARDs. Leflunomide and sulfasalazine have similar clinical efficacy and are considered the best alternatives.

Despite early treatment, substantial structural damage may still occur in some patients with early RA treated with synthetic DMARDs alone (Machold et al, 2007; Rezaei et al, 2012). In a cohort of patients with very early RA with symptom duration of <3 months, 64% had developed erosive disease by 3 years.

Earlier use of conventional synthetic DMARD therapy—in patients with UA, before the stage of fulfilling ACR criteria for RA—was first examined in the PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) study. In this double-blind RCT, 110 patients were randomised to treatment with MTX or placebo for 12 months. In 40% (22/55) of patients in the MTX group the disease progressed to RA compared with 53% (29/55) in the placebo group. In the MTX group patients also fulfilled the ACR criteria for RA at a later time point than in the placebo group ($p = 0.04$), and fewer patients showed radiographic progression over 18 months ($p = 0.046$). This study suggests that MTX may delay the development of RA and retard radiographic joint damage in patients with UA. Further analysis and long-term follow-up showed that these findings were mainly seen in the subgroup of patients who demonstrated the presence of ACPA (van Dongen et al, 2007; van Aken et al, 2014).

7.3.4 Conventional synthetic DMARD (csDMARD) monotherapy versus combination therapy

Several studies have investigated whether initial combination therapy of early RA is more beneficial than conservative strategies. In the COBRA trial, a combination of methotrexate (7.5 mg weekly), sulfasalazine (2 g/day) and prednisolone (starting with 60 mg/day and tapering over 6 months) had long-term beneficial effects on radiographic progression, compared with sulfasalazine monotherapy in 155 patients with RA of duration of <2 years (Boers et al, 1997; Landewé et al, 2002). These results were consistent with those from the FIN-RACo study, in which 197 patients with onset of RA within 2 years were randomly assigned to receive either a four-drug regimen, with methotrexate, sulfasalazine, hydroxychloroquine and prednisolone (maximum doses: 15 mg/week, 2 g/day, 300 mg/day and 10 mg/day, respectively) or a single DMARD (Mottonen et al, 1999; Korpela et al, 2004; Puolakka et al, 2004) for 2 years. After 18 months, a greater proportion of the combination therapy group was less likely to have radiographic progression, and the work disability rate was lower than for patients receiving monotherapy. Although in the latter study, steroid was permitted in the single-treatment group, this was introduced later, at up to 93 weeks from baseline. The effects achieved in the combination treatment arms may therefore be attributed, at least in part, to the use of steroids.

Other trials comparing the MTX/sulfasalazine combination versus single agents (Haagsma et al, 1997; Dougados et al, 1999) were unable to identify better outcomes for any treatment arm over the other. Results from the Behandel Strategieën (BeSt) study showed that after a failure of MTX 25 mg/week, adding sulfasalazine to MTX resulted in Disease Activity Score (DAS) of ≤ 2.4 in only 22% of patients. An equally low response was obtained when switching from methotrexate to sulfasalazine (van der Kooij et al, 2007).

Two recent RCTs have compared efficacy of MTX monotherapy and MTX in combination with other conventional synthetic DMARDs in early arthritis. In the single-blind Treatment in the Rotterdam Early Arthritis Cohort study (tREACH) study, 281 patients with recent-onset inflammatory arthritis at high risk of progression to persistent arthritis (Visser et al, 2002) were randomised to one of three arms: (A) combination csDMARD therapy (MTX, sulfasalazine and hydroxychloroquine) + IM glucocorticoids; (B) combination csDMARDs + oral GCs tapering scheme and (C) MTX monotherapy + oral GCs tapering (de Jong et al, 2013; de Jong et al, 2014). The area under the curve (AUC) of DAS and HAQ was lower in patients receiving combination csDMARDs than in those receiving MTX mainly owing to early treatment effects. At 3 months, disease activity was significantly lower with triple csDMARD therapy. However, at 1 year there was no significant difference in disease activity between the groups; mean (SD) DAS 1.4 (0.68) vs 1.41 (0.87) vs 1.68 (0.89) in arms A, B and C, respectively. Radiographic progression after 1 year was not different between the arms, 21%, 24% and 23% in arms A, B and C, respectively. There were fewer treatment intensifications but more drug changes due to adverse events in the combination therapy group. Both GC bridging therapies were equally effective and, therefore, both can be used in clinical practice.

The Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) study (Moreland et al, 2012; O'Dell et al, 2013), a double-blind RCT, validated the strategy of starting with MTX monotherapy or whether it is better to intensively treat all patients with early poor prognosis RA using combinations of drugs or to reserve this approach for patients who do not have an appropriate response to MTX monotherapy. This trial also assessed whether combination therapy with MTX + etanercept is superior to the combination of MTX + sulfasalazine (SSZ) + hydroxychloroquine (HCQ). The patients were randomized to 1 of 4 treatment arms: immediate treatment with MTX+etanercept, immediate oral triple therapy MTX+SSZ+HCQ, or step-up from MTX monotherapy to one of the combination therapies MTX+etanercept or MTX+SSZ+HCQ at week 24 if the DAS28-ESR was ≥ 3.2 . Remission was achieved earlier with initial combination therapy. However, the primary end-point, DAS28-ESR from week 48 to week 102, and DAS28-ESR remission at week 102 were similar between groups. Thus, the initial MTX monotherapy with the option to step-up to combination therapy resulted in similar outcomes to immediate combination therapy. Approximately 30% of patients in the initial MTX group achieved low levels of disease activity and did not need step-up combination therapy, and the 70% who needed it were clinically and radiographically indistinguishable from those who were randomized to receive immediate combination therapy. The results for either of the immediate combination approaches, whether triple therapy or MTX+etanercept, were also similar. It has been suggested that confounding by low recruitment (and therefore insufficient power) and other factors need to be considered in this trial and that perhaps more significant between-group differences might have been seen if this was not the case (Fleischmann et al, 2013).

In clinical practice, the rationale for the first line treatment in early RA has been investigated in the ESPOIR early arthritis cohort. In all, 370 patients receiving MTX or leflunomide for ≥ 3 months within the first year of follow-up were clinically assessed every 6 months. Presence of RF or ACPA and initial structural damage, but not DAS28 or CRP, were predictive of rapid radiographic progression at 1 year (Granger et al, 2016). This result supports the viewpoint that the early induction of remission may change the course of RA-disease.

Based on review of the published data, (Gaujoux-Viala et al, 2010; Gaujoux-Viala et al, 2014) EULAR recommendations for the management of RA have suggest that in DMARD-naïve patients, irrespective of the addition of GCs, synthetic DMARD monotherapy rather than combination therapy may be applied with following tight control and monitoring of therapy response. Where disease control is not achieved with the first line DMARD, switching to an alternative DMARD strategy should be considered in the absence of poor prognostic factors, while addition of a biological DMARD should be considered when poor prognostic factors are present (Smolen et al, 2014*).

7.3.5 Biological DMARD therapy

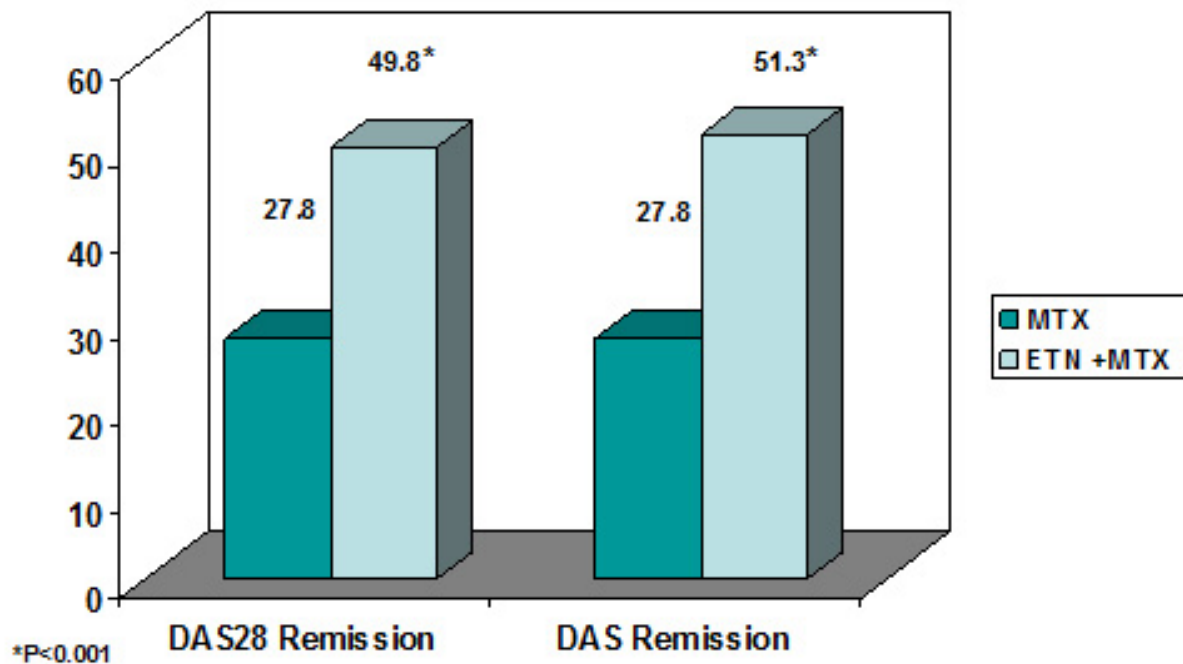
There is strong evidence in favour of traditional synthetic DMARDs combined with a remission induction scheme of glucocorticoids to achieve adequate efficacy in controlling early RA with good safety and feasibility in daily clinical practice. However, an alternative approach to treating DMARD-naïve patients with early arthritis is to target the subgroup of patients with moderate-to-severe, active, progressive RA and poor prognostic markers with a biological agent in combination with MTX.

Several RCTs in patients with early RA have shown an increased rate of inducing and sustaining clinical remission, improved physical function and slowing of radiographic progression with a TNF inhibitor in combination with MTX, compared with MTX monotherapy (Genovese et al, 2002; St Clair et al, 2004; Quinn et al, 2005; Breedveld et al, 2006; van der Heijde et al, 2010; Smolen et al, 2011; Kavanaugh et al, 2013; Emery et al, 2016). In patients offered early combination therapy, it has been shown dissociation between clinical and structural outcomes when even in cases in which clinical activity was not optimally suppressed, radiographic progression appeared to be significantly retarded (Smolen et al, 2005).

In the Combination of Methotrexate and etanercept study (COMET) (Emery et al, 2008), the first major study looking at remission as the primary endpoint in patients with early RA, patients with symptom duration of ≤ 2 years were randomized to receive MTX or MTX and etanercept for a year. At week 52, remission defined as DAS28 < 2.6 , was achieved in 50% of patients receiving etanercept + MTX vs 28% of patients receiving MTX alone ($p < 0.001$) (figure 10). Regardless of disease duration, no radiographic progression was seen in 80% of patients with etanercept + MTX. In contrast, a higher proportion of very early RA (≤ 4 months symptom duration) showed no radiographic progression compared with early RA (> 4 months and < 2 years) patients

treated with MTX (74% vs 50%) (Emery et al, 2012). This suggests that early suppression of disease activity is important to prevent damage in early arthritis and could be reached with a conventional DMARD as MTX.

Figure 10 Percentage of patients achieving 28-joint count Disease Activity Score (DAS28) remission (primary endpoint) and DAS remission at week 52 in the groups receiving methotrexate (MTX) versus MTX plus etanercept (ETN). (Reproduced with permission from Emery et al, Lancet 2008;372:375–82.)

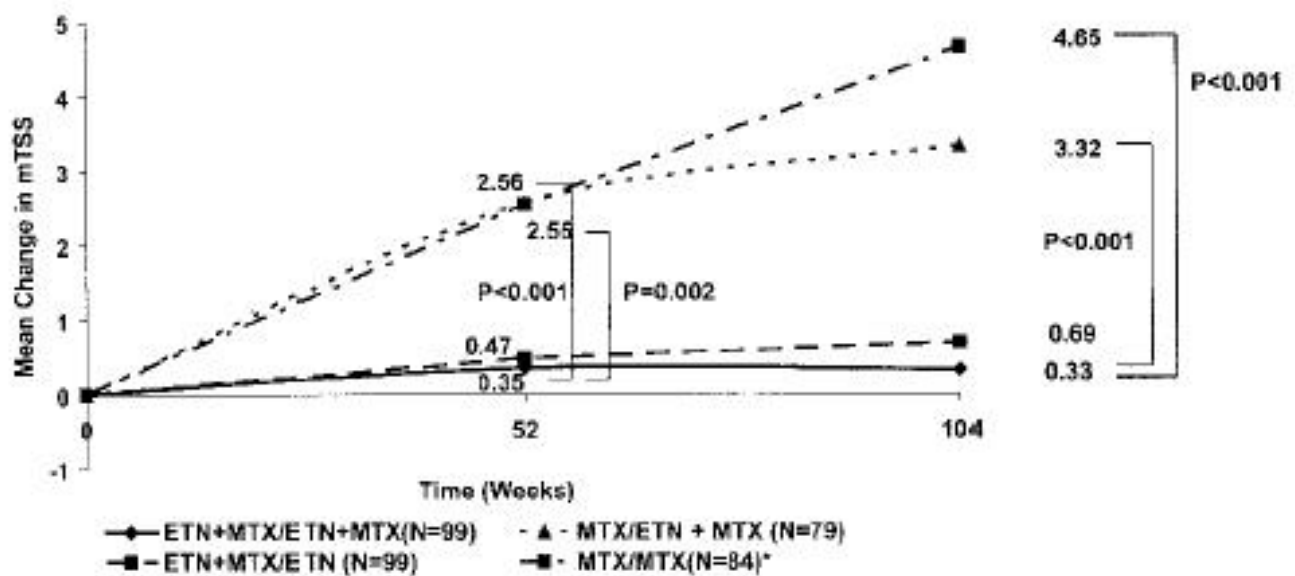


During the second year, patients in the MTX group were randomised to receive MTX (M/M) alone or MTX + etanercept (M/EM) and those in the MTX + etanercept group to continue with combination therapy (EM/EM) or to receive etanercept alone (EM/E). At year 2 clinical outcomes were better in the groups that received etanercept compared with the group receiving MTX alone. DAS28 remission was achieved in 62/108 (57%) and 51/88 (58%) of the EM/EM and M/EM groups, which was significantly greater than that in the M/M group 35%, ($p<0.05$, but not significantly greater than that in the EM/E group, 50%). Radiographic progression was also lower in those patients who received etanercept with the lowest rate of progression seen in the groups treated with etanercept early (figure 11) (Emery et al, 2010c).

Similar radiographic benefits have been shown in other RCTs in patients with early arthritis receiving non-anti-TNF biologic DMARDs (Nam et al, 2014a; Smolen et al, 2015). A double-blind, placebo-controlled study of abatacept in patients with ACPA-positive UA/very early RA (not fulfilling ACR criteria for RA), suggests that in some patients it is possible to change the natural history of the disease and alter the progression of RA by modulating T-cell responses at a very early stage of disease. In this study the patients were randomised to abatacept or placebo for 6 months (Emery et al, 2010b). Delayed progression to RA (by ACR criteria) at 1 year was found in the abatacept group, thus, 46% abatacept-treated versus 67% placebo-group patients developed

RA. A favourable effect was also shown on radiographic and MRI inhibition in the abatacept group. Of note, use of DMARDs and biological agents in patients with early undifferentiated disease is not established but is an area of growing research.

Figure 11 Radiographic progression over 2 years. Mean changes in modified Sharp/van der Heijde total score (mTSS) from week 0 to week 104, based on the last observation carried forward analysis. ETN, etanercept; MTX, methotrexate. *One subject did not have a valid radiograph at week 52 but did at baseline and week 106; changes from week 52 to week 104 cannot be assessed. (Reproduced with permission from Emery et al, *Arthritis Rheum* 2010;62:674–82.)



The biologic DMARDs provide rapid control of inflammation and have proven efficacy on clinical outcomes and structural damage in early disease. They are, however, substantially more expensive than traditional DMARDs (Schoels et al, 2010b). Selecting patients with poor prognostic factors and tapering a biologic agent when the patient is in stable remission may improve this cost–benefit balance. So far there is no convincing evidence that very early treatment with first-line biologics increases the proportion of patients with early arthritis achieving clinical remission and drug-free remission in comparison to treat-to-target conventional therapy.

7.3.6 Induction with biological agents and maintenance with csDMARDs

Induction therapy with a biologic agent very early in the disease course followed by withdrawal of the biologic agent and maintenance with csDMARDs might also be a feasible approach to attain sustained good outcomes, but currently available data are not strong enough to allow for such a conclusion to be reached. This concept was introduced in a placebo-controlled study by Quinn et al (2005). The study showed that patients with early RA with poor prognostic factors treated with infliximab and MTX developed fewer MRI-detectable erosions at 12 months than patients treated with MTX alone. The functional and quality-of-life benefits obtained in patients treated with infliximab after 1 year was sustained at 2 years without further infliximab infusion.

The BeSt trial compared the use of four dynamic treatment strategies and examined the optimal treatment paradigms for early RA with symptoms <2 years. The four treatment strategies included a sequential monotherapy (strategy 1), step-up combination therapy (strategy 2), initial triple therapy with MTX, SSZ and high-dose prednisone (strategy 3) and initial combination therapy with infliximab + MTX (strategy 4), all followed by targeted treatment adjusted at 3-monthly intervals aiming at low disease activity DAS of ≤ 2.4 (Goekoop-Ruiterman et al, 2005). The two groups with initial intensive treatment (strategies 3 and 4) showed a more rapid clinical response, a better radiographic outcome and required fewer treatment adjustments, than groups 1 and 2, at 2 years. No significant differences in toxicity were noted between the groups.

After 5 years, 48% of patients were in clinical remission (DAS < 1.6). Of those, 46%, 51%, 65% and 81% of patients in groups 1–4 had achieved DAS <1.6 with the initial treatment. Of note, 14% were in drug-free remission, irrespective of initial treatment, and in years 2–5 annual progression was comparable across the groups (Klarenbeek et al, 2011). Further follow-up analysis from the BeSt trial showed that these effects persisted after 10 year follow-up (Markusse et al, 2016). 53% and 14% of patients were in remission and drug-free remission, respectively, without differences among the strategies; and radiographic damage was limited for all strategies. The authors conclude that initial (temporary) combination therapy results in faster clinical improvement, and that targeted tight control treatment (all study strategies) determines long-term outcomes.

The clinical and radiographic outcomes of induction therapy with or without biologics in early RA have been assessed in the OPERA randomized trial (Optimized Treatment Algorithm for Patients With Early Rheumatoid Arthritis) (Hørsley-Petersen et al, 2015). The patients were randomized to receive adalimumab or placebo added to treat-to-target strategy with MTX and intra-articular triamcinolone during the first year. SSZ and HCQ were added if disease activity persisted after 3 months. During year 2, synthetic DMARDs continued and adalimumab was stopped. Addition of adalimumab did not increase the proportion of patients who reached the DAS28-CRP < 3.2 treatment target. One year after adalimumab withdrawal, treatment profiles, clinical responses and radiographic progression did not differ between groups. Thus, treat-to-target strategy in early RA provided excellent 2-year clinical and radiographic disease control independent of adalimumab induction therapy.

7.3.7 Tapering of therapy in early RA

During last years, the concept of early intervention with methotrexate and biological DMARDs for early arthritis allowing drug discontinuation after achieving remission has emerged. There are however, no current recommendations on implementation of this concept in daily clinical practice.

The possibility of achieving drug-free remission after 1 year after early remission induction treat-to-target steered therapy was analysed within the IMPROVED study in patients with undifferentiated arthritis or early RA (Wevers-de Boer et al, 2015). The patients started treatment with MTX + high dose prednisone. Those

patients who achieved remission 44/53 joints DAS < 1.6 after 4 months (early remission), tapered prednisone to zero, and those still in remission after 8 months tapered MTX to zero by protocol. After 1 year of remission-steered treatment, 32% of the patients who had achieved early remission after 4 months were able to taper medication and achieved drug-free remission. No baseline characteristics were independently associated with achieving drug-free remission at 1 year, but remission was less often sustained in ACPA-positive patients.

Early suppression of disease activity in early arthritis patients may result in drug-free remission and prevent damage. In the following analysis from the IMPROVED study, 2-year clinical and radiological outcomes of two DAS-remission-steered treatment strategies were assessed (Heimans et al, 2016). Patients in early remission DAS < 1.6 after 4 months tapered and stopped medication. Patients who did not achieve early DAS-remission after 4 months were randomized to either MTX + SSZ + HCQ + low dose prednisone (arm 1) or to MTX + adalimumab (arm 2). At 4-monthly intervals, medication was tapered and stopped if DAS was < 1.6 but restarted, increased or switched if DAS was ≥ 1.6 . Patients who achieved early remission more often achieved drug-free remission after 2 years (29% of patients) than patients who needed additional treatment steps in the randomization arms (7% and 9% in the arms 1-2), and more patients with undifferentiated arthritis than with RA achieved drug-free remission (34% vs 19%). However, disease activity and radiologic damage progression in all patients were well suppressed. A matrix model predicting rapid radiological progression based on risk factors identified in recent onset active RA (1987 criteria) performed poorly in recent onset RA (2010 criteria) and undifferentiated arthritis. It suggests that known risk factors for damage progression (baseline CRP, erosion score, autoantibody status, and initial treatment choice) lose their impact with early remission steered treatment tapering and even stopping of DMARDs is thus feasible, and drug-free remission is achievable in a subset of patients.

With early and intensive treatment many patients with early RA attain remission. Tapering conventional synthetic DMARDs in patients with early RA in sustained remission has been addressed in the tRECH trial (the Rotterdam Early Arthritis Cohort) (Kuijper et al, 2016). Patients were randomised to initial treatment with triple DMARD therapy GC bridging or MTX monotherapy with GC bridging. Patients were evaluated every 3 months. In case DAS was > 2.4 treatment was switched to a TNF-blocker. In case DAS < 1.6 at 2 consecutive time points, tapering was initiated according to protocol. During 2 years of follow-up, 57% of patients achieved sustained remission regardless of initial treatment strategy. Flare rates (medication increase after tapering) were 41% and 37% within 12 months in patients tapering conventional DMARDs and TNF-blockers, respectively. In this trial, after flare, only 65% of patients tapering conventional DMARDs re-achieved remission within 6 months after treatment intensification.

The effects of reduction and withdrawal of treatment has been addressed in early DMARD-naïve active RA, who had a remission while receiving etanercept+MTX therapy, in the PRIZE study (Productivity and remission in a randomized controlled trial of etanercept vs, standard of care in early rheumatoid arthritis) (Emery et al,

2014). All patients received 50 mg of etanercept +MTX weekly for 52 weeks (open-label phase). More than 60% of the patients achieved remission DAS28 < 2.6 at weeks 39 and 52 and were randomized to receive 25 mg of etanercept+ MTX (combination-therapy group), MTX alone, or placebo for 39 weeks (double-blind phase). Patients who had qualifying responses at week 39 of the double-blind phase had all treatment withdrawn at that time and were followed to week 65 (treatment-withdrawal phase).

More patients in the combination-therapy group than in the MTX alone group or the placebo group had sustained DAS28 remission < 2.6 at weeks 76 and 91 (double-blind phase) in 63% vs 40% vs 23%, respectively. Although more than half of the patients maintained remission while tapering, withdrawal of etanercept was possible in less than half of the patients and complete withdrawal of DMARDs only in one-quarter of the patients (44% who had received combination therapy, 29% who had received MTX alone, and 23% who had received placebo were in remission). These results imply that the level of treatment reduction is associated with the relapse rates. Continuing combination therapy at a reduced dose resulted in better disease control than switching to MTX alone or placebo, however, many patients in the MTX alone group and in the placebo group were in remission by the end of the study and no significant between-group difference was observed in radiographic progression.

An analysis from the BeSt trial, comparing patients who received initial infliximab treatment (strategy 4) with patients receiving infliximab at a later stage (strategies 1–3), showed that 56% of patients in group 4 were able to successfully stop infliximab compared with only 15% in the other groups at 2 years. This suggests that by achieving early remission within the ‘therapeutic window of opportunity,’ patients may require less treatment later on in the disease course (Castro-Rueda et al, 2008). Moreover, the BeSt study also showed the sequence of DMARD tapering by demonstrating that re-initiation of the last DMARD regimen prior to tapering can restore remission in case of disease relapse.

Several other studies have examined the potential for stopping biological DMARD treatment after achieving low disease activity in early RA. In the OPTIMA study (Optimal protocol for treatment initiation with methotrexate and adalimumab) patients with early RA were randomized to receive MTX or adalimumab+MTX (Smolen et al, 2014). Patients in the adalimumab+MTX group who achieved the stable low disease activity target DAS28-CRP<3.2 at weeks 22 and 26 were randomized to adalimumab-continuation or adalimumab-withdrawal for an additional 52 weeks. Although a high proportion of patients who achieved low disease activity target at 6 months with adalimumab +MTX were able to maintain low disease activity after withdrawing of adalimumab, 91% vs 81%, and to maintain remission, 86% vs 66%. Thus, even if numerically somewhat different, outcomes were much the same whether adalimumab was continued or withdrawn in patients who initially responded to adalimumab + MTX. On the other hand, 18% of OPTIMA study patients had radiographic progression, which may indicate that some patients had not achieved full disease control entering withdrawal phase as a therapy target of DAS28-CRP-low disease activity was applied after rather

short period time (6 months) and reassessed over 4 weeks with the possibility that the therapy target was not sustained.

Also studies in early RA, when remission was achieved with non-anti-TNF biologics in combination with MTX, examined withdrawal of a biologic agent. The AVERT trial (Assessing Very Early Rheumatoid arthritis Treatment) (Emery et al, 2015) showed that abatacept + MTX demonstrated robust efficacy compared with MTX alone in early RA (<2 years of symptom duration) with a good safety profile. Patients who reached remission DAS28-CRP<2.6 (no minimal duration required) at month 12, entered a 12-month period of withdrawal of all RA therapies. While 61% and 42% of the patients reached remission in the abatacept+MTX and MTX alone groups, only 15% and 8% of the patients maintained remission at 12 and 18 months following treatment withdrawal. The high relapse rate in this study may be attributed to the fact that the study included patients with poor prognostic markers (a relatively long symptom duration, ACPA-positive and mainly RF-positive) and that all therapies, i.e. both abatacept and MTX, were rapidly stopped, further, a sustained remission was not ensured before therapy withdrawal, thus, tapering of the drugs may have been initiated too early.

These recent studies provide evidence for the rationale for the use of early intensive induction-treatment strategies with the potential to de-escalate induction-treatment when targeted disease control is achieved, and subsequently to taper maintenance-treatment when remission is sustained.

7.3.7 Treatment strategies: practical points

- Non-pharmacological and lifestyle measures form part of the treatment strategy. Of these, smoking cessation and weight reduction in obese patients are known factors that have effect on response to anti-rheumatic treatment and disease outcomes, apart from lowering cardiovascular risk, and should therefore be strongly encouraged.
- Early institution of effective treatment is the cornerstone of treatment for early arthritis. Treatment delay may be considered (if at all) only in those with very mild disease <3 months from onset. A single dose of IM steroid therapy may be advocated in this group. Arthritis that is persistent for >12 weeks is unlikely to resolve spontaneously (Quinn et al, 2003): many of these patients will progress to develop RA. DMARD treatment should be started in all patients with early arthritis in whom the disease is likely to develop into a persistent and/or erosive arthritis classifiable as RA.
- Consideration of the risk–benefit ratio and the cost-effectiveness of these strategies suggests that a reasonable course of action in early arthritis should be initial conventional synthetic DMARDs with NSAIDs and steroids as adjunctive treatment. In most cases MTX is the first preferred DMARD. Other csDMARDs—for example, sulfasalazine and leflunomide, are suitable alternatives.

- In DMARD-naïve patients with significant disease activity and risk factors for poor prognosis - for example, high titre RF or ACPA, early use of a more intensive strategy i.e. triple therapy or combination therapy of MTX and a biological agent might be considered.
- Induction of remission with a short-term treatment with a biological DMARD, maintenance with a conventional DMARD and subsequent drug de-escalation and discontinuation after achieving sustained remission is a potential therapeutic strategy for the future.

7.4 Monitoring of disease activity and achieving tight control

The objective of treatment is to achieve a state of low disease activity and ideally remission in order to prevent structural damage and long-term disability. Regular monitoring of disease activity is therefore necessary, increasing treatment if the disease is not controlled, and tapering treatment if the patient is in persistent remission. Imaging may assist with decisions about treatment decisions. The 'best' initial treatment may be less a matter of drug choice but more a matter of whether treatment target as defined by available scores as DAS28 <2.6 or DAS <1.6) are followed. It is not demonstrated if the treatment goal should be remission or low disease activity, but remission as the therapy target is suggested as the optimal goal. As patients may still have some continuing disease activity despite fulfilling the criteria for remission, ACR/EULAR have proposed and published two new definitions for application in RA clinical trials—summarised in box 4 (Felson et al, 2011).

Box 4 American College of Rheumatology/EULAR 2011 provisional definitions of remission for clinical trials

Boolean-based definition

At any point, a patient must satisfy all of the following:

Tender joint count ≤ 1

Swollen joint count ≤ 1

CRP ≤ 1 mg/dL

Patient global assessment ≤ 1 (on a 0–10 scale)

Index-based definition

At any point, a patient must have SDAI ≤ 3.3

CRP, C-reactive protein; SDAI, Simplified Disease Activity Index.

Reproduced from Felson et al, *Ann Rheum Dis* 2011;70:404–13.

In the TICORA (Grigor et al, 2004) ('tight control in RA') study, 110 patients with RA of <5 years' duration were randomly assigned to an intensive treatment in order to reach a low activity state (DAS44 < 2.4) close to remission, or to regular clinical care. Patient in the TICORA group were examined monthly and DMARD treatment was escalated according to a predefined strategy if the DAS44 was >2.4. Those in the group receiving routine care were seen every 3 months without formal assessment or feedback on disease activity scores and treatment adjusted according to the clinical judgement of the rheumatologist. The group receiving intensive treatment had significantly more remissions and developed less radiographic damage than the control group after 18 months of follow up. This strategy also resulted in higher treatment retention rate, a

lower rate of discontinuations due to side effects and lower costs per patient (based on lower admission costs) than routine care over the 18 months of observation. Of note, however, more intra-articular steroids were used in this treatment group.

The CAMERA (computer-assisted management of early RA) trial (Verstappen et al, 2007) also showed that monitoring and intensive treatment tailored to the individual patient are more beneficial than routine care. Of all, 299 patients with early RA were randomised to receive intensive or routine treatment with oral MTX. If necessary, treatment was changed to subcutaneous MTX and cyclosporine was added to achieve disease control if patients had an inadequate response to maximal tolerated MTX doses. Patients in the intensive treatment group were seen more frequently in clinic and dosages were adjusted based on predefined criteria and tailored to achieve remission using a computer-assisted programme. At 2 years, more patients in the intensive-management group achieved sustained remission for at least 3 months than in the routine care group (50% vs 37%). There was a better clinical effect nearly in all clinical variables for the intensive treatment group compared with the conventional treatment group (ESR, EMS, VAS for pain and general wellbeing, swollen and tender joint counts). In the intensive strategy group 50% of patients achieved at least one period of remission during the two year trial, versus 37% in the conventional strategy group. Patients in the intensive-management group also used fewer NSAIDs than those receiving routine care. However, a large proportion in the routine group also achieved excellent outcomes, illustrating that the intensive strategy is not necessary in every individual patient.

Results of the BeSt study (Behandel-Strategieën), showing good long-term clinical outcomes in all patients irrespective of the initial treatment strategy and sustained clinical and functional benefit as well as favourable survival prognosis, reinforce the importance of early intervention and treat-to-target steered treatment of early RA (Klarenbeek et al, 2011; Markusse et al, 2016). With evidence for the benefit of tight control (Fransen et al, 2005; Saunders et al, 2008; Schoels et al, 2010a), increasing numbers of clinical trials have incorporated treat-to-target approaches when examining optimal therapeutic strategies for patients with RA (Bakker et al, 2012; de Jong et al, 2014; Heimans et al, 2014; Nam et al, 2014b).

Regular monitoring of disease activity and adverse events should guide decisions on choice and treatment adjustment when necessary. This includes both conventional synthetic and biological DMARDs. Monitoring of disease activity should include tender and swollen joint count, patient's and physician's global assessment, ESR and CRP. Arthritis activity should be assessed at 1–3-month intervals, for as long as the target (remission) has not been achieved. Structural damage should be assessed by X-ray examinations about once a year for the first few years. Functional assessment, eg, the HAQ score, can be used to complement the disease activity and structural damage monitoring (Smolen et al, 2010*).

Recommendations for the management of early arthritis are summarised in box 5.

Box 5 EULAR recommendations on the management of early arthritis

1. Arthritis is characterised by the presence of joint swelling, associated with pain or stiffness. Patients presenting with arthritis of more than one joint should be referred to, and seen by, a rheumatologist, ideally within 6 weeks after onset of symptoms.
2. Clinical examination is the preferred method for detecting synovitis. In doubtful cases, ultrasound, power Doppler and MRI might be helpful to detect synovitis.
3. Exclusion of disease other than rheumatoid arthritis requires careful history taking and clinical examination, and ought to include at least the following laboratory tests: complete blood cell count, urine analysis, transaminases and antinuclear antibodies.
4. In every patient presenting with early arthritis to the rheumatologist, the following factors predicting persistent and erosive disease should be measured: number of swollen and tender joints, ESR or CRP, level of RF and ACPA, and radiographic erosions.
5. For patients at risk of developing persistent or erosive arthritis, treatment would be started with DMARDs as early as possible, even if they do not yet fulfil established classification criteria for inflammatory rheumatological diseases.
6. Patient information about the disease and its treatment and outcome is important. Education programmes aimed at coping with pain, disability and maintenance of work ability may be employed as adjunct interventions.
7. NSAIDs have to be considered in symptomatic patients after evaluation of gastrointestinal, renal and cardiovascular status.
8. Systemic glucocorticoids reduce pain and swelling and should be considered as adjunctive treatment (mainly temporary), as part of the DMARD strategy. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.
9. Among the DMARDs, methotrexate is considered to be the anchor drug, and should be used first in patients at risk of developing persistent disease.
10. The main goal of DMARD treatment is to achieve remission. Regular monitoring of disease activity and adverse events should guide decisions on choice and changes in treatment strategies (DMARDs, including biological agents).
11. Non-pharmaceutical interventions, such as dynamic exercises, occupational therapy and hydrotherapy, can be applied as adjuncts to pharmaceutical interventions in patients with early arthritis.
12. Monitoring of disease activity should include tender and swollen joint count, patient's and physician's global assessments, ESR and CRP. Arthritis activity should be assessed at 1–3-month intervals, for as long as remission is not achieved. Structural damage should be assessed by radiographs of hands and feet every 6–12 months during the first few years. Functional assessment (eg, HAQ) can be used to complement the disease activity and structural damage monitoring.

ACPA, antibodies to citrullinated peptide; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor.

Reproduced from Combe et al, Ann Rheum Dis 2007;66:34–45.*

8 Further research

Areas for further research include:

- The development and validation of diagnostic tests and strategies that enable general practitioners to recognise patients with clinically suspect arthralgia and early forms of arthritis as soon as possible and refer these patients to the rheumatologist
- The diagnostic and therapeutic strategies in the preclinical phase of RA
- The therapeutic strategies in early UA which could prevent development of RA
- The development of treatment regimens which can be subsequently tapered to induce drug-free remission
- The comparative effectiveness and cost-effectiveness of different therapeutic strategies.

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SUMMARY POINTS

- Early diagnosis and treatment can prevent or delay the joint destruction, functional impairment and mortality associated with rheumatoid arthritis (RA).
- Early recognition of an inflammatory arthritis is therefore imperative.
- Patients with an inflammatory arthritis should be referred as early as possible to a rheumatologist for further management.
- In the earliest stages the arthritis may be undifferentiated. A combination of clinical, imaging and laboratory measures allow differentiation of inflammatory arthritis and RA.
- Patients with RA or undifferentiated arthritis must be evaluated for the risk of disease progression and severity.
- Early effective treatment should be instituted for those at risk of developing persistent and/or erosive arthritis.
- Treatment includes both pharmacological and non-pharmacological options.
- In the management of early arthritis combination of regular monitoring and optimal treatment interventions are paramount to achieve the target of therapy (remission or low disease activity) and improve outcomes of the disease.

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EULAR on-line course on Rheumatic Diseases

Early arthritis: diagnosis and management

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IN-DEPTH DISCUSSION I

**Magnetic Resonance Imaging and Ultrasonography in
Early Arthritis**

The earlier inflammatory arthritis (IA) is detected, and treated, the better the long-term outcome in terms of damage and function. In the ESPOIR cohort, mean radiographic progression in patients with IA receiving very early therapy (within 3 months of diagnosis) was lower compared to those starting DMARDs later (0.8 units versus 1.7 units; $P = 0.033$, adjusting for disease specific and demographic factors influencing initiation of DMARD therapy).¹ Further benefit is obtained with regular monitoring of disease activity and rapid therapeutic adjustment to gain disease control. It is therefore important to have measures that are sensitive for the assessment of disease activity/function and monitoring of treatment in early arthritis.

Although conventional radiography (CR) is able to detect structural joint damage in patients with established disease, it is not sensitive for the detection of bone or soft tissue changes in the earliest stages.²⁻⁴ Newer imaging techniques, such as magnetic resonance imaging (MRI) and ultrasound have shown promise in this regard.⁵⁻⁸

Magnetic resonance imaging

MRI has several advantages compared to CR. It provides multi-planar images and is able to image a range of joint structures including synovium, tendons, tendon sheaths, entheses, ligaments, cartilage and bone with a high degree of resolution. Unlike CR, ionising radiation is not used.

Relative disadvantages include limited access to this imaging modality and high relative cost. The need for prolonged immobility can also present difficulties, especially for patients with much pain and stiffness. More recently, low-field dedicated extremity MRI units have been used⁹ with the advantages of lower costs, less claustrophobia and more comfortable positioning for patients. Its ability to detect synovitis however may be relatively low.¹⁰

Diagnosis

Synovitis, tenosynovitis and bone marrow oedema are features of inflammation seen on MRI. Histopathology and mini-arthroscopy have confirmed that these findings represent true inflammation.^{11,12} Bone oedema, which is a specific MRI finding, probably represents a cellular infiltrate within bone,¹³ occurs in various arthritides. It is common in early RA¹⁴ and is regarded as a precursor of erosions (see below). MRI detected tenosynovitis has also recently been reported as a feature commonly seen in early disease.¹⁵

Synovitis can be assessed using T2-weighted imaging, dynamic contrast-enhanced MRI or diffusion weighted imaging. Bone marrow oedema can be detected on fluid-sensitive sequences such as short-tau inversion recovery or T2-weighted fast-spin echo sequences. For detection of small bone erosions in the early erosive phase, T1-weighted MRI has demonstrated similar sensitivity to CT.¹⁶

More efficient MRI techniques come recently available for evaluating of bone marrow oedema. Thus, it has been shown that a shorter MRI protocol with T1 post-gadolinium chelate images (T1Gd) can replace T2-weighted images (T2).¹⁷

There is good evidence that MRI is a sensitive indicator of active disease.³ It is more sensitive than clinical examination for detecting synovitis.¹⁸ Erosions on MRI are also detected earlier on MRI than CR.¹⁹ These MRI findings may suggest that patients with undifferentiated arthritis have RA. In a cohort of patients with undifferentiated polyarthritis followed up over 2 years, MRI of the most symptomatic hand and whole-body scintigraphy correctly classified RA according to the 1987 classification criteria and non-RA in 39 of 41 patients.²⁰ The positive and negative predictive values for the development of RA of were 1.0 and 0.87 respectively. In another study assessing the diagnostic value of MRI, the presence of symmetric periarticular enhancement in the wrists, metacarpophalangeal or proximal interphalangeal joints increased the sensitivity for the clinical diagnosis of RA from 77% to 96%.²¹ In patients with UA, the presence of bone marrow oedema has been shown to increase the sensitivity of RA diagnosis (1987 classification) and use of DMARD therapy at one year compared to the 2010 ACR/ EULAR RA classification criteria, but the specificity was reduced.^{22 23} Findings were similar using MRI erosions.²³

Few studies have examined the use of MRI to differentiate RA from other arthritides. Although some small studies have shown that MRI signals of inflammation in RA are more frequent in the synovium than at the insertion of ligaments and tendons (entheses) with the converse being true for the spondyloarthropathies and early psoriatic arthritis, other studies have not found this to be sufficiently common to be of diagnostic use.²⁴ In a study of 179 patients with early arthritis, patients with RA according the 1987 classification criteria had higher scores for synovitis, tenosynovitis and bone marrow oedema than patients without RA. Patients who fulfilled the 2010 ACR/EULAR RA classification criteria but not ACR 1987 criteria for RA had less synovitis than patients who fulfilled both sets of RA criteria.²⁵ ACPA-positive patients had more bone marrow oedema than the ACPA-negative patients. For all MRI features, the predictive value for RA however was low, <50%. Whether this indicates a common pathology and thus low discriminatory ability between RA and other early arthritis by means of MRI remains to be determined.

Prognosis

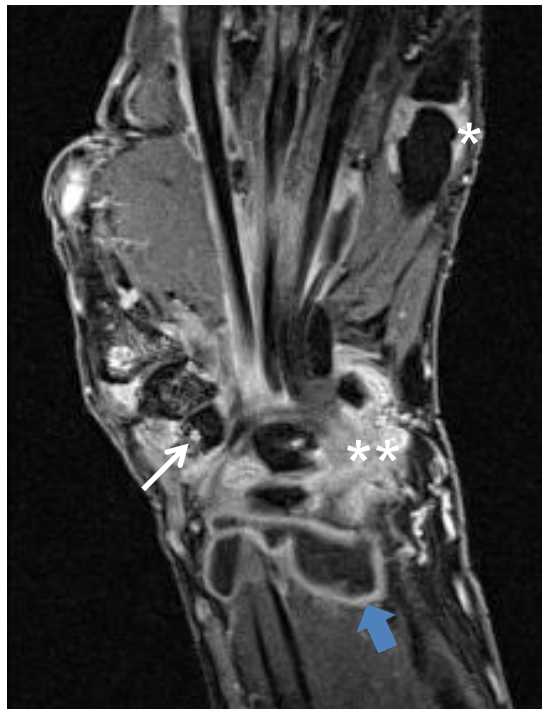
There is evidence that the presence of bone oedema in patients with UA is predictive of the development of RA.²⁶ In patients with RA, MRI-detected synovitis, and more specifically bone oedema, precedes the development of erosions; furthermore, in joints lacking synovitis / bone oedema, erosions are unlikely to develop.²⁷ MRI-evident erosions and bone oedema have also been shown to predict subsequent radiographic erosions.²⁸⁻³⁰

Imaging findings alone are not diagnostic. The recent study has evaluated the use of MRI as an imaging biomarker in patients with clinically suspect arthralgia but without clinical synovitis. MRI scans were performed on the unilateral wrist, MCP joints 2-4 and MTP joints 1-5 of 93 patients.³¹ MRI inflammation was defined by a combined RAMRIS score of synovitis, bone marrow oedema and tenosynovitis ≥ 3 . In total 44% of patients were found to have MRI inflammation. Patients with MRI inflammation were more frequently anti-CCP antibody positive than those without MRI inflammation. Of 29 patients with MRI inflammation who were followed, 10 (34.5%) developed overt arthritis within 4 months. In another study of 28 ACPA-positive arthralgia patients with three years of follow-up, MRI synovitis was found in the majority of patients (93%).³²

Monitoring

MRI has been used as an outcome measure in clinical trials. Changes in synovitis scores have been calculated following therapy^{33 34} with a differential reduction between treatment groups favouring more intensive treatment regimes. Studies have also shown that, despite clinical remission, MRI synovitis may persist.¹⁸ These findings suggest a possible role for MRI in monitoring response to therapy.

Figure 1 - Magnetic resonance imaging picture of the wrist of a patient with early rheumatoid arthritis.



*T1 3D VIBE with fat suppression sequence - coronal plane showing synovitis of the wrist. This is seen as a well-defined area of ring enhancement just proximal to the carpus (blue arrow). There are also diffuse hyperintense regions within the carpus (**). A small erosion can be seen in the scaphoid (white arrow). LMBRU, University of Leeds, U.K.*

Figure 2 – Images of the wrist of a patient with rheumatoid arthritis.



A. Conventional radiograph. B. Pre- and C. Post-contrast T1 3D VIBE MRI images with fat suppression – coronal plane

The scaphoid erosion is not seen on the conventional radiograph (A) or the pre-contrast MRI image (B) but can be visualised on the post contrast MRI image (C). LMBRU, University of Leeds, U.K.

Figure 3 - Magnetic resonance imaging picture of the knee of a patient with rheumatoid arthritis.



T1 3D VIBE fat suppression image in the sagittal plane showing the medial aspect of the femur and tibia with areas of bone oedema. These are seen here as hyperintense areas within the bone (arrows). LMBRU, University of Leeds, U.K.

Ultrasound

Rheumatologists increasingly use ultrasound as a part of their clinical practice. Advantages of US include the ability to image both bone and soft tissue structures without using ionising radiation, allowing for repeat testing. Ultrasound is also relatively rapid to perform, less expensive than MRI and allows dynamic assessment of multiple joints in multiple planes. The main drawbacks are the limited visualisation of some joints and the operator-dependant nature of the modality.

Diagnosis

Similar to MRI, several studies have shown that ultrasound is sensitive for the detection of synovitis and joint effusion. Use of the Doppler technique (power Doppler, PD) further assists in the detection of inflammation. PD³⁵ is particularly suited for assessing tissues with low velocity blood flow, such as the synovium. Findings of bone oedema on MRI scans correlate with grey scale or PD grade of joint synovitis or presence of US bone erosions,³⁶ thus, US findings of inflammation have proven reliability for detecting joint inflammation.

Ultrasound is also more sensitive than CR for detecting joint erosions in patients with arthritis. In one study 6.5 fold more metacarpophalangeal erosions were documented using ultrasound compared to CR in early RA.³⁷ The greater sensitivity relates to the multi-planar capability of ultrasound (compared to the two-dimensional image with CR) and its ability to detect smaller erosions.

The ultrasound-guided joint aspiration may be diagnostic and may help in differentiating septic or crystal arthritides from other form of inflammatory arthritis. Studies have suggested that ultrasound signs of inflammation are more frequent in the joint than at tendon insertions (enthesitis) in RA, whilst ultrasound features of enthesitis are more common in the spondyloarthropathies.^{38 39} Specific patterns of crystal deposition have been described in gout and calcium pyrophosphate crystal deposition disease^{40 41} and peritenon extensor tendon inflammation in psoriatic arthritis.⁴²

Prognosis

Ultrasound has been suggested to be of value in determining persistence of very early IA.⁴³ In a small study in RF and ACPA-negative patients with ≤ 12 weeks of inflammatory symptoms, the addition of clinical and radiographic features raised the probability of certainty of IA diagnosis/persistence of IA after 12 months from 6% to 30%, and additionally with certain ultrasound features the probability of IA rose to 94%.

Ultrasound measures of synovial thickening and vascularity at baseline have some correlation with future X-ray defined joint damage.⁴⁴ A study examining the progression of erosive disease in 21 patients with early RA has showed that, compared with CR (Sharp van der Heijde method), ultrasound detected 17-fold more joints with erosions at baseline (defined as cortical defects greater than 2 mm in diameter with an irregular floor) and 7.6-fold more joints with erosions after 6 months.⁴⁵ The detection of radiographic erosions is an essential diagnostic criterion in RA, and a valuable measure of prognosis and disease severity. Although US is more sensitive in establishing the presence of erosive joint disease, the prognostic value of US-detected erosions is unknown. Further, the specificity of US-detected erosions for diagnosis of RA, other arthritis and osteoarthritis is not clear.⁴⁶

A phase of preclinical RA, with rising titres of autoantibodies and suspect (inflammatory) arthralgia is now recognized. The role of ultrasound has also been evaluated in patients at risk for development of clinical arthritis. In anti-CCP positive individuals with new non-specific musculoskeletal symptoms but without clinical synovitis, tenderness of hand or foot joints, early morning stiffness ≥ 30 min, high levels of RF and anti-CCP autoantibodies, and positive PD strongly associated with progression to inflammatory arthritis, mostly within the first 12 months.⁴⁷ In another study examining the use of ultrasound in patients with RF-positive and/or anti-CCP positive arthralgia, ultrasound was found to be predictive of the development of IA at a joint level, but not at a patient level.⁴⁸

Monitoring outcomes

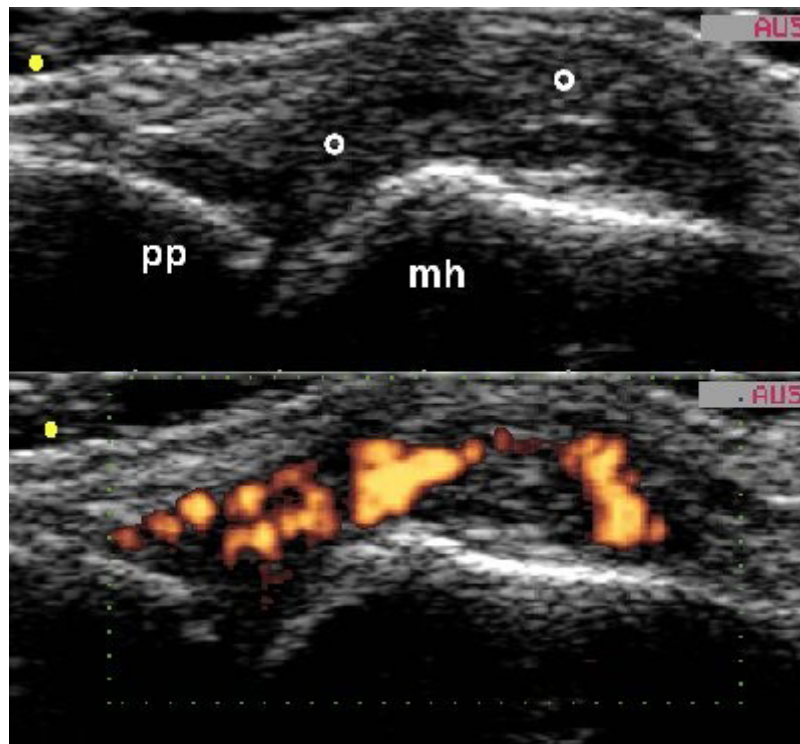
Ultrasound findings, in particular the presence of PD, are also found to be sensitive and reliable for longitudinal assessment of the inflammatory disease activity in early RA.⁴⁹ Some studies have shown that ultrasound synovitis may still be present in patients on DMARDs in clinical remission suggestive of subclinical inflammation that is not detected by clinical evaluation.^{50 51} However the randomised TaSER study in 111 patients with newly diagnosed RA or undifferentiated arthritis, followed for 18 months, has shown that ultrasound assessments, additionally used as a part of a treat-to-target treatment strategy, did not improve clinical or imaging (MRI and radiographic erosions) outcome in RA patients but led to significantly more treatment changes and more intensive treatment than DAS28-driven treatment strategy.⁵²

A systematic literature review and meta-analysis found US-detected synovitis to be prevalent in patients with RA in clinical remission.⁵³ Monitoring disease activity and remission, the time relationship between clinical and US findings is essential. However, so far the time-frame for these changes is not known. Interestingly, it has been reported that in clinical remission, DAS28<2.6, joints showing higher grey scale US-signals has significantly shorter time since last clinical swelling and positive US assessments as compared with those with lowered grey scale signals. A similar trend was shown with PD signals.⁵⁴

The presence of US findings is suggested to predict the relapse and progression of structural damage after discontinuation of treatment.⁵³ One of the recent studies has investigated the value of US for predicting a failure to taper a biologic agent in 42 patients with RA. Relapse rates were significantly higher in patients whose total ultrasound scores (grey-scale and PD scores in 40 joints) at discontinuation were high than in those whose total ultrasound scores were low, whereas the difference between DAS28 scores was not statistically significant. Positive and negative predictive values for the total grey-scale scores were 80% and 73%, and for the total power Doppler scores 89% and 74%, respectively.⁵⁵ In this study, residual synovial inflammation determined by US assessment predicted relapse within 6 months after discontinuing biological DMARD.

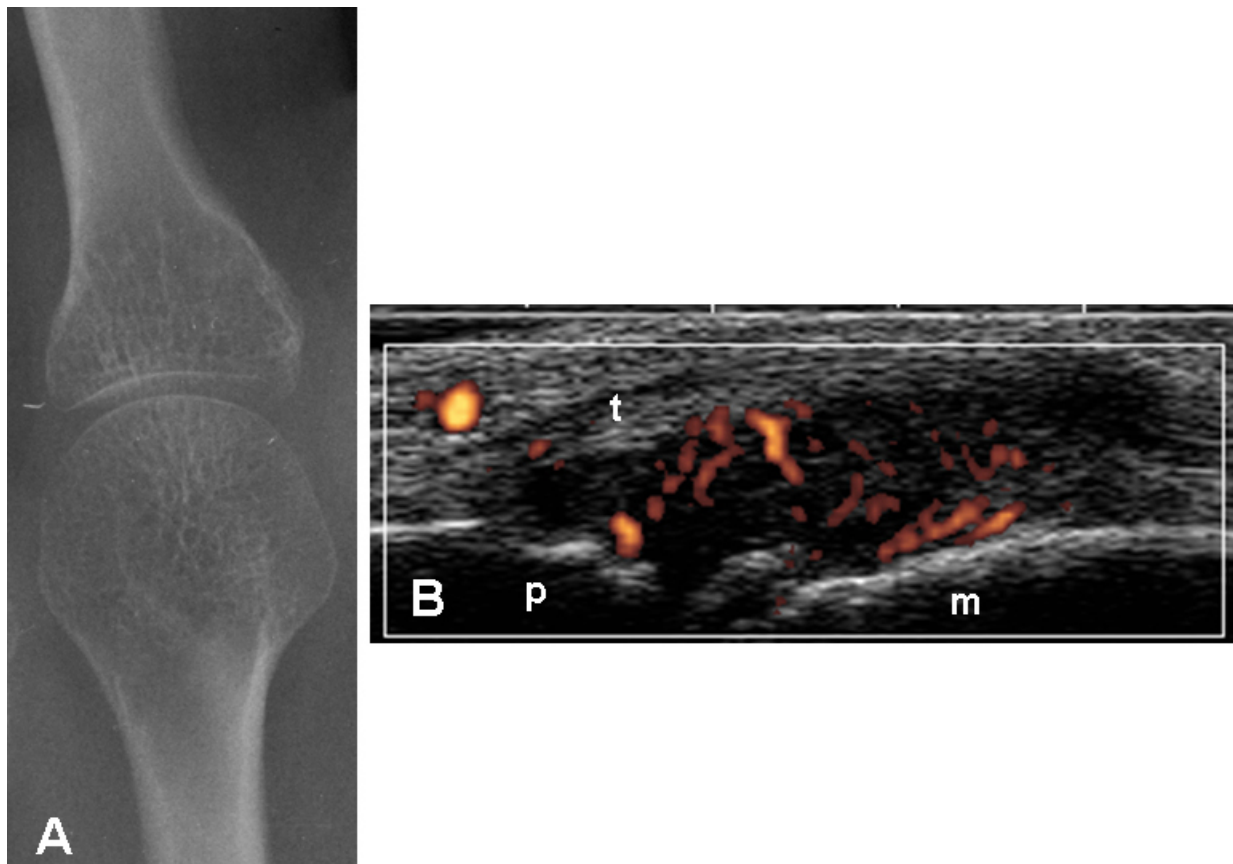
There are currently no standards on the optimal number and combination of joints to be assessed by US in daily practice. The time course relationship between anatomical, ultrasound and clinical changes is not defined which limits the value of US imaging for monitoring of disease activity/remission and response to treatments in arthritis.

Figure 4 - Longitudinal dorsal ultrasound scan of a metacarpophalangeal joint showing features of an inflammatory arthritis



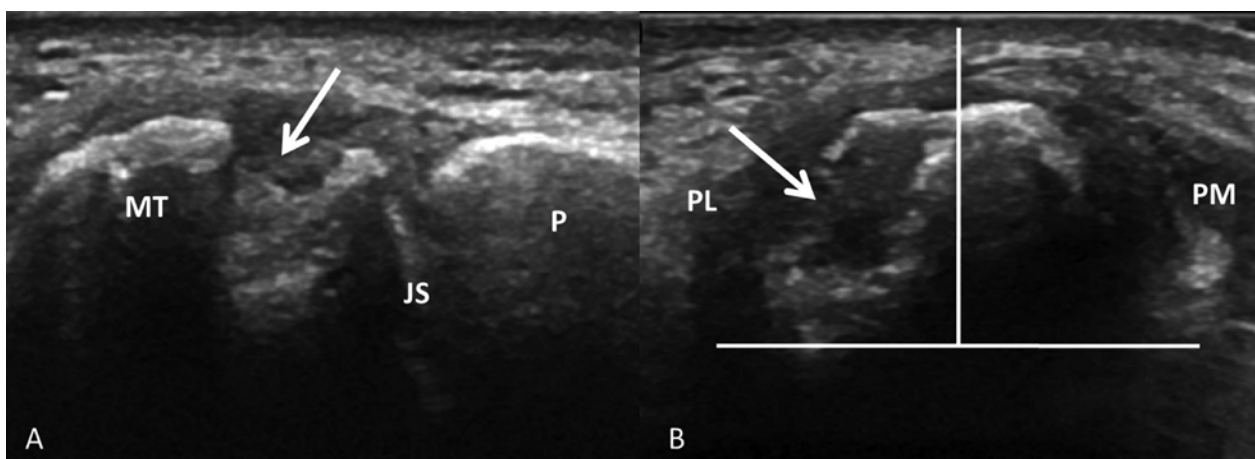
° = synovial hypertrophy, pp = proximal phalanx; mh = metacarpal head; pd = power Doppler. Ciapetti A, Filippucci E, Grassi W. Department of Rheumatology, University of Ancona, Italy

Figure 5: Imaging of the second metacarpophalangeal joint of a patient with rheumatoid arthritis. A. Conventional radiography shows juxta-articular osteoporosis. B. Ultrasonographic examination, in the longitudinal dorsal scan, reveals proliferative synovitis with marked intra-articular power Doppler signal.



m = metacarpal bone; **p** = proximal phalanx; **t** = extensor tendon

Figure 6: Erosion in (A) longitudinal view and (B) transverse view in 5th metatarsophalangeal joint.



PL, plantar lateral; PM, plantar medial; MT, metatarsal; P, Phalanx; JS, joint space.
Zayat A., LMBRU, University of Leeds, U.K.⁵²

In summary:

Accurate methods for the diagnosis, prognostic assessment and monitoring of treatment of early arthritis are essential. MRI and ultrasound are more sensitive imaging modalities than CR for visualising early inflammatory and destructive change in RA and predicting future radiographic damage. Relative high costs, long examination times and low availability, however, limit the widespread use of MRI. In comparison, ultrasound is relatively inexpensive, non-invasive and allows assessment of many joints. The main disadvantage of this modality is its dependency on the skills of the operator and potential problems with reproducibility. Table 1 shows a summary of some of the differences between the 3 imaging modalities.

The role of ultrasound and MRI in clinical practice and within clinical trial setting continues to grow (table 2). EULAR recommendations for the use of imaging modalities including CR, ultrasound and MRI of the joints in RA management have recently been published but the level of evidence is low (Table 3).⁵⁶ Therefore further research is ongoing to address various aspects of the role of these imaging modalities in assessment of early arthritis, including their role in the pre-clinical phase of the disease, differentiating early RA from other diseases and determining prognosis. So far imaging added to clinical assessment for monitoring of disease activity has not proven to be of benefit for the patient. Several studies are underway to determine whether targeting subclinical inflammation detected by MRI or ultrasound could improve outcomes in patients with early arthritis.⁵⁷

Table 1. Comparison of conventional radiography, MRI and ultrasound

	Conventional Radiography	MRI	Ultrasound
Tolerance	Excellent	Fair	Excellent
Ionizing radiation	Yes	No	No
Time to perform	Short	Long	Intermediate
Cost	Inexpensive	Expensive	Inexpensive
Ease of accessibility	Easy	Intermediate/difficult*	Easy- Difficult*
Operator dependant	No	No	Yes
Number of joints per session	Many	Few	Many
Planes	One	Multi	Multi
Real-time scanning	No	No	Yes
Bone visualisation	Good	Excellent	Good(cortex only)
Soft tissue visualisation	Non-specific	Excellent	Excellent
Allows intervention	Yes (fluoroscopy)	No	Yes

Table 2. Use of MRI and musculoskeletal ultrasound in the management of early arthritis in clinical practice and research

Diagnosis and classification of RA
Diagnosis of other inflammatory arthritides e.g. ultrasound guided joint aspiration for septic arthritis and gout
Predicting progression to RA in individuals at risk and in patients with UA
Determining treatment escalation as part of treat-to target strategies
Monitoring of disease activity on treatment
Predicting response to treatment
Determining treatment de-escalation in patients with RA in clinical remission

Table 3. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis⁵³

Recommendation*	SOR, mean VAS 0-10 (95% CI)	Level of evidence
1. When there is diagnostic doubt, CR, ultrasound or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone. †	9.1 (8.6 to 9.6)	III
2. The presence of inflammation seen with ultrasound or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis.	7.9 (6.7 to 9.0)	III
3. Ultrasound and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation.	8.7 (7.8 to 9.7)	III
4. CR of the hands and feet should be used as the initial imaging technique to detect damage. However, ultrasound and/or MRI should be considered if point (especially in early RA) conventional radiographs do not show damage and may be used to detect damage at an earlier time.	9.0 (8.4 to 9.6)	IV
5. MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic damage detected by conventional radiographs, MRI or ultrasound can also be considered for the prediction of further joint indicator. Joint inflammation (synovitis) detected by MRI or ultrasound as well as joint damage.	8.4 (7.7 to 9.2)	III
6. Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment.	7.8 (6.7 to 8.8)	III-IV
7. Given the improved detection of inflammation by MRI and ultrasound than by clinical examination, they may be useful in monitoring disease activity.	8.3 (7.4 to 9.1)	III

8. The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly ultrasound) is more responsive to change in joint damage and can be used to monitor disease progression.	7.8 (6.8 to 8.9)	III
9. Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed.	9.4 (8.9 to 9.8)	III
10. MRI and ultrasound can detect inflammation that predicts subsequent joint damage, even when clinical remission is present and can be used to assess persistent inflammation.	8.8 (8.0 to 9.6)	III

Recommendations are based on data from imaging studies that have mainly focused on the hands (particularly wrists, metacarpophalangeal and proximal interphalangeal joints). There are few data with specific guidance on which joints to image.

† In patients with at least one joint with definite clinical synovitis, which is not better explained by another disease.

Categories of evidence: Ia, evidence for meta-analysis of randomised controlled trials; Ib, evidence from at least one randomised controlled trial; IIa, evidence from at least one controlled study without randomisation; IIb, evidence from at least one other type of quasi-experimental study; III, evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies; IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

CR, conventional radiography; RA, rheumatoid arthritis; SOR, strength of recommendation; VAS, visual analogue scale (0-10; 0=not recommended at all, 10=fully recommended).

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module

EULAR on-line course on Rheumatic Diseases

Early arthritis: diagnosis and management

Sofia Ajeganova, Anca I. Catrina, Tom W.J. Huizinga

A previous version was co-authored by Jackie Nam, Anca Catrina, Paul Emery



IN-DEPTH DISCUSSION II

Pathogenic mechanisms at disease onset in early arthritis

The outcome of early, undifferentiated inflammatory arthritis may be one of spontaneous remission or persistent disease. If the latter, it may remain undifferentiated, or progress to rheumatoid arthritis (RA) or another distinct rheumatic disease. While mechanisms of self-limiting disease are poorly understood, new insights into the development of persistent disease - in particular anti citrullinated proteins antibody (ACPA)-positive inflammatory arthritis - have emerged in recent years.

The phases of development of seropositive RA-disease are described as seroconversion, antibody maturation, disease onset and disease outcomes.

The first insights in the pre-clinical phases of RA came with the observation that ACPA are present several years before disease onset in the peripheral blood of patients who eventually develop RA (1,2). Findings in this pre-clinical phase will depend on several factors including the individual at risk, the stage at which the person presents and if imaging techniques, e.g. ultrasound (US) and magnetic resonance imaging (MRI) are used, which joints are evaluated. Patients therefore may be ACPA-positive but have no clinical or imaging joint involvement or they may be at the stage of imminent RA in which there may be imaging findings in the absence of clinical synovitis (3).

Arthralgia with or without synovitis in individuals being ACPA-positive provides a high risk for future development of RA (4,5). Changes in bone metabolism have also been described in ACPA-positive individuals who do not yet have arthritis (6).

The occurrence of these autoantibodies without clinical and or imaging signs of joint inflammation (7) in individuals at risk for RA poses an interesting question in terms of the primary site of RA pathogenesis and has given rise to the idea that the initial immune challenge might happen at sites other than the joint.

Epidemiologic findings have previously revealed a very strong association between smoking and development of ACPA-positive RA, with those being smokers and having two copies of the shared epitope (SE) having a relative risk of 21 (CI 11.0-40.2) of developing rheumatoid arthritis compared to a relative risk of 3.3 (CI 1.5-8.9) in those who never smoked and had no SE genes (8). In contrast, no such association was observed in ACPA-negative disease.

The composition of the immune response to citrullinated antigens has been studied intensively. It appeared that many different citrullinated protein antigens present in the synovial compartment can be recognized by ACPA. This is most likely a consequence of the cross-reactivity the ACPA response displays to citrullinated proteins. It is now also clear that the isotype usage and the citrullinated epitope repertoire recognized by ACPA expands before the manifestation of full-blown Rheumatoid Arthritis and that this goes hand-in-hand with a rise in ACPA-level. Next to ACPA, several other auto-antibody systems directed against other post-translationally modified proteins, such as proteins containing an homo-citrulline residu resulting from protein carbamylation, have been identified. By and large, the evolution of these auto-antibody systems in time

mimics the evolution of the ACPA-response, indicating that the break of tolerance underlying different auto-immune responses present in RA occurs before disease onset, with a further maturation of these responses shortly before- or concurrent with the manifestation of clinical symptoms (reviewed in Dekkers et al 2016) (9).

Very interestingly the association of HLA class II antigens was less frequently present in healthy ACPA positive twins than in twins with ACPA-positive RA (10), neither in healthy ACPA-positive Japanese people there is no association with HLA class II antigens. A similar observation has been made for the RA-protective HLA alleles (HLA-DRB1*13), which do not protect from ACPA-positivity in individuals without RA but protect against the maturation of the ACPA response (11). These findings suggest that genetic predisposition has a role in transition from ACPA-seroconversion to early arthritis. How HLA class II locus links to T-cell responses leading to evolution of RA has been discovered in the recent study. Citrullinated vinculin, present in the joints of ACPA (+) RA patients, was identified as an autoantigen targeted by ACPA and CD4 (+) T cells. (12) These T cells recognize an epitope with the core sequence DERAA, which is also found in many microbes and in protective HLA-DRB1*13 molecules, presented by predisposing HLA-DQ molecules. Moreover, these T cells cross react with vinculin-derived and microbial-derived DERAA epitopes, suggesting that a microbial infection is the initiator of ACPA maturation and hence development of RA. Intriguingly, DERAA-directed T cells were not detected in HLA-DRB1*13(+) donors, indicating that the DERAA epitope from HLA-DRB1*13 mediates (thymic) tolerance in these donors and explaining the protective effects associated with HLA-DRB1*13. These data indicate the involvement of pathogen-induced DERAA-directed T cells as the molecular basis in the HLA-RA association. Currently research is ongoing to identify such a microbial contributor to the pathogenetic event that takes place during the pre-clinical phase of ACPA-positive RA (12).

It has been suggested that certain immunologic events, in the context of a signal that breaks self-tolerance, with enhanced expression of citrullinated antigens in extra-articular tissues may trigger auto-immunity and lead to formation of pathogenic ACPA antibodies, and thus, initiate and/or mediate immunological response in RA. Thus, smoking leads to more citrullinated antigens and ACPA formation in the lungs (13).

Apart from the lungs, the oral (14) and gut microbial dysbiosis could mediate the break of self-tolerance leading to excessive protein citrullination. Several clinical and epidemiologic studies have suggested that periodontitis is more prevalent in patients with RA and that periodontitis could be a causal factor in the initiation and maintenance of the autoimmune inflammatory response in RA. However, the strength and temporality of this association are uncertain. The epidemiological evidence for the association between chronic periodontitis and ACPA-positive RA is weak. One of the most known aetiological agents of periodontitis is *Porphyromonas gingivalis*, a bacterium possessing its own peptidyl arginine deiminase. It is unclear if this bacterial can induce or mediate citrullination of proteins in the human gingiva. Studies in individuals at risk for developing RA have demonstrated different results regarding titers of anti *P. gingivalis* antibodies compared to healthy controls. Patients with RA might show an increased risk of developing periodontitis through various

mechanisms. Exposure to common genetic, environmental and behavioural factors might contribute to a non-causal association between both conditions. This remains however to be established whether citrullination process in the extra-articular tissues precedes evolution to RA, whether citrullination in the extra-articular tissues and joints of RA patients shares immune targets and whether these immune targets are auto-antigenic.

While studies of pre-clinical and early phases of ACPA-positive RA have led to the insights into the development of the disease, studies in ACPA-negative RA have not been as successful. This fact might have several explanations: 1) more than one disease phenotype within the ACPA-negative subset; 2) lack of serological markers to identify healthy individuals at risk and distinguish the patients with seronegative RA; 3) insufficient knowledge of genetic, environmental and immune factors responsible for seronegative RA-disease. Studies to address this subset of disease are needed. Further research should also focus not only on understanding of mechanisms of persistent disease but also on mechanisms of self-limiting arthritis.

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Pathogenesis and clinical aspects of rheumatoid arthritis

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LEARNING OUTCOMES

- ➔ Describe how environmental, genetic and immunological mechanisms interact in the pathogenesis of the disease
- ➔ Explain the relationship between undifferentiated arthritis and rheumatoid arthritis (RA)
- ➔ Describe the characteristic pattern of joint involvement in early and established disease
- ➔ State and describe the typical extra-articular manifestations
- ➔ Describe the most commonly used tests for assessment of disease activity and health-related quality of life
- ➔ Use this knowledge in diagnosis and assessment of RA

1 Pathogenesis of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that typically affects small and medium-sized joints symmetrically. The primary lesion is synovitis whereby immune cells invade the normally relatively acellular synovium, leading to the formation of inflammatory 'pannus'. This hyperplastic, invasive tissue causes cartilage breakdown, bony erosion and, ultimately, loss of function of the affected joint(s). Systemic involvement—for example, of the respiratory, cardiovascular and haematopoietic systems, may also occur. Consequently, the risk of atherosclerosis and lymphoma development is increased. Because of this, uncontrolled RA is associated with a reduction in life expectancy, which in some studies amounts to 6–7 years.

For the clinician, the striking heterogeneity of clinical presentation, natural history and drug responsiveness in RA means that it remains as challenging to manage as it is fascinating to study. This heterogeneity extends to a molecular level and, intriguingly, recent analyses of genetic risk factors, autoantibodies and drug responsiveness indicate that it may one day be possible to stratify the disease into prognostically and therapeutically meaningful subsets close to the time of symptom onset, permitting individually targeted treatments, with obvious benefits in clinical outcomes and cost. These ideals remain far off, however, but lie behind the need for an ever improved understanding of the pathophysiology of RA.

In this section, current and evolving concepts in RA pathogenesis are considered (figure 1). We focus on RA as a putative autoimmune disease, the role of autoantibodies in disease stratification and the associated genetic epidemiology. We summarise the molecular pathways involved, emphasising established and emerging therapeutic targets.

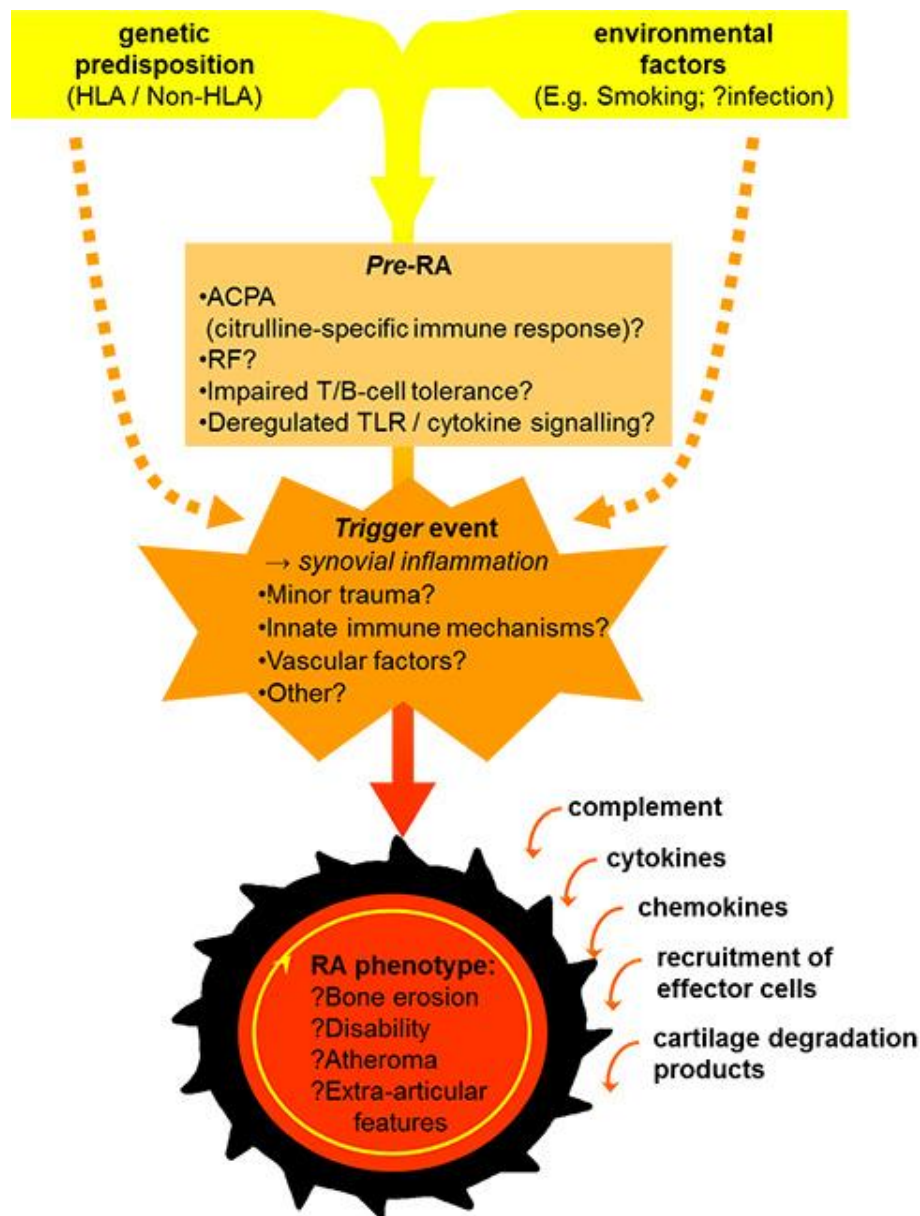
1.1 Epidemiology of RA

RA affects approximately 0.5–1% of European and North American adults, with considerable regional variation. Prevalence estimates for Southern European countries (median of 3.3 cases per 1000) are lower than for Northern Europe (5.0 per 1000) and highest rates are found in North America (10.7 per 1000) (Alamanos et al, 2006). Asian studies report between 2.8 and 3.5 cases per 1000, but the disease is said to be less common in rural Africa. In some Native American tribes up to 5% of individuals are affected.

Annual incidence rates are estimated to be 16.5 cases (per 105) in Southern Europe, compared with 29 in Northern Europe and 38 in North America (Alamanos et al, 2006). Women are about three times more frequently affected than men. The peak age of incidence for women is between 50 and 60 years and somewhat surprisingly for men is >70 years (Carbonell et al, 2008). RA presenting after the age of 60–65 is often referred to as late-onset RA or 'LORA'. It has long been documented that RA clusters in families: the likelihood that a first-degree relative of a patient will share the diagnosis is 2–10 times the population

prevalence of the disease, and recurrence risks are highest for relatives of the most severely affected index cases.

Figure 1 Schematic representation of factors relevant for the development of RA. Genetic and environmental determinants interact to create an adverse immune state in the predisposed individual, which may include the generation of circulating ACPA. When, how and why a 'trigger event' subsequently causes pathology to become focused in the synovium, is unknown, but it probably involves the innate immune system and further interaction of genetic and environmental factors. A self-perpetuating inflammatory cascade follows, producing the clinically recognisable, albeit heterogeneous, RA phenotype. ACPA, anti-cyclic citrullinated peptide antibodies; HLA, human leucocyte antigen; RA, rheumatoid arthritis; RF, rheumatoid factor; TLR, Toll-like receptor.



1.2 Autoantibodies: RA as an autoimmune disease

Witebsky postulated in 1957 that a disease must fulfil three criteria to be considered autoimmune in nature. A contemporary understanding of these postulates requires (1) the presence of autoantibodies or a cell-mediated immune response against an autoantigen, (2) that the respective autoantigen is known and (3) that a similar disease can be initiated in animals based on an analogous immune response (Witebsky et al, 1957; Rose and Bona, 1993). The status of RA as an autoimmune entity, while generally accepted, remains somewhat controversial based on these requirements. For example, although an array of antibodies targeting 'self' antigens (including collagen type II, calreticulin, cathepsin, BiP, CH65 and human collagen glycoprotein 39) has been described, the identity of a dominant arthritogenic autoantigen has remained elusive. Moreover, although inflammatory arthritis of autoimmune aetiology and with phenotypic similarities to human RA, may be artificially induced in animals (as in the example of collagen-induced arthritis), the direct relevance of such models to human disease has been difficult to demonstrate.

1.2.1 Rheumatoid factor

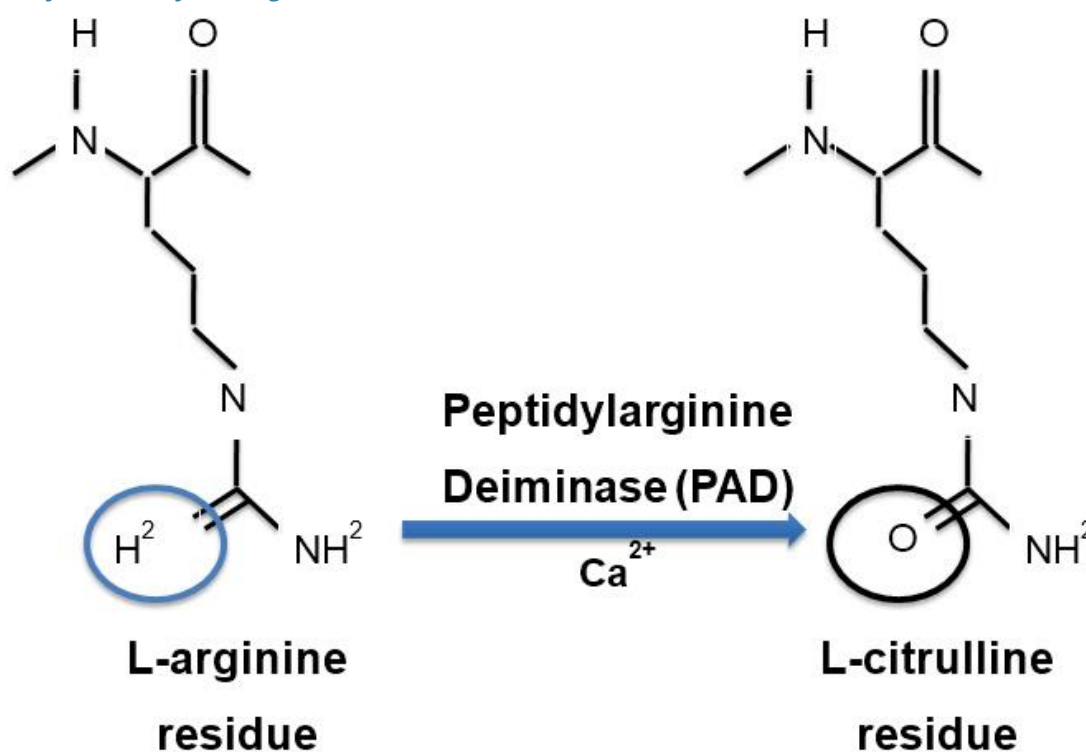
The initial notion that mechanisms of autoimmunity might underlie RA pathogenesis came from the discovery of autoantibodies targeting the Fc part of human IgG (so called 'rheumatoid factors' (RFs)) in the blood of affected patients (Franklin et al, 1957; Waaler, 2007). RFs, present mostly as IgM-RF, but detectable in subgroups of patients also as IgG-RF and IgA-RF, are thought to form immune complexes activating complement in the joint, which in turn leads to increased vascular permeability and the release of chemotactic factors recruiting immune-competent effector cells to the joint (Zvaifler, 1973). The mere presence of RFs, however, is insufficient to initiate arthritis development, as RFs are also found in infectious diseases, autoimmune diseases other than RA and in up to 15% of healthy, mostly elderly, individuals. Although the specificity of RF for diagnosis of RA is limited, raising the cutpoint for consideration of positivity to 50 IU increases its diagnostic test properties to those observable for ACPA (Nell et al, 2005; Nielen et al, 2005), i.e. providing a positive predictive value for RA in patients with early arthritis of >90%. For that reason the presence of RF was one of seven diagnostic criteria for RA put forward by the American College of Rheumatology in 1987 (Arnett et al, 1988*) and has also been included in the ACR/EULAR 2010 classification criteria for RA, particularly with additional credit for high positive RF levels (Aletaha et al, 2010).

1.2.2 Anti-citrullinated peptide antibody

Citrullination is a process by which arginine residues in a given protein are post-translationally modified ('deiminated') in the presence of high calcium concentrations by an enzyme called PAD (peptidylarginine deiminase) (figure 2). Citrullination is a physiological process, which is believed to be important for degradation of intracellular proteins during apoptosis. In 1998, two antibodies present in serum samples from patients with RA that had already been described years earlier (so called antiperinuclear factors, discovered in

1964 (Nienhuis and Mandema, 1964) and anti-keratin antibodies, first described in 1979 (Young et al, 1979) were found to share a common specificity for citrullinated filaggrin (Schellekens et al, 1998*; Girbal-Neuhauser et al, 1999). This observation placed citrullinated proteins at the centre of autoantibody research in RA. Citrulline-specific reactivities against a number of additional citrullinated proteins (eg, fibrinogen, vimentin and α -enolase) have since been identified. Using new assays that employ synthetic cyclic citrullinated peptides (CCP) as antigens, anti-citrullinated protein antibodies (ACPA) are found in 60–70% of patients with RA, with a high specificity for RA (van Gaalen et al, 2005). The extent to which ACPA are directly involved in RA pathogenesis is subject of continuing research.

Figure 2 Schematic representation of the enzymatic role of peptidylarginine deiminase (PAD) in the generation of citrulline from arginine residues.



Circumstantial evidence for their role in disease induction comes from observations that ACPA can be detected in sera several years before clinical onset of arthritis (Nielen et al, 2004), that their presence predicts progression from undifferentiated arthritis (UA) to RA (van Gaalen et al, 2004) and that they are associated with a more severe course of disease (Meyer et al, 2006). Longitudinal studies and studies in healthy relatives of ACPA-positive patients with RA have shown that the number of citrullinated epitopes recognised by ACPA increases during the development of RA (epitope spreading), that their avidity continues to increase until the onset of clinical disease (Suwannalai et al, 2012), and that the isotype repertoire of these autoantibodies concurrently expands (Ioan-Facsinay et al, 2008; Brink et al, 2013*). After diagnosis, however, the ACPA epitope recognition profile and the isotype repertoire remain remarkably constant. Interestingly, IgM-ACPA are detectable in samples from patients with early as well as longstanding RA, indicating that new antibody-secreting cells are continuously generated, which reflects an ongoing immune response (Verpoort et al, 2006).

Among the different ACPA specificities identified so far, citrullinated vimentin is identical to the previously described and highly RA-specific Sa antigen (Vossenaar et al, 2004). Specific mutations of vimentin have been detected in RA synovial fluid, and serum titres of antibodies targeting these mutated isoforms (called mutated citrullinated vimentin) correlate with disease activity (Bang et al, 2007). It is not clear if measurement of these autoantibodies will add value to CCP for diagnostic purposes in early arthritis (Mathsson et al, 2008; Raza et al, 2010).

Experimentally, elegant animal studies suggest that ACPA positivity may soon be said to define a subgroup of RA with a full set of 'autoimmune' credentials as originally defined by Witebsky (Kuhn et al, 2006; Hill et al, 2008; Uysal et al, 2009). Complementing these murine studies, additional data supporting ACPA pathogenicity come from in vitro experiments studying human ACPA. Human ACPA can activate complement by both the classic and the alternative pathway, and ACPA-containing immune complexes can induce tumour necrosis factor α (TNF α) production by human macrophages (Clavel et al, 2008; Trouw et al, 2009). The important influence of genetic and environmental factors on ACPA status in humans is outlined in detail below.

1.3 Genetic risk factors

Twin studies permit an estimation of heritability (the extent to which the likelihood of developing a condition in a population can be explained by genetic variation), and on the basis of studies in British and Finnish populations the heritability of RA has been calculated to be 60% (John et al, 1998). Many genetic variations that show an association with RA have been identified within the past few years owing to technical advances in genotyping and they are summarised here. Intriguingly, the majority of these associations apply primarily to ACPA-positive RA, being either absent or less robust for its ACPA-negative counterpart (table 1). Thus, there appears to be a genetic difference between ACPA+ and ACPA- patients, although the similarity of the clinical phenotype of disease and thus the clinical implications of this difference in genetic associations is currently still unclear. An important goal in the research of genetic contributions to RA is to investigate the specific functional role of each of the genetic variants. Functional roles have been described for only a handful of variants – some of them comprise increased susceptibility to developing RA and/or progressive disease, while others may even exert a protective effect. Furthermore, a growing interest has developed for genetic variants associated with efficacy and safety of medications used in RA. In addition to the efforts to describe the qualitative effect of each genetic factor, a quantitative approach is also required to assess the extent to which a genetic variant really contributes to a disease-related process. It should be taken into account that variants exerting a specific effect in one population may have almost no effect in another population (Chung et al, 2016).

For completeness, associations have been suggested for the following genes/loci listed in table 1. Most genetic associations have been shown for ACPA positive patients, while HLA-DRB1, PTPN22, STAT4, TNFAIP3, and IRF5 have been found also in ACPA negative patients.

Table 1 Genetic associations with ACPA-positive and ACPA-negative RA

<i>Gene/locus</i>	<i>Full name</i>	<i>Role of gene product</i>
HLA-DRB1	human leukocyte class II antigen	antigen presentation
HLA-DPB1	human leukocyte class II antigen	antigen presentation
HLA-B	human leukocyte class I antigen	antigen presentation
PTPN22	protein tyrosine phosphatase N22	regulator of T-cell receptor signaling
STAT4	signal transducer and activator of transcription 4	transcription factor
TNFAIP3	TNF α -induced protein 3	mediator of inflammation
BLK	BLK protooncogene	B-cell signaling and development
GIN1/C5orf30	gypsy retrotransposon integrase 1, chromosome 5 open reading frame 30	unclear
ANKRD55/IL6ST	ankyrin repeat domain 55/interleukin 6 signal transducer	signal transducer
PADI4	peptidyl arginine deiminase 4	converting arginine to citrulline
TRAF-1	TNF receptor associated factor 1	signal transducer
CTLA4	cytotoxic T-lymphocyte associated protein 4	inhibition of T-cells
KIF5A/PIP4K2C	kinesin family member 5A/phosphatidylinositol-5-phosphate 4-kinase type 2 gamma	intracellular microtubule motor
CCL21	C-C motif chemokine ligand 21	mediator of T-cell chemotaxis
CD28	cluster of differentiation 28	T-cell proliferation, Th2 development
PRDM1	PR domain 1	repressor of IFN- β expression

CD2/CD58	clusters of differentiation 2/58	T-cell surface antigen/adhesion of T-cells
IL2RA	interleukin 2 receptor subunit alpha	subunit of the IL-2 receptor
TYK2	tyrosine kinase 2	protein of the JAK kinase family
IRAK1	interleukin 1 receptor associated kinase 1	upregulator of NF-kappa-B
TLE3	transducin-like enhancer of split 3	role in the Notch pathway of cell development
RASGRP1	RAS guanyl releasing protein 1	regulator of T- and B-cell development
IL-6R	receptor of IL-6	cytokine receptor
IRF8	interferon regulatory factor 8	transcription factor
ARID5B	AT-rich interaction domain 5B	regulator of B-cell differentiation
IKZF3	IKAROS family zinc finger 3	regulator of B-cell differentiation
RUNX1	runt related transcription factor 1	development of haematopoiesis
POU3F1	POU class 3 homeobox 1	unclear
RCAN1	regulator of calcineurin 1	role in CNS development and dementia
CD5	cluster of differentiation 5	T-cell surface marker
GATA3	GATA binding protein 3	regulator of T-cell development
RBPJ	recombination signal binding protein for immunoglobulin kappa J region	regulator of the Notch pathway
CCR6	C-C motif chemokine receptor 6	B-cell maturation, T-cell migration
CD40	cluster of differentiation 40	receptor on antigen presenting cells
MMEL1	membrane metallo-endopeptidase-like 1	regulator of pain perception
AFF3	AF4/FMR2 family member 3	transcription factor in lymphoid tissue
REL	REL proto-oncogene, NF-kB subunit	regulator of immune response

DNASE1L3	deoxyribonuclease I like 3	mediator of apoptosis
IRF5	interferon regulatory factor 5	transcription factor
IL-2RB	interleukin 2 receptor subunit beta	subunit of the IL-2 receptor
DDX6	DEAD-box helicase 6	suppressor of translation
SPRED2	sprouty related EVH1 domain containing 2	regulator of the MAP kinase cascade
TAGAP	T-cell activation RhoGTPase activating protein	regulator of signaling pathways
PTPRC	protein tyrosine phosphatase, receptor type C	regulator of T- and B-cell antigen receptor signaling
PRKCQ	protein kinase C theta	T-cell and NF-kappa-B activation
FCGR2A	Fc fragment of IgG receptor IIa	Ig receptor involved in phagocytosis
IL-2/IL-21	interleukin 2 and 21	mediators of adaptive and innate immunity
TRAF-6	TNF receptor associated factor 6	signal transducer
UBE2L3	ubiquitin conjugating enzyme E2 L3	targets proteins for degradation
PTPN2	protein tyrosine phosphatase, non-receptor type 2	regulator of cell growth and differentiation
NKAPL	NFKB activating protein like	regulator of inflammation
CD247	cluster of differentiation 247	part of the T-cell receptor-CD3 complex

This table includes single nucleotide polymorphisms (SNPs) in genes and in genetic regions associated with ACPA-positive or ACPA-negative patients. Some genetic associations have been observed in both groups of patients with RA; however, the association is stronger with ACPA-positive RA for most SNPs. These association studies were performed in patients of European descent and some associations might not be relevant in other ethnic groups (eg, PTPN22 in an Asian population). Furthermore, associations with several other genes may be seen in the future years. The purpose of the list is to provide current information on genes predisposing to RA and to provide an overview of the biological role of their products.

ACPA, anti-cyclic citrullinated peptide antibodies; MHC, major histocompatibility complex; RA, rheumatoid arthritis.

1.3.1 HLA association

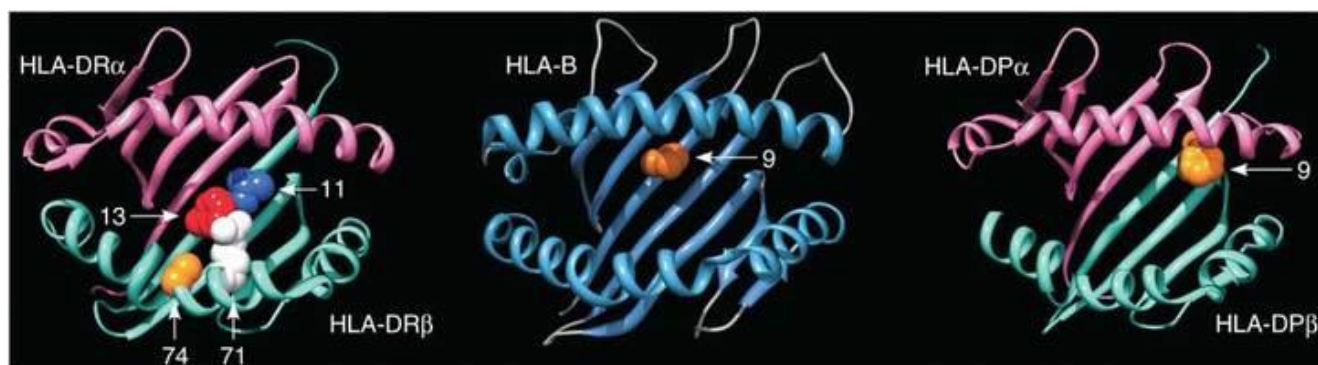
The strongest and most relevant genetic risk factor for the development of RA, contributing around 30% to the total genetic effect, is found in the HLA class II molecule-encoding locus (chromosomal position 6p21.3). Indeed, several HLA-DRB1 molecules (*0101, *0102, *0401, *0404, *0405, *0408, *1001 and *1402) sharing a common amino acid sequence at position 70–74 in the third hypervariable region of the DR β 1 chain have been associated with an increased risk of developing RA. This common amino acid sequence has been termed the ‘shared epitope (SE)’. Many studies underline the strong association between the SE and susceptibility to, as well as severity of, RA. Individuals heterozygous for the SE have more severe and erosive disease than SE-negative patients, an effect that is further increased by homozygosity. HLA-DRB1 SE homozygotes, whether simple (having two copies of the same allele) or compound, also have a higher risk of developing extra-articular disease manifestations, including vasculitis. But perhaps the most significant recent finding concerning the SE is the realisation that, rather than being a primary risk factor for RA itself, it represents first and foremost a risk factor for ACPA positivity (table 1) (Huizinga et al, 2005*), with these autoantibodies developing preferentially (but not exclusively) in patients that harbour one or two SE alleles. Importantly, the presence of two SE alleles does not induce higher ACPA levels than the presence of only one allele, indicating a dominant effect of the SE on the immune response (van der Helm-van Mil et al, 2006). A recent study examining the risk of developing ACPA-positive RA showed that the strength of association varied according to the different susceptibility HLA-DRB1 alleles, with HLA-DR1*0404, *0405, *0408 conferring the highest risk. Furthermore, individuals carrying two susceptibility HLA-DRB1 alleles had a higher risk than those with single dose genotype (Balandraud et al, 2013). Specifically, environmental exposures, such as smoking, show an interaction with SE haplotypes and may modulate the additional risk observed in homozygous carriers of SE alleles (Lee et al, 2014; Klareskog et al, 2009).

Recently, a large-scale association study in ACPA-positive patients with RA of European descent examining 3000 single nucleotide polymorphisms (SNPs) across the major histocompatibility complex (MHC), showed that the strongest signal mapped to amino acid 11 of HLA-DRB1. After accounting for the effect of amino acid 11, an independent association was also found with two amino acids within the shared epitope sequence (amino acids 71 and 74) (Raychaudhuri et al, 2012). These results were confirmed in another study using a high-density genetic mapping with testing of more than 129 464 SNPs (Eyre et al, 2012).

Two other SNP associations within the MHC region but outside HLA-DRB1 were found. Taking into account the effect of HLA-DR β 1 amino acids 11, 71 and 74, the most significant association maps to amino acid position 9 (Asp9) of HLA-B in the class I HLA region. A second significant association was found at HLA-DPB1 in the class II HLA region, which corresponds to amino acid position 9 (Phe9). Interestingly, the amino acid positions in the HLA-DR β 1, HLA-B and HLA-DP β 1 sequences are located within the peptide-binding groove (figure 3), thus suggesting that these polymorphisms have a functional role either by shaping the T cell repertoire during

thymic selection or in peripheral immune responses. Furthermore, the presence of these polymorphisms in both class 1 and class 2 HLA regions indicates a potential role on both CD8+ and CD4+ T cells, respectively. Of note, all these polymorphisms in HLA-DR β 1, HLA-B and HLA-DP β 1 proteins almost completely explain the MHC association with RA (Raychaudhuri et al, 2012).

Figure 3 Three-dimensional ribbon models for the HLA-DR, HLA-B and HLA-DP proteins. These structures are based on Protein Data Bank entries 3pdo, 2bvp and 3lqz, respectively, with a direct view of the peptide-binding groove. Key amino acid positions identified by the association analysis are highlighted. (This figure was prepared with permission using UCSF Chimera from Raychaudhuri et al, Nat Genet 2012;44:291–6.)



1.3.2 Non-HLA association

The first robust non-HLA genetic association with RA was found during investigation of the PTPN22 candidate gene, which encodes a lymphoid-specific protein tyrosine phosphatase, Lyp, that downregulates T cell receptor signalling. A SNP at position 1858 (C->T) leads to a loss-in-function mutation that mediates its effect by destabilising PTPN22, leading to degradation by proteases. This appears to predispose to autoimmunity in general. Indeed, variations of the PTPN22 gene have also been associated with the risk of other autoimmune diseases such as type 1 diabetes, vitiligo, autoimmune thyroid disease and systemic lupus erythematosus.

Several whole genome association scans have recently been performed on large RA cohorts and healthy controls originating from different countries. Such genome-wide scans test up to 500 000 SNPs distributed over the entire genome for their association with disease. One of the most important findings of such an approach in RA is the interaction between PTPN22 risk alleles and the HLA-DRB1 SE, conferring a multiplicative risk of developing ACPA-positive RA, especially in the presence of smoking (Kallberg et al, 2007). Additionally, these scans have identified polymorphisms in genetic regions encoding a large number of protein products that may have pathophysiological relevance in RA (reviewed by Viatte et al, 2013*). Initially, polymorphisms at STAT4 were identified as new risk factors for ACPA-positive disease (Kurreeman et al, 2007; Remmers et al, 2007; Wellcome Trust Case Control, 2007). STAT4 encodes a transcription factor (signal transducer and activator of transcription 4) involved in the differentiation of type 1 helper T cells (Th1) after stimulation by interleukin (IL)-12 (discussed later). Although direct evidence for specific gene disruption by risk alleles at the other two loci has not yet been forthcoming, the most biologically compelling candidate genes remain TNF α -

induced protein 3 (TNFAIP3) and TNF receptor associated factor-1 (TRAF-1), respectively. TNFAIP3 encodes a protein (A20) that is a negative regulator of nuclear factor kappa light-chain enhancer of activated B cells (NF- κ B), a transcription factor involved in TNF α and other inflammatory responses and thus plays a part in the regulation of TNF α signalling (Plenge et al, 2007a; Thomson et al, 2007). TRAF-1 is involved in signalling of TNF α via TNFR-1 and, interestingly, downstream NF- κ B (Kurreeman et al, 2007; Plenge et al, 2007b). A potential implication of the RA association with TNFAIP3 and TRAF-1 is therefore the importance of the NF- κ B pathway in disease induction, and several additional risk loci containing NF κ B-related genes have now been identified: CD40, PRKQC and TNFRSF14 (Barton et al, 2008; Raychaudhuri et al, 2008; Criswell, 2010; Orozco et al, 2010). Functional studies are needed to confirm and further explore the mechanism of such associations.

Additional RA-associated genetic variants have been found in regions or genes encoding CTLA4, KIF5A/PIP4K2C, CCL21, CDK6, CD28, PRDM1, CD2/CD58 and IL2-RA (Barton et al, 2008; Raychaudhuri et al, 2009). It is important to note that the majority of association studies performed to date have been in Caucasian populations and some important racial differences exist in risk profiles (Viatte et al, 2012a). For example, the PTPN22 risk allele is not seen in Asian populations (Shiozawa et al, 1998), whereas, conversely, convincing evidence exists for an association of RA with a SNP in the PADI4 locus, which encodes the enzyme PAD (Suzuki et al, 2003). A recent study performed in patients with RA of European descent confirmed an association with the PADI4 locus and also with 13 new RA loci (Eyre et al, 2012). The association with the PADI4 locus was stronger amongst ACPA-positive than ACPA negative patients (table 1). It is important to mention, however, that the non-HLA genetic variants described here invariably confer only a modest independent disease risk, often displaying individual odds ratios of little more than 1. The additive effects of such minor genetic determinants are unlikely ever to describe all of the unaccounted heritability of RA and it seems likely that distinct genetic risk factors may provide multiplicative, rather than merely additive, with combined risk because of their compound molecular consequences, with gene–environment interactions further completing the picture.

Robustly validated genetic risk factors have yet to be convincingly identified for ACPA-negative RA (table 1). Some factors are associated with both ACPA-positive and -negative RA (Viatte et al, 2012b). An association with ACPA-negative RA has been found with the MHC-class II gene HLA-DR3, which is part of a conserved haplotype (A1; B8; DRB1*03) that includes the MHC class III region, itself comprising many immune-related genes. In addition, polymorphisms defining several haplotypes in the promoter region of the gene coding for IRF5 (interferon regulatory factor 5) were found to be associated with ACPA-negative RA. IRF5 is involved in signalling via Toll-like receptors 7 and 9 and the polymorphisms might influence the induction of IRF5-dependent type I interferons (Sigurdsson et al, 2007). One partial explanation for the relative lack of identified risk factors for ACPA-negative RA is the challenge of recruiting sufficient numbers of well-ascertained patients into studies and the potential heterogeneity in this group of patients defined by the absence of a specific

autoantibody. Nevertheless, family-based studies do show that the degree of heritability is similar between the two subtypes, indicating that additional, as yet unidentified genetic factors must exist that predispose to ACPA-negative RA (van der Woude et al, 2009).

1.3.3 Smoking, genes, ACPA and other autoantibodies

Cigarette smoking is the most important environmental risk factor for RA. Several years of smoking confer an increased risk of the disease and are associated with more severe disease, with the risk increasing in proportion to the number of pack-years (Ostergaard et al, 2003a). Importantly, and analogous to the case with SE and PTPN22 risk alleles described above, smoking is seen to represent a risk factor for ACPA-positive, but not ACPA-negative, RA.

Indeed, this risk is further increased in the presence of SE alleles (up to an estimated 21-fold as compared with SE-negative non-smokers), illustrating the multiplicative effect of combined risk factors (Klareskog et al, 2006*; Kallberg et al, 2007). The combinatory effect of cigarette smoke and genetic factors (SE and PTPN22) has been predominantly observed for some specific ACPA, including anti-citrullinated α -enolase and anti-citrullinated vimentin (Lundberg et al, 2013) (table 2). The mechanism by which smoking may induce anti-citrulline immune responses has been investigated in smokers and non-smokers. The results showed that protein citrullination was present in a higher percentage of bronchoalveolar lavage cells of smokers than of non-smokers. Thus, it is plausible that enhanced protein citrullination and local inflammation may favour specific immune responses against citrullinated autoantigens in genetically susceptible individuals. However, how and why this response eventually targets the joints, remains unknown, although the participation of additional environmental factors is probably required.

It has become increasingly clear that ACPA status delineates two pathophysiologically distinct subsets of a similar clinically defined phenotype. Current classification criteria therefore include ACPA as one – but obviously not the essential feature for RA. The pathogenesis of autoantibody-negative disease is less clear. Importantly, other autoantibodies may exist in the absence of RF and ACPA, and the more recently discussed anti-carbamylated protein (CarP) antibodies may be one of these (Shi et al, 2011). Like citrullination, carbamylation is a post-translational modification by which lysine residues in a given protein are non-enzymatically converted into homocitrulline in the presence of cyanate. Although trace amounts of carbamylated proteins were detected in healthy individuals (suggesting that carbamylation is a physiological process), excess of carbamylation has been described in three states of cyanate abundance: inflammation (generation of cyanate from thiocyanate and hydrogen peroxide by myeloperoxidase (MPO)), cigarette smoking (direct inhalation of cyanate) and uraemia (abundance of urea as a source of cyanate) (Shi et al, 2014). As in the case of citrullination, an array of proteins is expected to be carbamylated in inflamed joints, although the exact identity of targeted proteins is yet to be explored (Prujin et al, 2015).

Anti-CarP antibodies were detected in the serum of over 40% of patients with RA (IgG in 45% and IgA in 43%). Despite their partial overlap with the presence of ACPA, it is noteworthy that about 16% of ACPA-negative patients harboured anti-CarP IgG antibodies and 30% displayed anti-CarP IgA antibodies (Shi et al, 2011). Such a finding narrows the percentage of “true seronegative” RA patients, especially given that anti-CarP antibodies seem to display prognostic features similar to those of ACPA (Trouw et al, 2012). The presence of anti-CarP antibodies at baseline was associated with more severe radiological damage. Unlike their IgA isotype, this role of the anti-CarP IgG isotype remained even after correcting for ACPA and RF positivity (Shi et al, 2011). Anti-CarP were also detected in patients with arthralgia in the absence of signs of arthritis and their presence predicted the development of RA independently of ACPA (Shi et al, 2013). Future studies will have to show the diagnostic and prognostic value of these new autoantibodies.

In addition to citrullination and carbamylation, malondialdehyde-acetaldehyde (MAA) adducts have recently been described as the third post-translational modification class serving as a target of antibodies in patients with RA (Thiele et al, 2015). MAA are produced during oxidative stress typically caused by inflammation. The presence of anti-MAA antibodies was associated with ACPA and RF positivity, but anti-MAA did not cross-react with these antibodies (Thiele et al, 2015). Interestingly, neutrophils have been identified as a site where all of the three post-translational modifications take place (Darrah and Andrade, 2015). However, the role of anti-MAA antibodies, as well as the possible mechanistic link of the three modification classes require further elucidation.

1.4 Additional environmental risk factors

Scope for additional robust gene–environment interactions to be found in the aetiology of RA remains, but that of smoking in relation to the SE is the only one discovered to date (table 3). In RA, some environmental factors may have specific effects directly related to RA pathogenesis (as suggested for smoking), whereas others might have non-specific effects promoting inflammation in general (eg, triggers of innate immunity). Thus, the former will only be relevant for subtypes of RA (eg, ACPA-positive RA), whereas the latter will influence the disease in a broader sense.

Coffee consumption has shown association with RA in several cohorts, although stratification for smoking usually reduced the significance of this finding. In a Danish cohort, however, coffee consumption did show an association with ACPA-positive RA after adjustment for smoking. A recent meta-analysis of nine studies showed that alcohol intake was inversely correlated with the development of ACPA-positive RA, but had no significant effect on ACPA-negative RA (Scott et al, 2013). Occupational exposure to mineral oils (eg, motor oils, hydraulic oils, etc.) was found to be a risk factor for ACPA-positive RA in men in a Swedish cohort,

Table 2 Odds ratio for disease risk according to genetic factor and tobacco smoke. (Reproduced from Lundberg et al, Ann Rheum Dis 2013;72:652–8)

CEP-1 /Cit-vim	HLA-DRB1 SE	Smoking	PTPN22	Cases/ controls	OR*	95% CI
–/–	–	–	–	106/178	1	Ref
–/–	–	–	+	41/49	1.4	0.9 to 2.3
–/–	+	–	–	168/200	1.4	1.0 to 1.9
–/–	+	–	+	47/43	2	1.2 to 3.2
–/–	–	+	–	140/233	1	0.8 to 1.4
–/–	–	+	+	61/81	1.4	0.9 to 2.1
–/–	+	+	–	223/252	1.6	1.1 to 2.1
–/–	+	+	+	76/61	2.4	1.5 to 3.6
+/–	–	–	–	4/178	1	Ref
+/–	–	–	+	2/49	1.9	0.3 to 10.7
+/–	+	–	–	32/200	7	2.4 to 20.3
+/–	+	–	+	18/43	20.1	6.4 to 63.2
+/–	–	+	–	13/233	2.6	0.8 to 8.2
+/–	–	+	+	10/81	5.7	1.7 to 18.8
+/–	+	+	–	80/252	15.4	5.5 to 43.1
+/–	+	+	+	29/61	24.4	8.2 to 73.1
–/+	–	–	–	10/178	1	Ref
–/+	–	–	+	4/49	1.7	0.5 to 5.7
–/+	+	–	–	47/200	4.3	2.1 to 8.8
–/+	+	–	+	22/43	9.9	4.3 to 22.8
–/+	–	+	–	21/233	1.7	0.8 to 3.8
–/+	–	+	+	4/81	1	0.3 to 3.3
–/+	+	+	–	83/252	6.3	3.2 to 12.7
–/+	+	+	+	33/61	11.5	5.3 to 25.3
+/+	–	–	–	6/178	1	Ref
+/+	–	–	+	5/49	3.4	1.0 to 11.7
+/+	+	–	–	43/200	6.4	2.7 to 15.6
+/+	+	–	+	40/43	30.4	12.0 to 76.9
+/+	–	+	–	14/233	1.8	0.7 to 4.8
+/+	–	+	+	7/81	2.7	0.9 to 8.2
+/+	+	+	–	212/252	26.6	11.5 to 61.7
+/+	+	+	+	92/61	50.1	20.6 to 121.8

*Adjusted for age, gender, residential area.

This case–control study provides the odds ratio (OR) for development of CEP-1 and Cit-vim ACPA in the presence of tobacco smoke or SE, or PTPN22 or various combinations thereof. The OR of having CEP-1 and/or Cit-vim (24.4, 11.5 or 50.1) were significantly higher in smoking subjects who were positive for SE and PTPN22.

Specific ACPA, anti-cyclic citrullinated peptide antibodies, assessed here were; CEP-1, anti-citrullinated α -enolase (CEP-1); Cit-vim, anti-citrullinated vimentin; SE, shared epitope.

Table 3 Environmental factors and development of RA

Predisposing factors	Protective factors
Tobacco smoke (ACPA+)	Alcohol consumption (ACPA+)
Periodontal disease (<i>P. gingivalis</i>) (ACPA+)	Younger age at menarche (≤ 12)
Coffee consumption (ACPA+)	
Exposure to mineral oils (ACPA+)	
Silica dust + tobacco smoke (ACPA+)	
Older age at menarche (≥ 15)	
Pregnancy*	

*Increased rate of RA onset 1 year after delivery. Multiparity (>3) favours a more severe course, whereas contraceptive use decreases RA severity, neither of them influence the development of RA.

ACPA, anti-cyclic citrullinated peptide antibodies; RA, rheumatoid arthritis.

independent of the presence of shared epitope alleles. This finding is of interest, as mineral oils are arthritogenic in certain rat strains due to a yet unknown mechanism (Bartfai et al, 2007). A study performed in the Malaysian population showed that professional exposure to silica was associated with increased risk of developing ACPA-positive RA. Notably, the risk was particularly high in cigarette smokers exposed to silica dust, thus emphasising the combination between two environmental factors inducing lung inflammation (Yahya et al, 2013).

Infections are major candidates for the induction of autoimmunity and have, therefore, been intensively studied also in RA. Although there is still no pathogen-derived antigen clearly linked to RA pathogenesis, the interplay between the human microbiome (especially in the oral cavity, the gut and lungs) and the host's immune system is being increasingly investigated. A shift from a normal symbiotic towards a “dysbiotic” microbiome, characterized by overgrowth of pathogenic and a lack of commensal bacteria, may be responsible for changes in the innate and adaptive immunity responsible for the development of RA (Sandhya et al, 2016). The presence of periodontal disease has been reported in different reports as an increased risk factor of developing RA. It is particularly interesting to note that *Porphyromonas gingivalis*, one of the micro-organisms involved in periodontal disease uniquely expresses a bacterial form of peptidylarginine deiminase (PAD) and enolase. *Porphyromonas gingivalis* PAD can citrullinate different peptides in vitro and can thus, generate self-antigens. PAD can also be autocitrullinated, and antibodies against PAD have been detected in patients with RA (Scher et al, 2014). Furthermore, anti- α -enolase antibodies cross-react with recombinant bacterial citrullinated enolase suggesting that *Porphyromonas gingivalis* infection can induce autoimmune responses in susceptible individuals by ‘molecular mimicry’. Notably, antibodies against *Porphyromonas gingivalis* were detected in autoantibody (ACPA and RF) positive individuals at risk of developing RA (first-degree relatives of patients with RA) (Mikuls et al, 2012). Together, several data indicate that periodontal disease, particularly in

the presence of *Porphyromonas gingivalis*, is probably associated with an increased risk of developing RA, even more pronounced in smokers (table 3). Furthermore, there is evidence suggesting that smoking may be associated with translocation of supraglottic bacteria, species such as *Prevotella* and *Porphyromonas*, to the lungs, leading to increased activity of PAD and airway inflammation (Sandhya et al, 2016).

Alterations of the gut microbiome (observed through its “window” – the stool microbiome) have also been described in patients with RA, offering new insights in the complex relationship between pathogens and commensals on one side and the host’s immune system on the other. An abundance of *Prevotella copri* with loss of *Bacteroides* has been demonstrated in the stool of patients with new onset RA (Scher et al, 2013). Another study demonstrated fewer *Bifidobacterium*, bacteria of the *Bacteroides-Porphyromonas-Prevotella* and the *Eubacterium rectale-Clostridium coccoides* groups of patients with RA compared to those with non-inflammatory fibromyalgia (Vahtovuo et al, 2008). Interestingly, the gut and oral dysbiosis were shown to correlate with each other and with laboratory measures such as the CRP, RF and anti-CCP antibodies in a recent metagenomics study of RA patients; the same study also demonstrated a partial resolution of the dysbiosis after treatment with DMARDs (Zhang et al, 2015). Despite these findings and evidence based on animal studies, a beneficial effect of probiotics has not been unequivocally demonstrated in the treatment of RA. *Lactobacillus casei* has been the only probiotic the effect of which has been revealed both on disease activity and levels of inflammatory mediators in a randomized trial (Vaghef-Mehrabany et al, 2014). However, the effect is probably strain- and dose-specific and this finding is not sufficient to recommend the routine use of probiotics in RA.

Female predominance in various autoimmune diseases, including RA, suggests that sex hormones and reproductive factors influence both RA development and severity. Women with lower age at menarche have a comparatively low risk for the development of RA. In the Danish cohort, for example, women with older age at menarche (≥ 15) had an almost twofold risk of developing RA as compared with women aged ≤ 12 years at menarche. Pregnancy is in itself a risk factor for the development of RA, as around 12% of women with RA experience disease onset within 1 year after pregnancy. During pregnancy, most women with RA (in older studies up to 90%) experience a significant reduction in disease activity (including complete remissions), but almost all patients relapse within 3 months after delivery (table 3)(Ostensen and Villiger, 2007). Multiparity (>3 children) favours a more severe course of disease, but does not additionally increase the risk for developing RA. Use of oral contraceptives, on the other hand, lowers disease severity, but data from initial studies showing a protective effect on RA development could not be confirmed after adjustment for age (Jorgensen et al, 1996; Sverdrup et al, 2005; Pedersen et al, 2006).

1.5 Epigenetic modifications

Epigenetic modifications take into account all the changes in chromosomal regions that do not affect the DNA sequence, but include DNA methylation and covalent histone modifications such as acetylation, deacetylation, methylation and ubiquitination. All these changes will alter the accessibility to the transcriptional machinery, thus influencing gene expression. A wide range of environmental exposures can alter the epigenome—for example, cigarette smoke can decrease DNA methylation. Epigenetic changes can be inherited during cell mitosis, and stochastic epigenetic instability can also occur over time in multiple cell types without any obvious stimulation. Most research has focused on the role of DNA methylation. Methylation of cytosine residues at the carbon 5 position occurs primarily in CpG rich regions, known as CpG islands on gene promoters in the vicinity of transcriptional start sites. DNA methylation is associated with gene silencing and is regulated by DNA methyl transferases. Histones are proteins that act as spools for DNA. For effective transcription this condensed chromatin structure needs to be loosened. Histone acetylation on lysins (through histone acetyl transferase, HAT) weakens the interaction between histones and DNA, and thus promotes transcriptional activity; vice versa, deacetylation of histones (through histone deacetylases, HDACs) strengthens these interactions, which thus leads to suppression of transcription. Histone methylation can lead to transcriptional activation or repression and histone ubiquitination can also alter gene transcription.

Several of these epigenetic modifications may affect the expression of cytokines, chemokines and matrix metalloproteinases (MMPs) in RA (reviewed by Klein and Gay, 2013). Synovial fibroblasts from patients with RA display a different DNA methylation signature than those of patients with osteoarthritis. Notably, an altered methylation of genes encoding different cytokines has been described in RA peripheral blood mononuclear cells and synovial fibroblasts. HDACs are differentially expressed in RA synovial cells and have been shown to regulate the expression of cytokines such as TNF and IL-1. Overexpression of sirtuin 1, a member of the HDAC family, promotes cytokine production by monocytes and RA synovial cells and inhibits apoptosis (Niederer et al, 2011). Of note, the expression of HDAC can also be altered by stimulation of synovial fibroblasts with TNF (Kawabata et al, 2010). Finally, in addition to histones, a growing number of other intracellular molecules are targets for acetylation, including transcription factors, signalling molecules and structural proteins. It has been shown that HDACs act on all these different targets to regulate autoimmune manifestations and HDAC inhibitors are the best studied epigenetic therapeutic agents. The anti-inflammatory properties of these compounds include reduction of cytokine levels (Bosisio et al, 2008) and increased Foxp3+ regulatory T cell function (Beier et al, 2012). The use of an HDAC inhibitor ameliorated joint inflammation and prevented structural damage in different models of arthritis (Joosten et al, 2011) and thus, might represent an interesting therapeutic approach for RA.

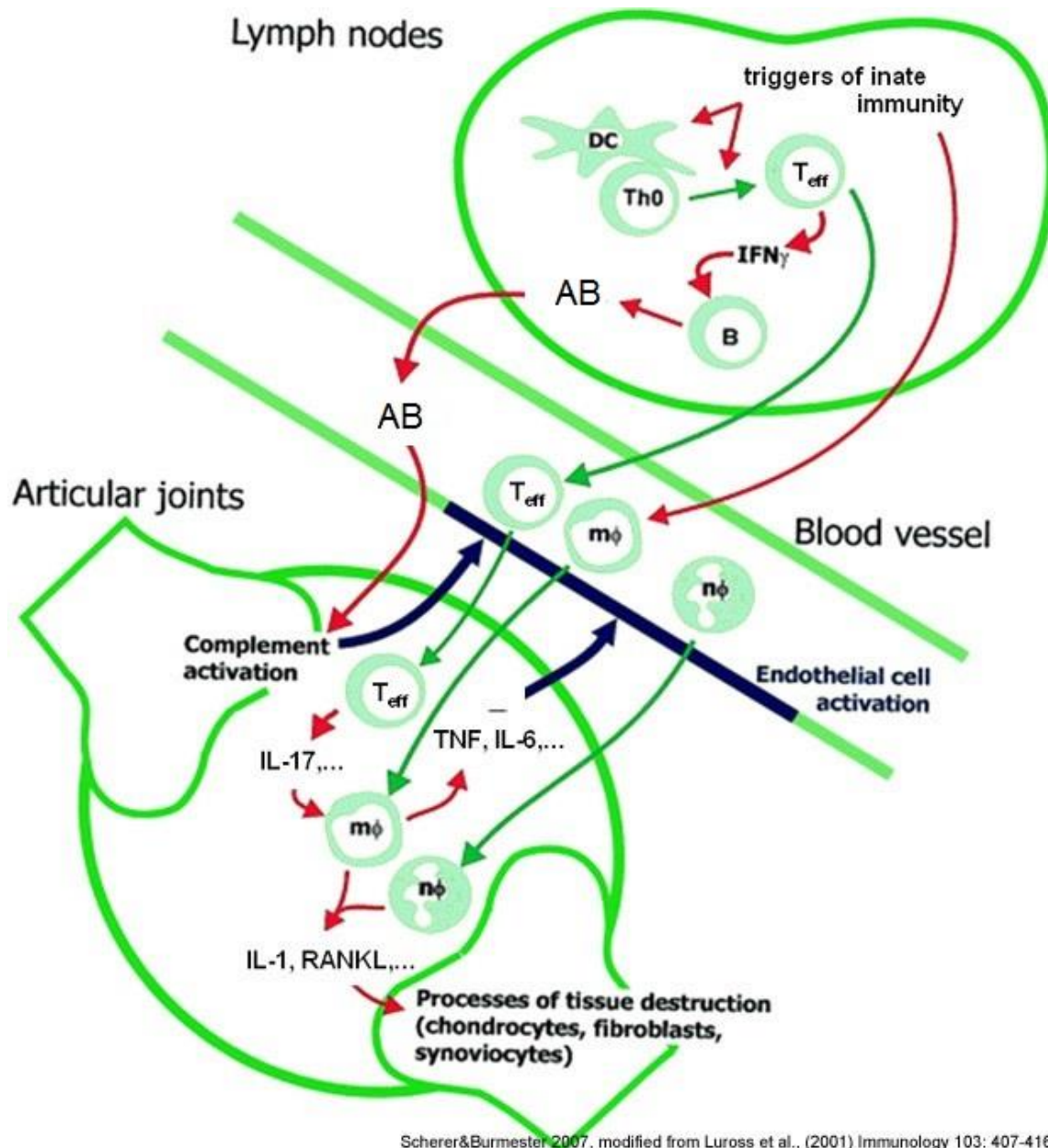
1.6 Disturbances of the immune system

The heritability of RA, together with the presence of autoantibodies that precede clinical onset in a subset of patients, supports a now widely held pathogenetic model in which autoimmune propensity is long established by the time joint inflammation is ‘triggered’. The following sections review the different cell types involved in the pathogenesis of RA during the preclinical phases before the development of RA and in the joints during established RA (figure 4).

1.6.1 *T cells*

T cells are one of the most abundant cell types in RA synovium, comprising 30–50% of synovial tissue cells. The majority are CD4+, Th cells, matured from naïve precursors, which can be divided into different subsets, including Th1, Th2 and Th17 cells, according to the patterns of cytokines that they produce and their role in host defence. Th1 cells produce mainly interferon (IFN) γ and play a major role in controlling infections with intracellular micro-organisms (ie, *Mycobacterium tuberculosis* and viruses). Th2 cells produce mainly IL-4, IL-5 and IL-13 and play a critical role in the defence against parasitic infections. Th17 cells produce IL-17, IL-22 and granulocyte-macrophage colony stimulating factor (GM-CSF) and activate immune responses against extracellular bacteria and fungi. The responses of different innate immune cells that act as effectors in the control of infection (e.g. macrophages, eosinophils and neutrophils) to the cytokines produced by these different types Th cells are referred to as Th1, Th2 and Th17 responses, respectively. Naïve Th cells (Th0) are polarised into these different subsets according to the cytokine ‘milieu’ present during their activation by antigen-presenting cells. Classically, IL-12 induces the polarisation of Th1 cells, IL-4 stimulates the polarisation of Th2 cells and transforming growth factor β in combination with IL-6 polarises Th0 into Th17 cells. In addition, IL-1 β and IL-23 also play an important role in the generation of Th17 cells. Master transcription factors are associated with the different Th subsets, including T-bet for Th1, GATA-3 for Th2 and ROR γ T for Th17 cells. In addition to their role in the control of infection, Th cell subsets are also associated with specific immunopathological manifestations: Th1 cells in cell-mediated autoimmune diseases and Th2 cells in allergic conditions. Th17 cells have been shown to be involved in the pathogenesis of several experimental models of autoimmune diseases (figure 5). Th17 cells are critical orchestrators of collagen-induced arthritis in mice (Murphy et al, 2003), and evidence for their importance in human RA comes from the observation that both IL-17 and IL-23 are found in serum samples, synovial fluid and synovial biopsy specimens of patients, but are mostly absent from the same compartments in osteoarthritis. IL-17 itself is highly pleiotropic, acting on a variety of cell types to perpetuate local inflammation while promoting angiogenesis, osteoclastogenesis and, ultimately, the destruction of cartilage and bone. Ironically, in contrast to the – partly impressive – clinical effects in psoriasis, psoriatic arthritis, and ankylosing spondylitis, the clinical trials of IL-17 inhibitors in RA have been disappointing (Smolen et al., Lancet 2016). The first IL-17 inhibitors have been approved for psoriatic arthritis and axial spondylopathies in 2015.

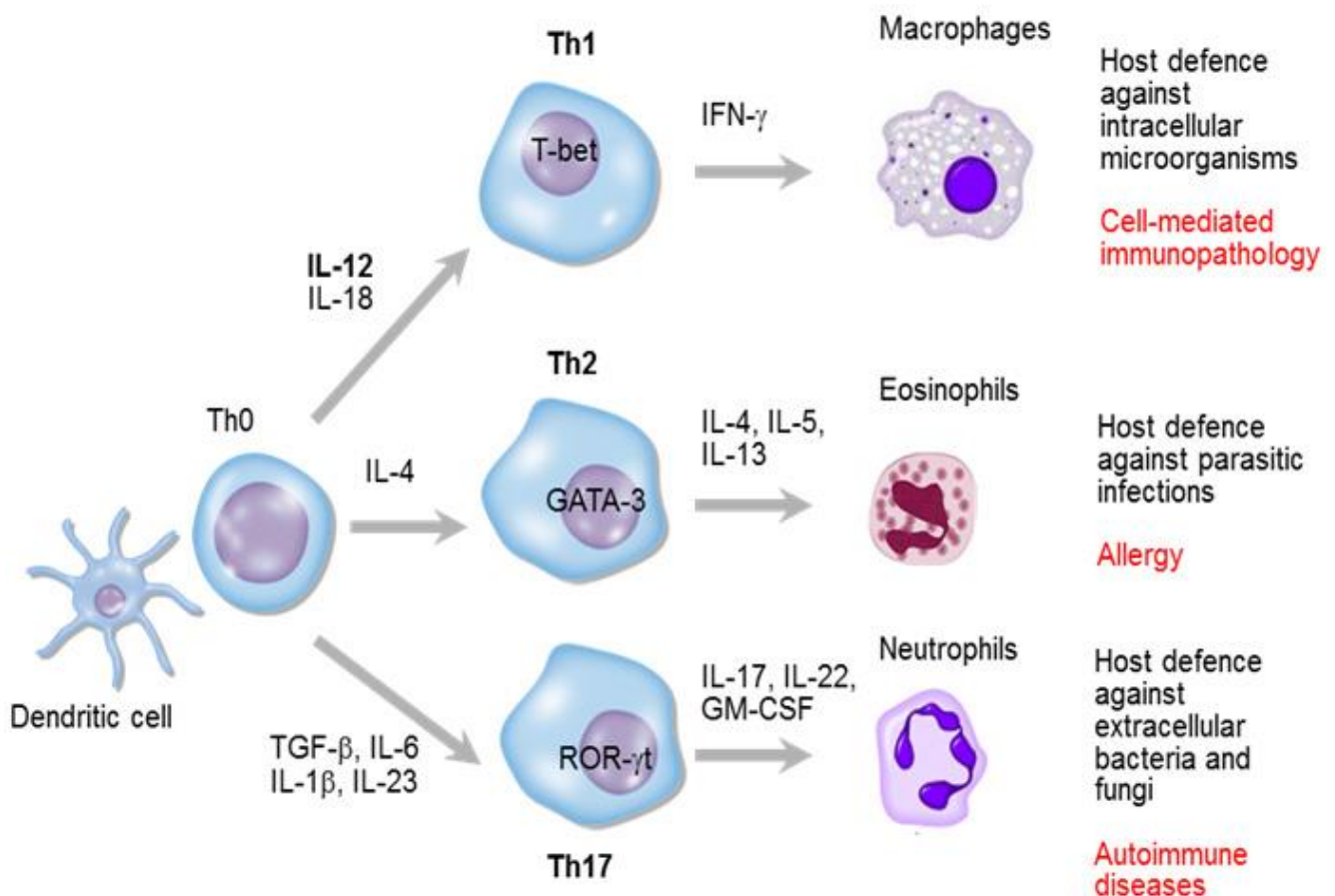
Figure 4 Suggested mechanism of the development of the immune response in RA. Antigen-specific T cell activation by DC–T cell interaction usually occurs in lymph nodes. Naïve T cells thereby differentiate into effector T cells that give help to B cells, which leads to production of autoantibodies (eg, anti-cyclic citrullinated peptide antibodies, and others). These antibodies then form immune complexes, accumulate in joints, and activate complement. This leads to recruitment of effector cells (macrophages, neutrophils, etc.), which secrete proinflammatory cytokines and chemokines and activate osteoclastogenesis. AB, autoantibody; DC, dendritic cell; IFN, interferon; IL, interleukin; RANKL, receptor activator of the NF- κ B ligand; TNF, tumour necrosis factor. (Adapted from Luross et al, *Immunology* 2001;103:407–16.)



Two other Th cell subsets may polarise after antigen-experience, which also play important roles in immune responses—namely, follicular helper T cells (Tfh) and regulatory T cells (Tregs). Tfh are located in the periphery within B cell follicles of secondary lymphoid organs (e.g. lymph nodes, spleen, Peyer's patches). By their close contact with B cells they contribute to class switching and affinity maturation. They secrete IL-21 and also other cytokines (IFN γ and IL-4) and their master transcription factor is Bcl-6. Tregs play a critical role in

immune suppression and tolerance in autoimmunity. These cells also regulate inflammation and adaptive immune responses. Tregs are produced either in the thymus and termed natural Tregs, or in the periphery and known as induced Tregs (iTregs). They both have the transcription factor Foxp3 in common. Transforming growth factor β stimulates the polarisation into iTregs. Although Tregs are present in large amounts in the joints of patients with RA, these cells have an impaired suppressive function. TNF α in the synovial fluid has been shown to participate in the functional Treg defects (Ehrenstein et al, 2004). Recently, the molecular mechanism involved in the inhibitory effect of TNF α on Treg activity has been characterised. TNF α -induced dephosphorylation of the Foxp3 DNA-binding domain leads to the impairment of Foxp3 transcriptional activity and Treg function. This effect is dependent on the enzyme protein phosphatase 1, the expression of which is stimulated by TNF α (Nie et al, 2013).

Figure 5 The cytokine ‘milieu’ influences the polarisation of Th0 cells into different Th subsets, including Th1, Th2 and Th17 cells. These T cells express distinct cytokines and transcription factors. The cytokines produced by different Th cells recruit and stimulate different innate effector cells, including macrophages, eosinophils and neutrophils (Th1, Th2, or Th17 “responses”, respectively). These different Th responses are involved in the protection against microorganisms (in black) and also in different immunopathological conditions (in red). GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; TGF, transforming growth factor.



For efficient effector T cell maturation, the recognition of antigen by naïve T cells in the context of MHC molecules requires additional costimulatory signals, without which T cells become anergic. Interaction of surface-expressed CD28 (T cells) and CD80/86 (antigen-presenting cells) generates one of the most important of these co-stimulatory signals, with excessive signalling normally controlled by T cell derived CTLA-4, which is therefore an important “immune checkpoint”: when bound to CD80/86 (instead of CD28) it off regulates the co-stimulatory signal and T-cell activation. The exploitation of this mechanism using abatacept (CTLA4-Ig fusion protein) is now an established treatment option: the therapeutic efficacy of CTLA4-Ig (abatacept) provides perhaps the most compelling evidence that these cells are important drivers of RA, although its effects are still not fully understood, and there might off-target effects of this compound, or simply retrograde effects affecting the monocyte/macrophage and not (only) the T-cell (Bonelli et al, 2013).

1.6.2 B cells

The importance of B cells in RA pathogenesis has only recently been appreciated. The realisation that circulating autoantibodies often predate arthritis onset by many years implicates early involvement of autoantigen-specific B cell activation and plasma cell differentiation. The frequent occurrence of germinal centre-like structures in RA synovium, ideally suited to humoral immune responses, along with the recognition that B cells can themselves present antigenic peptides (even priming naïve T cells in some cases (Edwards and Cambridge, 2006)) has made the case for their role in the pathology (Dorner, 2006). This is borne out by the success of therapeutic B cell depletion using, for example, rituximab.

During inflammation, B cells infiltrate RA synovium, although the degree of infiltration and local structural organisation varies significantly between patients. Fibroblast-like synoviocytes and dendritic cells in synovium secrete factors which attract B cells and influence their differentiation and survival and, in some patients, orchestrate the formation of tertiary lymphoid structures, which themselves perpetuate autoimmunity. These factors include BAFF, CXCL12, CXCL13 and APRIL, some of which are currently being evaluated as therapeutic targets.

Far from being mere ‘antibody producers’, accumulating evidence assigns key roles to B cells in many aspects of immune functions. B cells can take up antigen via surface immunoglobulin and are efficient antigen-presenting cells. Moreover, recent evidence suggests that immunoglobulin class switching and somatic hypermutation, which are classically dependent on CD40–CD40L interactions with CD4+ T cells, may also occur independently of T cells. This process again requires BAFF, which is present in increased amounts in RA synovium and additionally prolongs B cell survival (Dorner, 2006; Mauri and Ehrenstein, 2007). B cells are also prolific producers of cytokines. By secreting TNF α and IL-6, they contribute to the activation of macrophages and directly participate in inflammation. IL-6 is also an important autocrine differentiation factor for B cells.

1.6.3 Monocytes/macrophages

Activated macrophages in RA synovium are central to driving and maintaining chronic inflammation. Macrophages are multipotent effector cells that efficiently integrate innate and adaptive immune responses. They are abundantly present in the rheumatoid synovial membrane and at the cartilage–pannus junction. Important functions include strong phagocytic activity, antigen processing and presentation, expression of Fc receptors responsive to (auto-) antibodies and immune complexes, complement activation and regulation, Toll-like receptor expression and tissue degradation and remodelling. As macrophages reside in tissue in most organs they are, together with dendritic cells, likely to be the first to encounter pathogen-derived antigen and are well placed to present it to autoreactive T cells, providing the initial trigger necessary to start an immune response on the basis of genetic predisposition. Macrophages are important producers of proinflammatory cytokines (eg, TNF α , IL-1, IL-6), cartilage-degrading enzymes (MMP-9 and MMP-12) and growth factors (GM-CSF), among other mediators of pathology. The relative importance of these various macrophage functions during the course of the disease may change over time (Kinne et al, 2007). With such a central role in the disease process, it is perhaps not surprising that expression of the CD68 macrophage surface marker has shown promise as an early biomarker for drug responsiveness in RA (Chomarat et al, 1995). Indeed, most of the currently used agents effective in RA have been shown to decrease the number of CD68 positive macrophages in the synovial sublining: prednisone, methotrexate and leflunomide, as well as biologics such as infliximab and rituximab (Cascao et al, 2015). Furthermore, a decline in disease activity has also been associated with this effect (Haringman et al, 2005).

1.6.4 Mast cells

Mast cells are highly granular cells best known for their role in allergy and anaphylaxis, as components of the innate immune system. They may be stimulated to degranulate in response to direct injury. Once activated, the many mediators released by mast cells appear to act in concert, driving neighbouring immune cells towards an inflammatory phenotype, promoting angiogenesis and, both directly and indirectly, degrading cartilage. Also, a potentially crucial role for mast cells has been discovered as producers of IL-17 (Maruotti et al, 2007).

1.7 Synovial histopathology

The normal synovium consists of a cellular lining layer in direct contact with the synovial fluid and a sublining layer underneath the lining. The lining is a one to four-cell thick membrane comprised of macrophage-like and fibroblast-like synoviocytes (MLS and FLS, respectively). The sublining is a loose connective tissue composed of extracellular matrix, fibroblasts, macrophages, blood and lymph vessels, as well as nerve fibres (Barland et al, 1962). Both layers undergo changes in inflammatory arthritis. The lining becomes up to 15 cells thick, with ultrastructural changes of FLSs (enlargement of the rough endoplasmic reticulum, Golgi apparatus and

lysosomes) suggestive of increased metabolic activity. The sublining hosts an inflammatory infiltrate consisted of T and B lymphocytes, plasma cells, macrophages and - to a lesser extent - dendritic cells, mast cells, natural killer cells and more rarely, neutrophils, which are predominantly present in the synovial fluid (Kiener and Karonitsch, 2011). Three distinct histological patterns have been recognized in chronic synovitis of RA. The most common is a diffuse inflammatory infiltrate including lymphocytes and macrophages. The second pattern is characterised by the presence of lymphoid follicles. In some cases the lymphoid follicles become organised with germinal centres similar to those of secondary lymphoid organs such as in lymph nodes and can be considered as tertiary lymphoid organs. The third and rarest form of synovitis includes the presence of granulomas resembling rheumatoid nodules (Weyand and Goronzy, 2003). The first histological pattern has been associated with a milder course of the disease. Apart from this classification, histological differences have been described between early and long-standing disease: biological processes involving T cells, granulocytes, the cell cycle and macrophages seem to be associated with late rather than early disease (Lequerre et al, 2009).

In addition to hyperplasia of the lining and accumulation of the inflammatory infiltrate, neoangiogenesis is the third histological hallmark of synovitis of RA. Despite a more pronounced vascularization in SpA compared to RA, routine synovial histology does not allow to discern between the major types of arthritis. More sophisticated molecular methods may serve this purpose, but they still require validation (van de Sande and Baeten, 2016).

The examination of synovial characteristics in patients with RA with and without ACPA resulted in conflicting data. Some authors observed a higher number of infiltrating lymphocytes in ACPA-positive patients, whereas ACPA-negative patients had more extensive fibrosis (van Oosterhout et al, 2008). However, these findings were not confirmed by subsequent studies (Gomez-Puerta et al, 2013) and an association of histological patterns and distinct clinical subsets has not yet been confirmed.

Insight into the molecular pathways involved in the rheumatoid synovium has emerged recently using whole genome-wide analysis of gene expression. These studies showed considerable molecular heterogeneity. Some subsets exhibited genes associated with predominant macrophagic infiltration or with the presence of lymphoid infiltrates and lymphoid follicle-containing synovial tissue. Alternatively, expression of genes involved in matrix remodelling was detected in synovial samples with low inflammation and predominant fibrous tissue (van Baarsen et al, 2009). The presence of a few predictive markers of response to TNF antagonists has been identified in large expression studies (Lindberg et al, 2010). A recent whole genome expression study identified intercellular adhesion molecule 1 (ICAM1) and C-X-C motif chemokine 13 (CXCL13) as predictive markers of response to adalimumab (anti-TNF antibody) and tocilizumab (anti-IL-6R antibody), respectively. These data were confirmed using the serum levels of soluble ICAM1 and CXCL13 from patients who participated in a head-to-head clinical trial comparing the efficacy of adalimumab and tocilizumab in

monotherapy (Dennis et al, 2014). These results indicate that the heterogeneity in synovial tissue infiltrates and their associated molecular signatures may be useful for predicting the therapeutic response. In that context, it seems that RA patients with a “pauci-immune” phenotype of low-grade synovial inflammation are less prone to a favourable response to TNF- α inhibitors (Townsend, 2014). In general, these markers and putative specific histopathological subtypes have been proposed as guidance for therapeutic decision making in RA (Astorri et al, 2015), but are still controversial regarding their practical meaningfulness.

1.8 Cartilage and bone degradation: the role of fibroblasts and osteoclasts

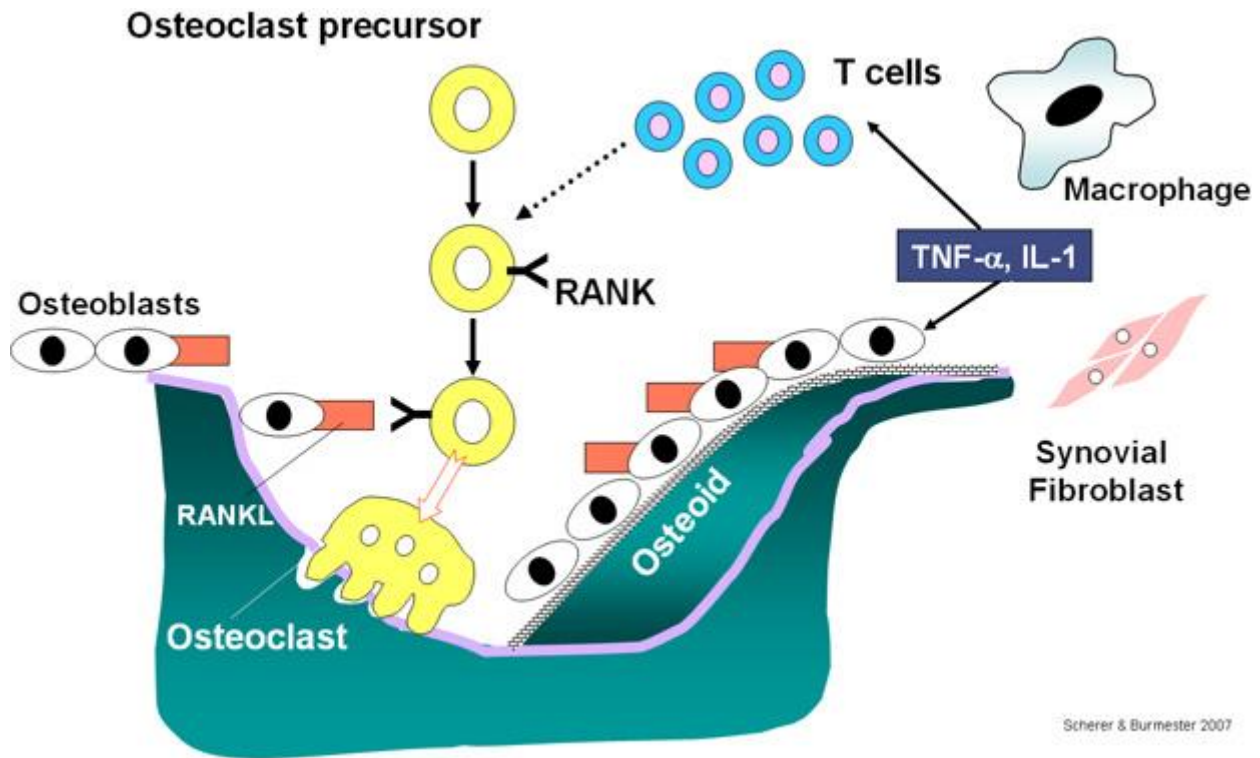
Changes in the synovium of chronic RA result in the formation of the pannus – synovium remodelled into an inflammatory tissue invading the adjacent cartilage and subchondral bone (Kiener and Karonitsch, 2011), being responsible for the development of bone erosions and irreversible damage. The process of cartilage and bone degradation is initiated in the mineralized cartilage close to the junction between synovium and the joint end (Hayer et al, 2007), given that this type of cartilage is particularly susceptible to bone resorption mediated by osteoclasts (Schett, 2007).

Two cell types are of prime importance for destruction of cartilage and bone. Synovial fibroblasts adhere to cartilage and degrade extracellular matrix. Osteoclasts, on the other hand, are mainly involved in bone destruction. Both cell types closely interact with cells of the immune system and, by secreting large amounts of cytokines, themselves help to maintain inflammation. Synovial fibroblasts in RA are characteristically found in the sublining layer of the synovium. Expression of various transcription factors indicates that they proliferate locally in disease, contributing to synovial hyperplasia. Functionally, they adhere to cartilage and display an aggressive invasive behaviour. Synovial fibroblasts are an abundant source of cytokines and chemokines such as IL-15, IL-16, CXCL12, CXCL13, BAFF and members of the IL-6 family (eg, IL-11). These cytokines activate T cells and influence B cell migration and survival. Large amounts of secreted prostaglandin E2 additionally support inflammation. In addition, degradation of cartilage by synovial fibroblasts is due to the secretion of MMPs and cathepsins. Specifically, synovial fibroblasts produce MMP-1, -3, -13, -14 and -15 as well as cathepsins B, K and L. These enzymes degrade extracellular matrix, providing a rich source of potential neoantigens for T and B cell polyclonal proliferation (Karouzakis et al, 2006).

Bone degradation in RA is mainly mediated by osteoclasts (figure 6). Osteoclastogenesis—that is, the differentiation of osteoclasts from precursor cells, requires M-CSF and RANKL (receptor activator of the NF- κ B ligand), a molecule first identified in activated T cells (Sato and Takayanagi, 2006). Meanwhile, RANKL has been found in RA synovium. RANKL is expressed by T cells, which thereby directly drive osteoclastogenesis (Toh and Miossec, 2007), and also by neutrophils and in large amounts by synovial fibroblasts (Poubelle et al, 2007). TNF α accelerates this process by inducing RANKL expression and enhancing RANKL signalling. Interestingly,

Th1- and Th2-cytokines (IFN γ , IL-4, IL-10) as well as IL-12 and IL-18 inhibit osteoclastogenesis, whereas IL-17 induces RANKL expression in osteoblasts.

Figure 6 Factors contributing to osteoclastogenesis. Macrophages, synovial fibroblasts and T cells express IL-1, TNF α and RANKL, factors important for differentiation of osteoblasts to osteoclasts. Multinucleated osteoclasts degrade bone, thereby creating radiographically detectable erosions. IL, interleukin; RANKL, receptor activator of the NF- κ B ligand; TNF, tumour necrosis factor.



Summary points

- Rheumatoid arthritis is a heterogeneous disease with a polygenetic background, that typically, but not always presents with autoantibodies (including ACPA and RF, anti-CarP etc.).
- The presence of ACPA and RF and rising C-reactive protein (CRP) levels years before onset of clinical symptoms indicate that relevant immune responses for RA development are initiated very early.
- High titer RF (>45UI) and positive ACPA are highly and similarly specific for RA; low positive RF can also be found among healthy (elderly) individuals and patients with other autoimmune diseases.
- The most important genetic risk factor for RA development resides in the MHC class region and includes polymorphisms in HLA-DR (including the shared epitope alleles), HLA-B and HLA-DP genes. These predisposing MHC alleles are particularly associated with the development of ACPA-positive RA.
- Smoking is thus far the most important environmental risk factor associated with the development of RA. Similar to shared-epitope alleles, smoking is a risk factor only for ACPA-positive RA.
- CD4+ T cells (also termed T helper cells) consist of different subsets (Th1, Th2, Th17, Tfh, Tregs). Th17 cells might be more crucially involved in RA and other autoimmune diseases, and efficacy of B cell depleting therapy and the ACPA response indicate that B cells are more relevant than previously expected.
- RA development requires several factors acting at different times in an orchestrated manner.
- Epigenetic changes, such as DNA methylation and histone acetylation, are present in immune cells and stromal cells (synovial fibroblasts) of patients with RA and may contribute to the pathogenesis of the disease. Treatments targeting histone deacetylases have shown some promising results in preclinical models of arthritis.

2 Clinical aspects of RA

2.1 Introduction

Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory joint disease. No single clinical sign, symptom or test reliably distinguishes it from other joint diseases, and the pathological features of synovitis, the hallmark of RA, are not unique. Rather, the diagnosis of RA is based on a combination of clinical findings, laboratory tests and imaging. RA is a heterogeneous condition with a variable mode of disease onset and disease course. Some patients have a very acute disease onset with fever, polyarthritis and extra-articular manifestations, whereas other patients have a more gradual and insidious onset. The latter presentation is more common. Typical articular signs and symptoms include pain, stiffness and swelling. Redness and warmth of affected joints are less common findings. Concomitant tenosynovitis, bursitis and even carpal tunnel syndrome may be present. RA is a systemic disease as may be manifested by generalised weakness, weight loss or low-grade fever and extra-articular features such as sicca syndrome, nodules and interstitial lung disease.

A particular type of early RA characterised by episodic attacks is known as 'palindromic rheumatism'. The clinical picture includes variable episodes of polyarthritis, which suddenly affect one or more large or peripheral joints. The duration varies from a few hours to a few days, followed by spontaneous improvement and complete disappearance of all rheumatic signs between attacks. About one-third of these palindromic cases will eventually evolve into typical RA.

Both prevalence and incidence rates of RA are about two to four times higher in women, and symptoms are more severe than in men (Kvien et al, 2006). The female/male ratio decreases with age. The reasons for the greater prevalence of RA among women have not been firmly established. A decline in the incidence of RA over recent decades has been reported in a number of countries (eg, Finland, England/Wales, United States and Japan). The decreasing incidence has been especially apparent in women, possibly as a consequence of some environmental factor such as the introduction of oral contraceptives in the 1960s (Heiberg et al, 2005). A shift in the incidence towards a higher age at disease onset has been observed across several cohorts. The incidence rate seems to increase with age up to a plateau around the age of 60 (Symmons et al, 1994).

2.2 Disease onset

2.2.1 Articular manifestations

The typical joint involvement at disease onset is swelling of the proximal interphalangeal (PIP) joints, the metacarpophalangeal (MCP) joints, the wrists (figure 7) and the metatarsophalangeal (MTP) joints. However, the disease may also start gradually with involvement of one or a few joints and then over time develop from

an undifferentiated oligoarthritis or polyarthritis into a more polyarticular and classically symmetrical disease. Occasionally, the disease may present with a monoarthritis, for example of the knee.

Figure 7 *Symmetrical swelling of the proximal interphalangeal joints and the metacarpophalangeal joints, typical of rheumatoid arthritis.*



2.2.2 Extra-articular manifestations

The dominating feature at disease onset is usually joint involvement. However, the disease may start much more dramatically with fever and inflammatory manifestations of internal organs—for example, with pericarditis or pleuritis. In such cases, other systemic diseases may be the most important differential diagnoses, such as systemic lupus erythematosus. Other extra-articular manifestations such as sicca syndrome, vasculitis, nodules, bronchial dilatation and interstitial lung fibrosis are more commonly seen in established seropositive RA. For more detail see section 2.4.7, 'Extra-articular manifestations and RA-related comorbidities'.

2.2.3 Symptoms

The symptoms of the patient will typically reflect the most prominent disease manifestations at disease onset. Joints with inflammation are painful, tender and the patient perceives stiffness on movement. The patients may also find that the joints are swollen. Morning stiffness is common and generally exceeds 30 min. Other frequently occurring general symptoms include fatigue and loss of energy.

2.2.4 Clinical findings

The typical clinical finding of inflamed joints is soft tissue swelling and tenderness (figure 8) and is often associated with a limited range of motion. The ‘squeeze test’ across the MCP and MTP joints has been considered a useful screening technique to detect synovitis of the respective joint regions (figures 9a and 9b). Detection of synovitis is essential for the diagnosis (figures 9–11). Swelling of the finger joints will generally be symmetrical, as is also the case for the middle-sized joints, such as the wrists and the mid-foot. Involvement of shoulders and hips at disease onset is rare.

According to the 2010 ACR/EULAR criteria, definite clinical synovitis in at least one joint assessed by clinical evaluation (i.e. palpation) is a minimum prerequisite for a classification attempt (Aletaha et al, 2010). In other words, the classification criteria should not be used on patients with tender but no swollen joints (arthralgia without arthritis). At the same time, the “squeeze test” is a classical screening method for inflammatory joint disease, based on the hypothesis that joint tenderness in patients with early arthritis may be a harbinger of subclinical inflammation. However, the squeeze test itself was clinically correlated with tenderness, and not with swelling (Wiesinger et al, 2013). Despite being recommended as a part of the early referral (screening) algorithm for newly diagnosed RA (Emery et al, 2002), both the MCP and MTP “squeeze tests” have demonstrated a rather low sensitivity (53% and 54%, respectively), and only a moderate specificity (82% and 74%) for identification of arthritis – up to 50% of swollen MCPs and MTPs were missed by the test (van den Bosch et al, 2015). Since the “squeeze test” still remains a quick and inexpensive method, it may be considered in the screening algorithm, but in conjunction with the more thorough approach including tender and swollen joint counts.

Figure 8 Early synovitis of proximal interphalangeal and metacarpophalangeal joints.



Figure 9a The 'squeeze test' to screen for synovitis of the metacarpophalangeal joints.



Figure 9b The 'squeeze test' to screen for synovitis of the metatarsophalangeal joints.



Figure 10 Detecting swelling of the metacarpophalangeal (MCP) joints with the two-finger technique, flexing the MCP joints at 30° and pushing on the palmar aspect with the index fingers.



Figure 11 Detecting proximal interphalangeal joint swelling; four-finger technique, alternating compression with the left and right hands.



Figure 12 Detecting wrist synovitis.

The clinical examination should include a general physical examination as extra-articular manifestations may be present. Patients with suspected serositis should be examined for clinical signs of pericarditis and pleuritis. Bibasilar inspiratory crepitations can point to underlying interstitial lung disease. Splenomegaly should be sought in the setting of Felty's syndrome. A general organ examination is also important for the assessment of possible concomitant diseases, since many of the relevant drugs may lead to adverse reactions and interfere with existing concurrent conditions.

2.2.5 Laboratory investigations

Typical findings are raised levels of the erythrocyte sedimentation rate (ESR) and/or CRP. Thrombocytosis and leucocytosis can be seen in active inflammatory disease. Reduced haemoglobin is also common. Serum iron may be lowered whereas ferritin concentration may be increased as a reflection of the acute phase reaction. It is important to do a general laboratory screening, including liver function tests and creatinine as well as urine examination to determine whether there are any indications of underlying liver or kidney abnormalities.

Tests for RF and ACPA are important both for the diagnosis and staging of the disease, since the presence of RF and ACPA are associated with a more severe disease course. The presence of RFs is generally determined by nephelometry for IgM RF or by ELISA for specific isotypes, including IgM RF, IgA RF or IgG RF. The anti-CCP2 ELISA, which uses different artificial CCPs, is the most common method for the detection of ACPA. Multiplex approaches for the simultaneous detection of ACPA directed against different citrullinated peptides are under investigation for routine practice, but for the moment these are limited to clinical research.

The levels of RF and ACPA have also been included in the recent ACR/EULAR 2010 classification criteria for RA (table 4). The detection of anti-CarP antibodies is not available in routine practice. The likelihood of radiographic progression after 5 years is significantly greater among patients with ACPA (OR = 2.5) (Meyer et al, 2003). Other immunological examinations may be important for differential diagnoses. It is common to test for the presence of antinuclear antibodies, but the value of this test can be questioned if there is no clinical evidence of any systemic connective tissue disease. The presence of antinuclear antibodies has not been shown to have any prognostic value in RA. However, secondary Sjögren's syndrome can be seen together with RA and infrequently, the typical immunological markers of Sjögren's syndrome (anti-SSA and anti-SSB) may also be present in RA.

2.2.6 Imaging procedures

Conventional radiographic examinations remain the 'gold standard' for diagnosing joint damage in RA. The majority of patients with newly diagnosed RA will not have any erosive changes and thus the absence of erosions on X-ray examination does not rule out a diagnosis of RA. Many patients will have completely normal X-ray findings initially or only soft tissue swelling and periarticular osteopenia. Radiographic examinations of the hands, wrists and feet are important as a baseline examination and for the subsequent monitoring of the disease.

Many clinicians perform only a posteroanterior (PA) view of the hands (with the wrists included) and a PA view of the feet (figure 13). The addition of three-quarter views (also known as the Nørgaard view or supinated-oblique view) may increase the probability of detecting erosions (Norgaard, 1965). In a pivotal paper published in 1977, it was shown that 71% of patients with early RA (defined by the authors as disease duration of <12 months) developed 'diagnostic' erosions in the first 5 years and of those developing erosions, 43% did so in the first year (Brook and Corbett, 1977). The MTP joints are commonly affected before involvement of the MCP joints and the 5th MTP joint particularly. Some patients demonstrate erosive changes of the MTP joints without involvement of the MCP joints. It is therefore recommended that hand and feet X-ray examinations are always performed together, even in patients without symptomatic involvement of the feet.

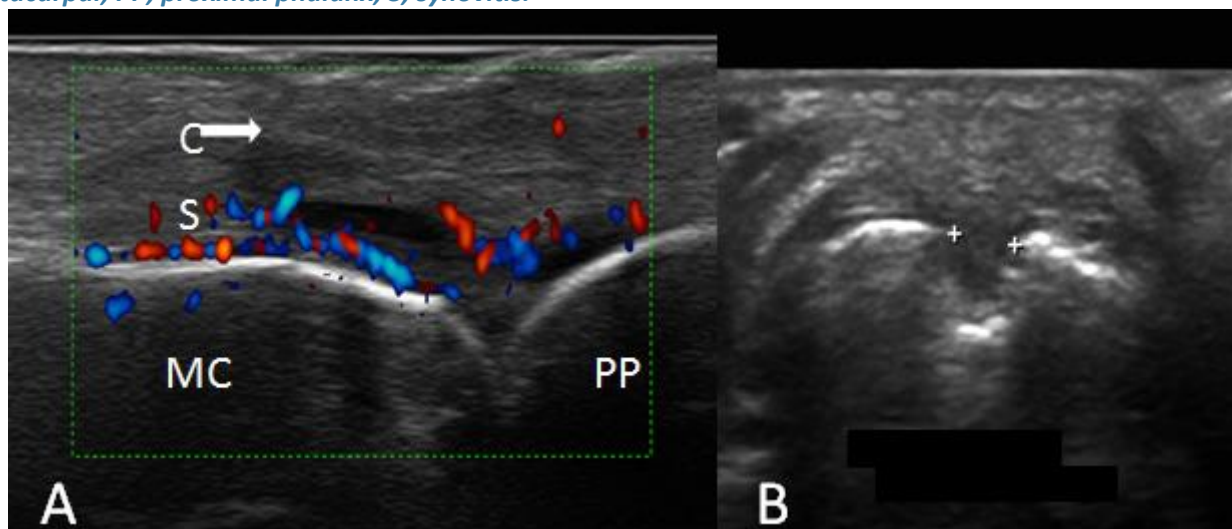
A baseline radiographic assessment is important in order to detect future radiographic progression, which is considered an unfavourable prognostic sign. Follow-up hand and feet radiographs are recommended annually in the early stages of the disease (Smolen et al, 2010*). Scoring systems have been developed and validated to assess the extent of, and changes in, radiographic damage, such as the modified Sharp–van der Heijde score, which is commonly used in clinical trials (van der Heijde, 2000).

Figure 13 Left: Plain X-ray picture of the metatarsophalangeal (MTP) joints of the right foot with erosions and joint space narrowing of the 4th and 5th MTP joints. Right: X-ray picture of the left hand with advanced carpal disease and involvement of the proximal interphalangeal and metacarpophalangeal joints.



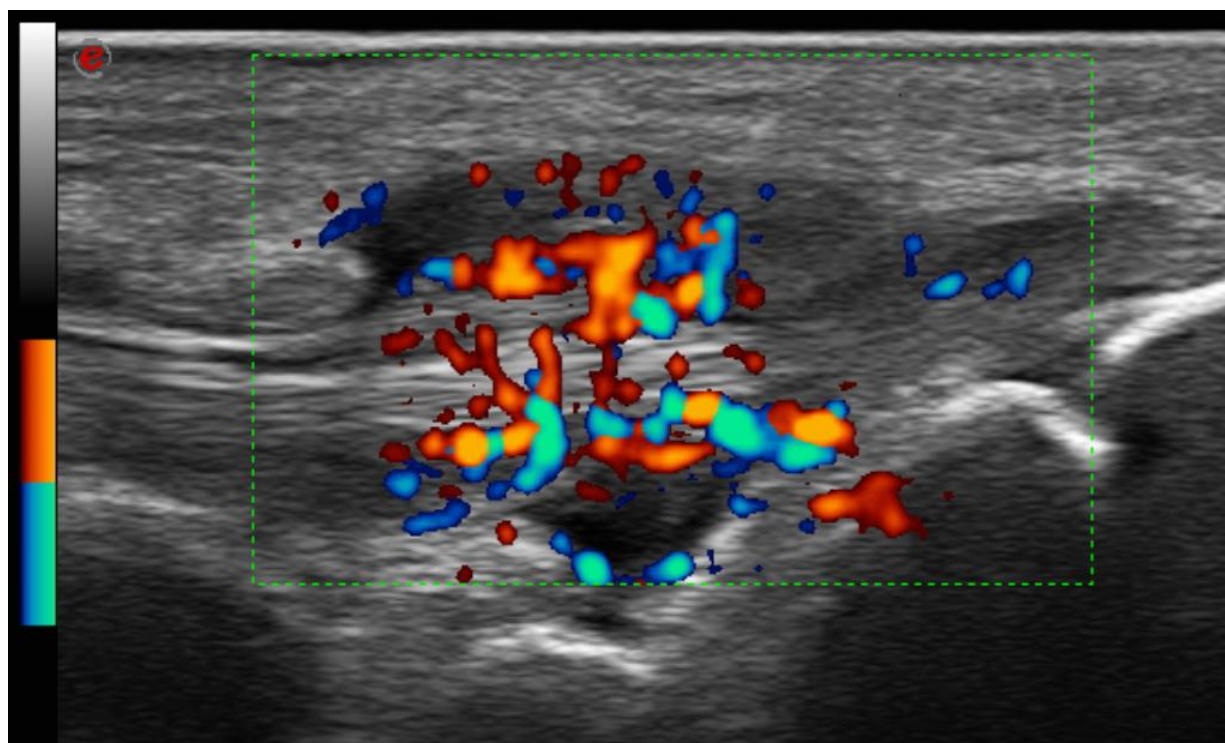
Ultrasonography may be helpful in the identification of subclinical synovitis, both at disease onset to assist with diagnosis and throughout the course of the disease to evaluate disease activity. Grey-scale ultrasonography with Doppler imaging has been found to be more sensitive in detecting signs of inflammation and destruction in RA finger joints than clinical and radiographic examinations, without loss of specificity (Szkudlarek et al, 2006) (figure 14). The exact role and timing of ultrasonography is currently undergoing investigation.

Figure 14 Ultrasonography with Doppler of the metacarpophalangeal (MCP) joints. (A) Longitudinal view of the dorsal aspect of a MCP joint, with marked synovitis and presence of a strong Doppler signal. (B) Axial view of a metacarpal head with discontinuity of the cortical surface, representing an erosion. C, capsule; MC, metacarpal; PP, proximal phalanx; S, synovitis.



Ultrasonography can detect erosions of smaller joints at an early stage of the disease and often before the erosion is visible on conventional radiographs. This is particularly the case for the second and fifth MCP joints and the first and fifth MTP joints. A common presentation in early RA is extensor carpi ulnaris tenosynovitis of the wrist, which is easily demonstrated with joint ultrasound (see figure 15).

Figure 15 Wrist ultrasound with a longitudinal view of tenosynovitis demonstrating blurred tendon margins, an abnormal hypoechoic zone, representing fluid within the tenosynovial sheath and marked Doppler activity.



Magnetic resonance imaging (MRI) of the wrist and finger joints may be an important tool for early diagnosis and staging of the disease. The detection of synovitis is enhanced when the imaging procedure is performed with gadolinium contrast. Bone marrow oedema is also a typical finding, which is considered to be a predictor of subsequent erosions. Nevertheless, bone marrow oedema is a rather unspecific finding, which may also be seen in other joint diseases, such as osteoarthritis. Erosions are seen earlier with MRI than with conventional radiography. Routine use of MRI has not yet been introduced into clinical practice because of its high cost and lack of availability (Ostergaard et al, 2003a).

2.2.7 Diagnosis

RA is a clinical diagnosis based on the signs and symptoms that are considered typical of RA, by consideration of numerous contextual, personal, and geographic factors, and by excluding other diseases. Diagnosis cannot be established by using classification criteria, which are developed for clinical research purposes. However, the result of a classification may inform the ultimate clinical diagnosis. The 1987 ARA classification criteria (Arnett et al, 1988*) were found to be too insensitive in early arthritis, and the requirement of nodules or radiographic

damage in a 4/7 criteria system was considered not timely anymore (Aletaha et al, 2005). Subsequently, the 2010 ACR/EULAR classification criteria have been developed (Aletaha et al, 2010*), and it has been shown that these criteria show higher sensitivity at the cost of some specificity (Radner et al, 2014). Importantly, erosive disease that is typical for RA does not require the application of the classification system, but allows direct classification as RA. The erosiveness typical for RA has been defined (van der Heijde et al, 2013).

Table 4 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA). (Reproduced with permission from Aletaha et al, *Arthritis Rheum* 2010;62:2569–81)

Domain	Parameter	Points
A Joint involvement	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints (≥ 1 small)	5
B Serology	Negative RF <i>and</i> negative ACPA	0
	Low positive RF <i>or</i> low positive ACPA	2
	High positive RF <i>or</i> high positive ACPA	3
C Acute-phase reactants	Normal CRP <i>and</i> normal ESR	0
	Abnormal CRP <i>or</i> abnormal ESR	1
D Symptom duration	<6 weeks	0
	≥ 6 weeks	1

RF or ACPA measurements between one and three times the upper limit of normal are designated 'low'; higher measurements are designated 'high'. CRP and ESR above the upper limit of normal are considered 'raised'. Scores for each of four domains are added; maximum score = 10. A score ≥ 6 indicates RA.

ACPA, anti-cyclic citrullinated peptide antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid arthritis.

2.2.8 Differential diagnoses

The differential diagnosis of RA is broad, especially given that RA does not always present in the classical polyarticular symmetric fashion. A comprehensive approach is necessary to differentiate RA from similar entities, which is a prerequisite to classify a patient according to the new ACR/EULAR classification criteria (Aletaha et al, 2010).

When arthritis is of acute onset, it is necessary to exclude infectious arthritis. While bacterial (septic) arthritis most commonly affects one joint and is associated with a severe clinical presentation with fever, leukocytosis and prostration, viral arthritis usually occurs in a polyarticular fashion similar to RA and may occasionally be associated with a rash. History taking is particularly important for an infection such as parvovirus B19, to explore potential contact with young children as a source of infection. Serological testing for parvovirus B19,

hepatitis B (HBV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), rubella and human immunodeficiency virus (HIV) should be performed in the setting of recent-onset oligo- or polyarthritis. It is useful for detecting an acute IgM antibody response in the first 3 months followed by the presence of IgG antibodies against the suspected agent. HCV-related arthritis may yield a high titer of RF (often with cryoglobulins), however, with an unremarkable level of ACPA. Arthritis associated with HCV, HIV, as well as Lyme and gonococcal arthritis may follow a more chronic pattern. Clues for gonococcal arthritis may be skin lesions such as pustules and blisters, as well as concurrent genital discharge. Lyme disease and gonorrhoea, however, infrequently cause arthritis in Europe.

Unlike the previously listed infectious arthritides, reactive arthritis is defined as a sterile oligo- to polyarthritis of acute or subacute onset, most commonly affecting the ankles and knees in an asymmetric fashion, but may resemble a symmetric polyarthritis of the hands as well. The typical presentation of reactive arthritis can be defined as a common syndrome that includes the co-presence of reactive arthritis, sterile conjunctivitis and urethritis. Reactive arthritis is induced by a variety of infectious agents, usually occurring 7 to 14 days following the (symptomatic or asymptomatic) infection of the urinary or gastrointestinal system caused by *Shigella*, *Salmonella*, *Campylobacter*, *E. coli*, *Yersinia*, *Chlamydia*, *Mycoplasma* or *Ureaplasma*. Rheumatic fever also causes reactive arthritis associated with *Streptococcus pyogenes*-related pharyngitis and commonly a positive anti-streptolysin titer, almost exclusively in younger patients. Reactive arthritis is RF negative and self-limited in most cases, although it can also persist and recur in a relapsing-remitting manner. A similar presentation can develop in the context of inflammatory bowel disease. Arthritis of acute or subacute onset with oligo- or less commonly polyarthritis similar to reactive arthritis may also develop in the context of adult-onset Still disease and Löfgren's syndrome as the acute-onset variant of sarcoidosis (acute arthritis, hilar lymphadenopathy and erythema nodosum).

Hand osteoarthritis is the most frequent differential diagnosis of chronic polyarthritis affecting the hands, especially in the elderly and middle-aged population. Several distinct features make the differentiation from RA relatively clear in the routine clinical setting: OA is characterized by non-inflammatory joint pain, normal levels of serum inflammatory markers and a non-inflammatory synovial fluid pattern (the analysis of which is rarely needed in the context of hand OA); furthermore, it has a predilection for DIPs and first CMC joints of the hands, sparing the radiocarpal and MCP joints. However, MCP joints may be affected by OA secondary to hemochromatosis. Differentiation between RA and OA may be less clear in the context of "inflammatory" OA when clinical signs of inflammatory polyarthritis, as well as erosive joint destruction develop.

Psoriatic arthritis is an important entity to discern both from RA and OA. It belongs to the spectrum of RF-negative (seronegative) arthritides and is not necessarily associated with psoriasis. A thorough screening for psoriasis should be performed (including the nails and less visible skin areas such as the navel, the scalp, the posterior auricle and the buttocks), as well as a detailed history of enthesitis, dactylitis and other extra-

articular signs of peripheral spondyloarthritides. The arthritis may be erosive as RA but has a greater predilection for DIPs and, despite resembling OA, is usually more destructive. Signs of bony proliferation on X-rays are typical for PsA and speak against RA.

Polymyalgia rheumatica (PMR) is the most important differential diagnosis of recent onset symmetric polyarthritis in the elderly population, given its similarity to seronegative late-onset RA (the so called “LORA”, late onset RA) and important prognostic implications if associated with giant cell vasculitis and not recognized. Despite the similarity, LORA does not typically present with myalgias and usually affects small joints of the hands unlike PMR that more commonly affects larger joints. Sudden onset polyarthritis in the elderly may also be associated with paraneoplastic syndromes, drug-induced lupus and remitting seronegative symmetric synovitis with pitting oedema (RS3PE).

Connective tissue diseases (CTDs, collagenoses) are another important, but less frequent, differential diagnosis, the onset of which is more common in younger and middle-aged patients. Systemic lupus erythematosus (SLE) may present with arthralgias and symmetrical polyarthritis, as well as Jaccoud’s arthropathy, a reversible mimic of RA with deformities. Although RA can be ANA positive as well as SLE and Sjögren’s syndrome, the latter two are associated with a variety of other typical organ-specific symptoms, as well as antibodies against specific antigens within the ANA spectrum. Despite SLE rarely being RF-positive, increased RF titers are a common finding in Sjögren’s syndrome. RF positive erosive arthritis in patients with SLE is considered to be an overlap syndrome of RA and SLE and is often termed “rhumus”. The “puffy” hands of systemic sclerosis, mixed connective tissue disease and polymyositis (in the context of anti-synthetase syndrome, often in conjunction with interstitial lung involvement) should also be considered in the differential diagnosis. The anti-synthetase syndrome is the most important differential diagnosis of RA with lung affection.

Crystal deposition disorders (gout and calcium pyrophosphate deposition disorder, CPPD) may cause various patterns of arthritis, most commonly oligo- or monoarthritis. A polyarticular pattern develops in approximately 10% of both and may resemble RA. Gout is more frequent in the context of metabolic syndrome, whereas CPPD is frequently seen in the elderly. A joint tap reveals intraarticular crystals. Ultrasound and dual-energy CT (in the case of gout) may help detect signs of crystal deposition. If not treated adequately, gout can transform to a chronic tophaceous disorder mimicking RA with rheumatoid nodules.

The incidence of various inflammatory arthropathies has been examined in Sweden (Soderlin et al, 2002) and in Finland (Savolainen et al, 2003) and these results highlight the fact that many different inflammatory arthropathies have to be considered in patients with recent-onset joint swelling (box 2).

Box 2 The most common inflammatory joint diseases that have be considered as differential diagnoses to rheumatoid arthritis

<p>Spondyloarthritis:</p> <ul style="list-style-type: none"> • Peripheral spondyloarthritis • Psoriatic arthritis • Reactive arthritis • Spondyloarthritis associated with inflammatory bowel disease <p>Polymyalgia rheumatica with peripheral arthritis</p> <p>Viral associated arthritis (eg: parvovirus B19)</p> <p>Lyme arthritis</p> <p>Acute sarcoid arthropathy (Löfgren's syndrome)</p> <p>Connective tissue disease:</p> <ul style="list-style-type: none"> • Systemic lupus erythematosus • Inflammatory myositis • Sjögren's syndrome <p>Crystal arthropathies:</p> <ul style="list-style-type: none"> • Calcium pyrophosphate deposition disease • Gout

2.2.9 Disease assessment

Several quantitative measures can be used to evaluate the activity and severity of the disease, as well as the disease consequences for the individual (table 5). The EULAR disease activity and response criteria are based on the Disease Activity Score, but several other scores mentioned below have been validated and are used in clinical practice. Core measures of disease activity include tender and swollen joint counts, patient and investigator global assessments of disease activity on a visual analogue scale (VAS), intensity of joint pain on a VAS, a patient-reported measure of physical disability (Health Assessment Questionnaire (HAQ)) and acute phase reactants (ESR and CRP).

Table 5 Three of the principal quantitative measures used to evaluate the activity and severity of RA and the predefined thresholds for remission, low, moderate and high disease activity

	DAS 28 (van Gestel et al, 1996)	SDAI (Smolen et al, 2003)	CDAI (Aletaha et al, 2005)
Scoring items:			
Number of variables	3 or 4	5	4
Tender joint count	✓	✓	✓
Swollen joint count	✓	✓	✓
CRP	✓ (CRP or ESR)	✓	
ESR			
Patient global assessment of disease activity	(✓)*	✓	✓
Physician global assessment of disease activity		✓	✓
Disease activity: (range)	0–9.3	0–86	0–76
Remission	≤2.6	≤3.3	≤2.8
Low	>2.6–≤3.2	>3.3–≤11	>2.8–≤10
Moderate	>3.2–≤5.1	>11–≤26	>10–≤22
High	>5.1	>26	>22

*This item is included in the DAS28 score with four variables.

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS28, 28-joint count Disease Activity Score; SDAI, Simplified Disease Activity Index.

These individual disease activity measures can be combined into composite measures. The Disease Activity Score 28 (DAS28) includes the 28-swollen joint count (28-SJC) and the 28-tender joint count (28-TJC) in addition to patient global assessments of disease activity on a VAS, and ESR or CRP. The scores according to EULAR criteria are: ≤2.6 for remission, >2.6 and ≤3.2 for low disease activity, >3.2 and ≤5.1 for moderate disease activity and >5.1 for high disease activity (van Gestel et al, 1996). The Simplified Disease Activity Index (SDAI) (Smolen et al, 2003) is the numerical sum of five outcome parameters: tender and swollen joint counts (28-TJC and 28-SJC), patient and physician global assessments of disease activity (VAS 0–10 cm) and the level of CRP. The Clinical Disease Activity Index (Aletaha et al, 2005) is a simplification of the SDAI, without the laboratory evaluation of CRP to allow immediate clinical assessment. The DAS28 has repeatedly been reported to fail to provide criteria for remission with face validity, as it allows for multiple swollen joints in remission. Therefore, it has more recently been abandoned, and the 2011 ACR/EULAR remission criteria propose only SDAI as a score based criterion, in addition to the main Boolean definition (Felson et al, 2011).

Functional disability in RA is most commonly measured with the Stanford HAQ. The shortened version, the Modified HAQ, reduces the number of items from 20 to 8, one for each of the eight components and does not allow upgrading of scores by use of technical devices or help by another person. However, several other

generic and disease-specific measures are available for assessment of physical disability and other important dimensions of health-related quality of life (see online in-depth discussion I).

Joint damage is usually assessed by imaging modalities, using one of the accepted scoring systems to assess erosions and joint space narrowing. The most widely used radiological scoring systems are the Larsen score and the Sharp score (with modifications by Genant and van der Heijde). Clinical scores of deformities are also available (Zijlstra et al, 2002). Standardised scoring systems for synovitis and erosions on ultrasonography and MRI have also been published and validated for the hand and wrist joints with different qualitative (0/1) and semiquantitative (0–3) measuring systems (Ostergaard et al, 2003b; Mandl et al, 2011).

According to the most up-to-date ACR/EULAR definitions, RA can be considered to be in remission if either the SDAI is ≤ 3.3 , or if the scores for tender and swollen joint count, CRP (in mg/dL) and the patient's global assessment (0–10 scale) are all ≤ 1 (Felson et al, 2011*). Nevertheless, it is possible to be in remission according to these criteria and to still demonstrate ultrasound or MRI evidence of synovitis. Future definitions of remission may well incorporate these imaging modalities.

2.2.10 Identification of prognostic markers

Since RA can have a variable disease course, it is of particular importance and relevance to identify markers that may predict the disease outcome. In the ideal situation, one would be able to tailor treatment according to such indicators—that is, to treat patients with predictors of severe disease aggressively and to spare patients with mild disease from drugs that are associated with potentially severe adverse reactions.

Three different outcomes can be considered to be of particular relevance: radiographic damage, functional disability and mortality. Table 6 shows known predictors for these long-term outcomes. Radiographic progression is considered a key outcome variable, as it is thought to reflect the cumulative effect of inflammation on bone and cartilage. Further, joint damage accounts for a considerable amount of the disability in RA, in both the established and early phases of the disease (Odegard et al, 2006).

An optimal treatment strategy should include considerations of the presence or absence of predictors of joint damage, since prevention of such damage is a major treatment goal. Several studies have shown that female gender and the presence of erosions are predictors of progressive radiographic abnormalities in RA.

The prognostic markers that are most relevant to consider in clinical practice are one of the composite disease activity scores (such as the DAS28) and laboratory markers. Serum IgM RF and ACPA are strong predictors of radiographic damage, especially when present in high titres. Several studies have also shown that ESR and CRP are independent predictors of radiographic damage.

Table 6 Predictors of outcome in rheumatoid arthritis

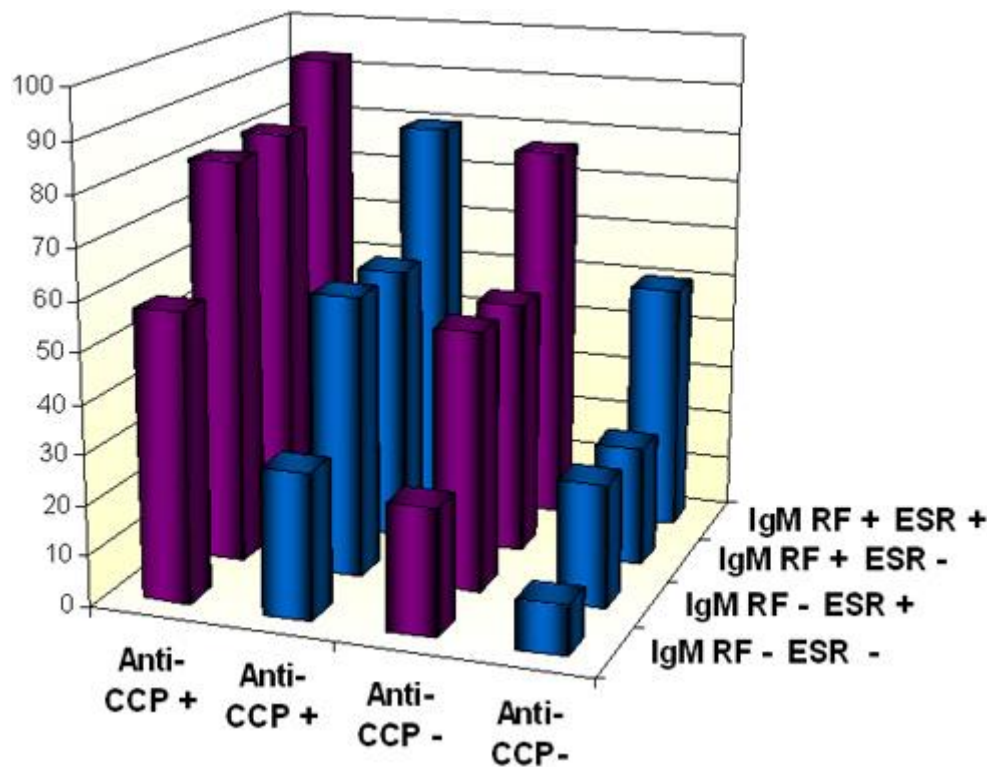
Prediction of future physical disability (HAQ score)	Prediction of future structural damage	Prediction of increased mortality
<ul style="list-style-type: none"> ● HAQ score at 1 year ● Functional grade III or IV disease at 1 year ● Age > 65 ● Initial disease severity ● Comorbidities (diabetes, HT, CVD) ● Rheumatoid factor ● Baseline Larsen score ● DAS28 at 1 year ● Baseline haemoglobin ● Acute phase reactants (?) ● Gender (?) ● Level of education (?) 	<ul style="list-style-type: none"> ● ACPA ● Baseline erosive disease ● Female gender ● Acute phase reactants ● Rheumatoid factor ● TNF and IL-6 ● Genetic markers: HLA-DR4 and HLA-DRB1(shared epitope) ● HAQ score ● MRI activity 	<ul style="list-style-type: none"> ● Age ● Level of education/coping ● Physical status ● Rheumatoid factor ● Comorbidities ● Infections ● Extra-articular manifestations ● Increasing HAQ scores ● Baseline poor health status ● Use of glucocorticoids ● Gender (?) ● Acute phase reactants (?) ● Structural damage (?)

ACPA, anti-cyclic citrullinated peptide antibodies; CVD, cardiovascular disease; DAS28, 28-joint count Disease Activity Score; HAQ, Health Assessment Questionnaire; HT, hypertension; IL, interleukin; TNF, tumour necrosis factor.

One Norwegian study showed that ACPA, IgM RF, ESR and female gender were all independent predictors of radiographic progression and could be combined into an algorithm for better prediction of disease outcome. ACPA was the strongest contributor to the overall prediction model. In this study, patients with high levels of ACPA were 10 times more likely than ACPA-negative patients to develop radiographic progression and about five times more likely than patients with low–moderate levels (Syversen et al, 2008). The algorithm with ACPA, IgM RF, high ESR and female gender predicted radiographic progression at the individual level with good accuracy (figure 16). Prediction of mild disease (specificity), however, is more difficult than prediction of progressive disease (sensitivity).

In summary, an appropriate investigation in early RA should include the evaluation of both diagnostic and prognostic markers by assessing signs of structural damage, acute phase reactants, number of swollen joints, rheumatoid factor, ACPA and disability level. Patients with markers indicating potentially severe and progressive disease should have the highest priority for early and aggressive treatment.

Figure 16 Probability of radiographic progression – blue bars: male subjects, red bars: female subjects. CCP, cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor. (Reproduced from Syversen et al, *Ann Rheum Dis* 2008;67:212–7.)



2.3 Recent-onset arthritis

In new-onset polyarthritis, while awaiting confirmation of the diagnosis or when the diagnostic investigations do not establish a precise diagnosis, the term ‘undifferentiated arthritis’ (UA) or undifferentiated inflammatory arthritis is often employed. UA is a diagnosis of exclusion, defined as an *early* form of arthritis not meeting classification/diagnostic criteria for a more definitive disease (McNally et al, 2014). *Nota bene*, there is no consensus on the temporal definition of “early arthritis”, although a time span of 3-6 months of symptom onset is usually understood under this term.

The definition of UA depends on the current armamentarium of criteria used to describe and classify various diseases that should be considered in the differential diagnosis of recent-onset arthritis. Until the 2010 ACR/EULAR criteria for the classification of RA were published (Aletaha et al, 2010), the 1987 ARA criteria (Arnett et al, 1988) were used as the classification standard and most of our current knowledge about the progression from UA to RA is still based on the fulfilment of the 1987 criteria as the outcome. Up to one-half of UA patients experience spontaneous remission, whereas one-third develop RA, i.e. meet the 1987 criteria (van der Helm-van Mil et al, 2007). Based on data from the Leiden Early Arthritis Clinic, nine features were identified as predictors of one-year progression from UA to RA in a prediction rule validated on several cohorts (van der Helm-van Mil et al, 2007; McNally et al, 2014): age, female gender, distribution of affected joints (favouring small joints, symmetric involvement, involvement of both upper and lower extremities), tender and

swollen joint counts (TJCs and SJs), duration of morning stiffness, level of CRP, as well as RF and anti-CCP positivity (van der Helm-van Mil et al, 2007). A similar prediction rule was constructed using exclusively MRI findings and serologic variables (Tamai et al, 2009). It is noteworthy that not only ACPA positivity, but also the titer of anti-CCP2 antibodies as the standard of ACPA detection, serves as a predictor of transformation of UA to RA – the time span between symptom onset and fulfilment of the 1987 criteria is shorter in patients displaying high anti-CCP2 titers at baseline (Bizzaro et al, 2013). This is in line with the approach used in the 2010 criteria ascribing a higher score to high-titer compared to low-titer antibody levels (Aletaha et al, 2010). On the other hand, the already mentioned role of RF positivity in predicting evolution of UA to RA (Rantapää-Dahlqvist et al, 2003; van der Helm-van Mil et al, 2007) is not unequivocally accepted (Bizzaro et al, 2013; Chen et al, 2013), possibly due to their lower specificity. Furthermore, although a likelihood of persistent arthritis increasing with the titer of RF has been demonstrated (Mjaavatten et al, 2010), this role of RF is not unequivocally confirmed to be independent of the ACPA status (Bizzaro et al, 2013).

With the emergence of the more sensitive 2010 ACR/EULAR criteria, a proportion of patients previously considered UA became classified as RA (Jung et al, 2012). The new criteria contain most of the clinically relevant features included in the Leiden prediction rule and their employment successfully discriminates patients with a high from those with a low risk of radiographic progression (Mueller et al, 2015). In the IMPROVED study, patients with UA not fulfilling the 2010 criteria have been shown to be less active (according to DAS) with lower TJCs and SJs, a much lower percentage of ACPA and RF positivity compared to RA (ACPA: 3% vs 68%; RF: 4% vs 69%), as well as a more favourable outcome in terms of radiographic progression (Heimans et al, 2015). However, the fact that 23% of UA patients from the Leiden Early Arthritis Clinic not fulfilling the 2010 criteria still fulfilled the 1987 criteria within one year of symptom onset indicates the need of careful monitoring of UA patients, at least over the first years of the disease course (Krabben et al, 2012).

Nevertheless, given that the 2010 classification criteria exclude only those UA patients identified to have a low risk of RA development according to the previously mentioned prediction rule (van der Helm-van Mil, 2007), it is reasonable to initiate therapy when a given patient fits in the new classification (Smolen et al, 2014). Otherwise, treatment with a DMARD should be considered as early as possible in patients with UA under risk of persistent or erosive arthritis and in patients already having joint erosions (Combe B et al, 2007).

Tight control of disease activity in the early period following symptom onset is critical to induce remission or to achieve a low disease activity and to prevent future damage and disability, because of the close relationship between level of inflammatory activity and future damage. It is therefore recommended that patients should be followed up and disease activity assessed by the DAS28 and by a patient-reported outcome such as the HAQ.

The 'treat-to-target' approach represents a treatment strategy tailored to the disease activity of the individual patient with RA with the aim of achieving a predefined level of low disease activity or remission. The patient's disease is reviewed regularly (1–3 monthly during active disease) and treatment is adjusted until the target is achieved. An international taskforce of RA experts developed 10 recommendations to inform patients and practitioners about strategies to reach optimal outcomes and concluded that treat to target is an important concept in the induction of remission in the treatment of RA (Smolen et al, 2016*).

In the Dutch 'DREAM' RA registry, treating to the target of remission (DAS28 < 2.6) in early RA has been found to be cost-effective as compared with 'usual care' and to lead to high rates of sustained remission (62% of patients in DAS remission after 3 years) (Vermeer et al, 2013a; Vermeer et al, 2013b). This concept of treat to target is supported by other studies, such as the TICORA study (Grigor et al, 2004*), in which patients who were followed up with tight control of disease activity had less radiographic progression than patients followed up by a standard regimen.

2.4 Established disease

The clinical challenge in patients with established disease is different from that of recent-onset or early RA. The joint involvement can be dominated by deformities as a consequence of longstanding inflammation and radiographic damage. However, active inflammation may still be present and should be treated, in order to prevent further radiographic damage, deformities and disability. Imaging modalities such as ultrasound and MRI may be useful to assist the practitioner in distinguishing between mechanical and inflammatory joint pain.

In established RA, it is also particularly important to be aware of the extra-articular manifestations and the possibility of involvement of internal organs. Surgical procedures with joint replacement may be required for certain patients and a detailed examination of joints, with particular focus on the functional consequences of the deformities, may be clinically relevant.

2.4.1 Involvement of hands

The MCP and PIP joints are frequently involved in RA. Involvement of the DIP joint is uncommon and is more likely to indicate concurrent osteoarthritis, psoriatic arthritis or gout. Deformities of the PIP joints usually result from lack of ligament support. Boutonnière deformity (figure 17) describes a finger with flexion of the PIP joint and hyperextension of the DIP joint, due to relaxation and volar displacement of the central tendon slip at the PIP joint. A similar deformity of the thumb is known as a 'Z-shaped' deformity due to flexion of the MCP joint and hyperextension of the IP joint at 90 degrees (figure 18). A swan-neck deformity of the finger describes hyperextension of the PIP joint and flexion of the DIP joint (figure 19). Deformities of the MCP joints include volar subluxation, which may be seen as a step-like, ulnar drift (often in combination with radial deviation of the wrist) and flexion deformities.

Figure 17 Boutonnière deformity of the ring finger. (Source: Cofer, <http://www.lecofer.org>.)



Figure 18 Z-shaped deformity of the thumb.



Figure 19 Swan-neck deformity of the 5th digit.



Wrist deformities include volar subluxation with a visible step opposite the radiocarpal joint, and radial deviation of the carpus from the axis of the wrist and hand. Arthritis of the distal radio-ulnar joint results in instability and dorsal subluxation of the ulnar head with a 'piano key' movement on downward pressure. Dorsal subluxation of the ulnar head with erosive abnormalities will often lead to rupture of the neighbouring extensor tendons (figure 20).

Figure 20 Rupture of the extensor tendons. (Source: Cofer, <http://www.lecofer.org>.)



2.4.2 Elbow and shoulder

The elbow joint is frequently involved in established RA and much less commonly in OA, unless there is a history of local trauma. Loss of extension with a fixed flexion deformity is a typical early sign. Functionally, loss of supination is disabling when eating and performing daily activities. The other disabling limited motion is reduced flexion. This may lead to an inability to perform personal grooming of the hair and face. Thus, the maintenance of flexion and supination is an extremely important functional objective.

Shoulder involvement in RA is less common, but in most patients with severe disabling RA the shoulder will be affected to some degree. Shoulder symptoms usually appear when joint destruction has become advanced and this tends to limit daily self-care activities. Synovitis leads to erosion and damage of both the humeral head and the glenoid fossa. The long head of the biceps tendon may rupture. The rotator cuff is also frequently involved, with inflammation, tendon rupture and bursitis. Involvement of the acromio-clavicular joint is uncommon.

2.4.3 Cervical spine

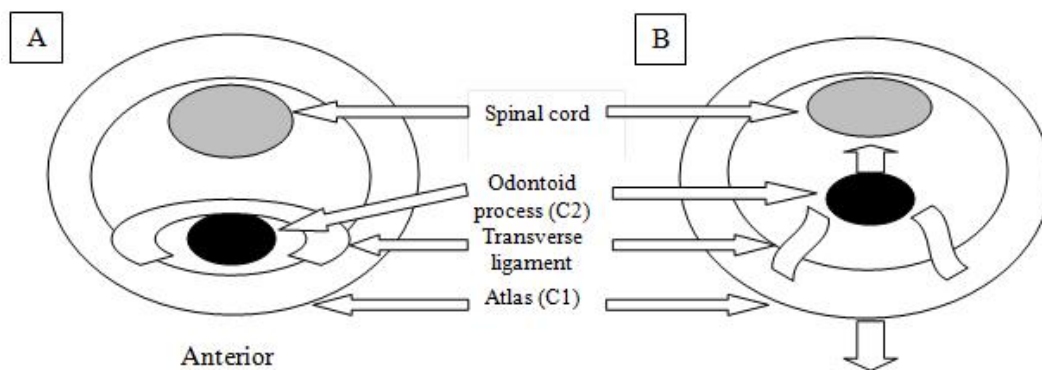
Involvement of the cervical spine is relatively rare but potentially life-threatening. There is a synovial articulation between the transverse ligaments of the atlas of the posterior aspect of the odontoid (dens). This thick strong transverse ligament acts as a sling in maintaining the odontoid process against the posterior surface of the atlas and thus prevents forward movement of C1 on C2. Persistent synovitis of this joint may produce erosions of the dens, compromising the transverse ligament and resulting in instability. The space between the anterior aspect odontoid process (C2) and the posterior surface of the anterior arch of the atlas (C1) normally measures ≤ 3 mm. If this space exceeds 5 mm (some clinicians will say 3 mm) the condition is defined as atlantoaxial (or C1–C2) subluxation. Synovial involvement may also affect the apophyseal joints in the cervical spine. The consequence of synovitis in this area may be an atlantoaxial subluxation with neurological symptoms due to cervical myelopathy.

When considering the cervical spine at the C1–C2 level it is helpful to divide the space through the arch of the atlas into thirds, one-third for the odontoid process, one-third for the spinal cord and one-third free (figure 21). If the C1–C2 subluxation exceeds 10 mm, the free third is lost and cervical cord damage becomes a significant risk owing to direct contact between the odontoid process and the spinal cord.

In severe cases, vertical dislocations may also occur with the odontoid process penetrating upwards into the foramen magnum, compressing the brainstem (basilar invagination), which may be fatal. Thankfully, this is now an exceedingly rare occurrence.

When a patient with RA requires surgery, the presence of cervical subluxation presents a significant risk during general anaesthesia, due to intubation with the neck in an extended position. Consequently, routine lateral cervical radiographs with the head in a neutral and a flexed position are recommended before surgical procedures. An open-mouth frontal X-ray examination demonstrating the odontoid may also be useful. Special precautions are required preoperatively to prevent cervical cord damage when atlantoaxial subluxation is detected.

Figure 21 Schematic axial representation of the atlantoaxial joint from above. (A) In a healthy state; (B) after rupture of the transverse ligament with anterior translation of the atlas ring.



The use of other imaging modalities such as MRI to determine the degree of active synovitis and pannus formation (figure 22) and CT to better visualise the presence of erosive disease (figure 23), is becoming increasingly frequent. Nevertheless, these techniques are ‘static’ and do not replace the need for ‘dynamic’ radiographs.

Figure 22 MRI of the cervical spine with sagittal T1 FLAIR (left) and sagittal T2-weighted images (right). Pannus formation (long arrow) with low signal intensity on T1- and T2-weighted sequences behind the odontoid process with compression of the spinal cord at the level of C1. (Reproduced with permission from Del Grande et al, *Semin Arthritis Rheum* 2014;43:738–44.)

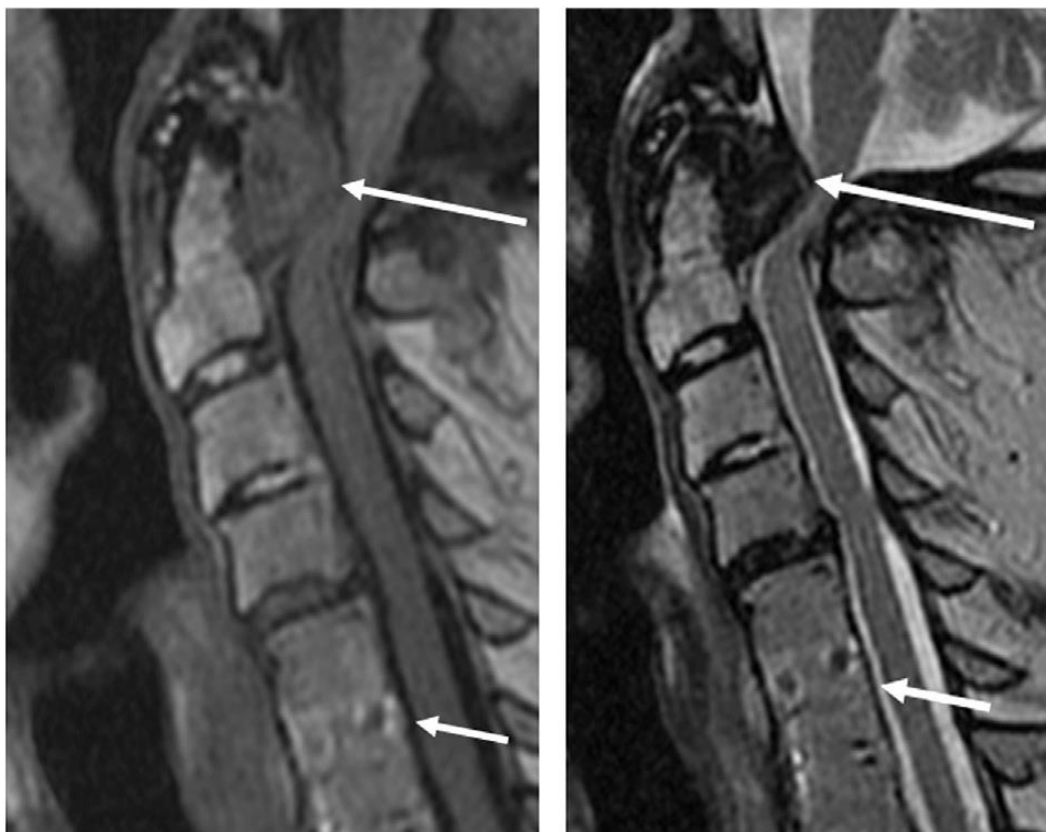
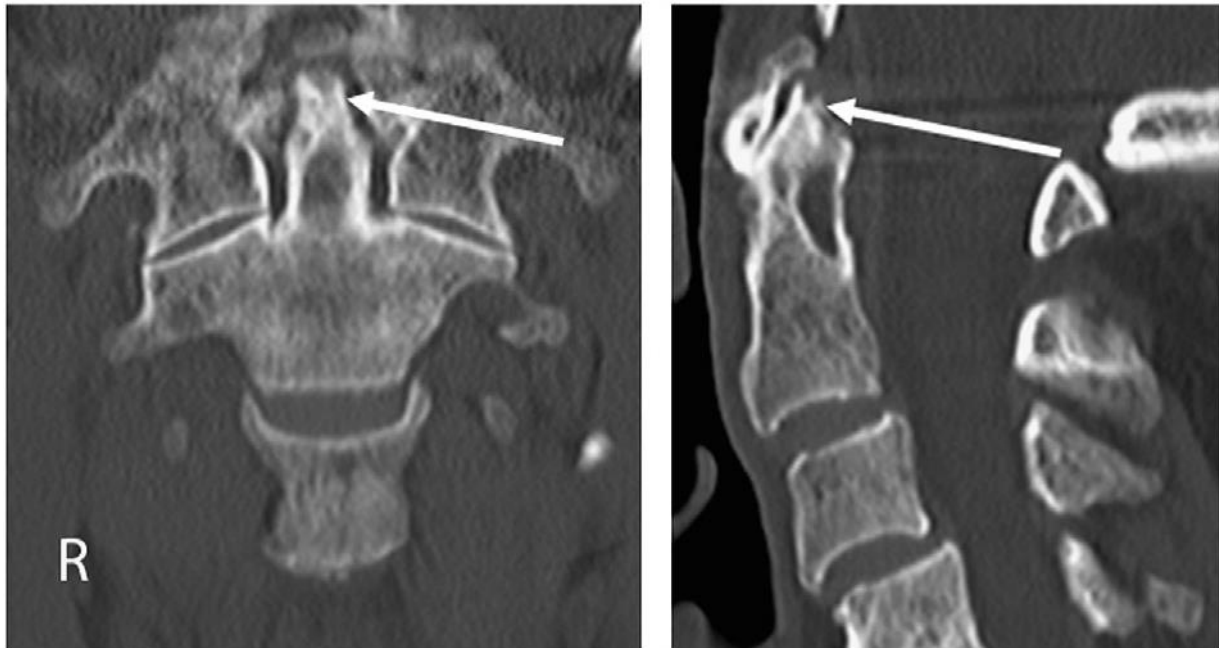


Figure 23 CT scan of the cervical spine with coronal (left) and sagittal (right) images, with presence of erosions of the odontoid process (arrow). (Reproduced with permission from Del Grande et al, Semin Arthritis Rheum 2014;43:738–44.)



Wearing a stiff cervical collar can be an important treatment for patients with atlantoaxial subluxation, especially when there is risk of neck injury. Some patients with significant cervical instability and/or neurological impairment will require surgical procedures with fixation to stabilise the cervical spine.

2.4.4 Joints of the lower limbs

The hip is infrequently involved in RA, but may be affected either directly by the disease or indirectly via secondary OA. Knee involvement, however, is much more common in RA. Synovial effusion is the typical sign of inflammatory activity of the knee. Patients with knee swelling have a tendency to assume a more comfortable position with the knee flexed and if this becomes a habit, a loss of full knee extension eventually results.

Posterior knee pain may be due to a cyst in the popliteal region, called a Baker's cyst. This cyst can extend from its location in the gastrocnemius bursa down into the medial aspects of the calf. This is best seen when the patient is standing. The Baker's cyst arises as an extension from the joint cavity. Rupture of this cyst can result in generalised swelling of the calf and a clinical picture which mimics deep vein thrombosis. Destruction of the knee joint may lead to instability due to laxity of the collateral and cruciate ligaments. This laxity is detected by stressing the knee joint for lateral and medial collateral stability. A particular problem arises in women with physiological valgus. This valgus increases the load on the lateral compartment and as the valgus increases due to arthritis, the loading will also increase so that a vicious cycle occurs. Varus deformity is more common in OA than in RA.

Within the foot, the subtalar and mid-tarsal joints are more frequently involved than the talocrural joint (figure 24). The ankle is usually quite stable, but reduced dorsal flexion may interfere with walking, particularly on an incline. The subtalar and talonavicular joints are commonly affected in RA. Synovitis causes pain and stiffness and may occasionally lead to subtalar dislocation. As cartilage loss progresses and bone erosions develop, valgus deformity increases with progressive flattening of the longitudinal arch. Involvement of the MTP joints is common in RA, causing pain and disability. Forefoot deformity starts with synovitis of the MTP joints and involvement of the flexor tendons, which can result in clawing of the toes and dorsal dislocation of the MTP joints (figure 25). The metatarsal heads can be destroyed owing to the synovitis and this can lead to extreme pain. The forefoot in longstanding RA takes on a triangular appearance (figure 26).

Figure 24 Ankle involvement in early RA.



Figure 25 Rheumatoid foot with clawing of multiple toes.



Figure 26 Characteristic deformity of the feet in rheumatoid arthritis with lateral deviation at the metatarsophalangeal joints and a triangular shape with *halux valgus* and *quintus varus*.



2.4.5 Other joint areas

The temporal mandibular joint may be involved with tenderness and painful limitation of mouth opening. Occasionally the cricoarytenoid joint may be involved and associated with voice hoarseness. The ossicles of the ear may rarely be involved with hearing loss independent of medication-induced effects.

2.4.6 Nodules, tenosynovitis and bursitis

Rheumatoid nodules are the most frequent inflammatory extra-articular feature of RA, affecting approximately 40% of South European and up to 65% of patients from Anglo Saxon countries (Carmona et al, 2003). Histologically, they are Th1 granulomas containing three main cell types: activated macrophages, T lymphocytes and dendritic cells. The cytokine pattern within the nodule is similar to that in the synovial lesion (Hessian et al, 2003). Nodules may form over pressure locations such as the dorsal elbow, occiput, palms of the hands and Achilles tendon (figure 27). Gouty tophi may have a similar appearance and distribution, although they tend to be in close proximity to the joint or in a bursa.

Rheumatoid nodules are almost exclusively seen in seropositive disease, they occur more commonly later in the disease course, and are associated with other extra-articular features of RA (Turesson et al, 2008). Despite the fact that early occurrence of rheumatoid nodules was univariately associated with greater radiographic progression within five years, this association did not turn out to be independent of baseline damage and ACPA positivity (Nyhall-Wahlin BM et al, 2011). Similarly, rheumatoid nodules have been associated with the occurrence of cardiovascular events when adjusted for traditional cardiovascular risk factors, but not independently of RA-specific variables (Kaushik et al, 2015). Thus, rheumatoid nodules may be perceived as a useful clinical indicator of worse prognosis, but in the context of other relevant disease features.

Figure 27 Rheumatoid nodules in rheumatoid arthritis. (Source: Cofer, <http://www.lecofer.org>.)



Flexor tenosynovitis can lead to loss of active flexion. A trigger finger is a frequent feature of flexor tenosynovitis. The pathology is a thickening of the tendon with stenosis within the tendon sheath. A rupture of flexor tendons may occur but these are much less common than extensor tendon ruptures.

Flexor tenosynovitis at the level of the carpal tunnel may lead to entrapment of the median nerve and development of a carpal tunnel syndrome. The patients will have weakness and finger tingling and sensory loss, especially in the index and middle finger. Diagnosis can be established by nerve conduction studies or by ultrasonography. Extensor tendon involvement often manifests as a swelling of the dorsum of the wrist, below the extensor retinaculum. Asking the patients to extend the fingers will accentuate the swelling. One of the most common sites of tenosynovitis in active RA is the extensor carpi ulnaris on the ulnar aspect of the wrist joint.

Bursae should not be overlooked in the evaluation of any joint region. The bursae are lined by a synovial membrane that secretes synovial fluid and may develop rheumatoid synovitis. Involvement of the olecranon bursa by RA is a typical example of bursitis. Other bursae that are frequently involved are the subacromial bursa (in the shoulder), the trochanteric bursa (at the greater trochanter) and the retro-calcaneal bursa (adjacent to the Achilles tendon).

2.4.7 Extra-articular manifestations and RA-related comorbidities

Extra-articular manifestations and RA-related comorbidities are listed in table 7.

2.4.7.1 Secondary osteoporosis

RA is associated with an increased generalised bone loss, as diagnosed by a reduced bone mineral density (Haugeberg et al, 2000). Increased occurrence of vertebral and non-vertebral fractures has also been demonstrated. It has also been shown that RA is independently associated with increased occurrence of vertebral fractures (Orstavik et al, 2004). There is a twofold increase in the occurrence of osteoporosis both in men and women with RA. It is generally assumed that osteoporosis is due to inflammation (eg, cytokine release with osteoclast activation), but the use of glucocorticoids and immobility are also significant risk factors. It is important to assess bone mineral density in patients at risk. Preventive treatment (with vitamin D and calcium) should be considered, with the addition of anti-resorptive therapy when indicated.

Table 7 Extra-articular manifestations of rheumatoid arthritis

Haematological	Anaemia Thrombocytosis Leucopenia and thrombopenia (with Felty's syndrome)
Pulmonary	Diffuse interstitial fibrosis Pleural effusion Nodules Fibrosing alveolitis Bronchial dilatation Pneumoconiosis (Caplan's syndrome) Pulmonary hypertension (rare) Obliterative bronchiolitis (extremely rare)
Hepatic	Liver function abnormalities
Ocular	Keratoconjunctivitis sicca Episcleritis or scleritis
Vasculitis	Nail fold Systemic
Cardiac	Pericarditis Pericardial effusion Valvular heart disease Conduction defects
Neurological	Nerve entrapment Cervical myelopathy (atlantoaxial subluxation) Neuropathy: peripheral neuropathy or mononeuritis multiplex
Cutaneous	Subcutaneous nodules Pyoderma gangrenosum Vasculitic rashes Leg ulceration Amyloidosis

2.4.7.2 Muscles

Muscle weakness and atrophy (figure 28) are common in RA and may be secondary to neuropathy, glucocorticoid use, or immobility due to joint pain and swelling.

Figure 28 Interosseous muscle atrophy. (Source: Cofer, <http://www.lecofer.org>.)



2.4.7.3 Secondary Sjögren's syndrome

Secondary Sjögren's syndrome is a relatively frequent manifestation of RA with 'sicca symptoms', signifying dry eyes and dryness of the mouth. The exocrine function of tear glands and salivary glands may be altered in rheumatological disorders such as Sjögren's syndrome, or secondary to RA and other connective tissue disorders. Some studies have shown that RA with secondary Sjögren's syndrome may present with mild clinical manifestations or may even be asymptomatic, although there are usually clear histological changes in the salivary glands. Sicca symptoms are common in RA and about 10% of patients have secondary Sjögren's syndrome. The diagnosis can be established by testing for reduced saliva and tear production. Tear production can be assessed with the Schirmer test and it is performed by placing a test strip inside the lower eyelid. Local anaesthetic drops can be placed into the eye before the test to prevent tearing due to irritation from the test strip. After 5 min the strips are examined and a positive result is recorded if the strips show moistening of ≤ 5 mm in one or both eyes.

2.4.7.4 Other eye complications

Scleritis, episcleritis or both can occur in patients with RA, but are rather infrequent. Episcleritis may have an extremely rapid onset with the eye becoming red within minutes. Unlike other inflammatory conditions of the eye, episcleritis results in no discharge other than tearing. Loss of vision does not occur as a direct result of episcleritis but cataracts may develop secondarily and cause visual loss. Scleritis causes severe ocular pain and a dark red discolouration and can lead to vision-threatening perforation.

2.4.7.5 Infections

The incidence of bacterial infections is increased in patients with RA, partly owing to the disease itself and partly owing to the use of immunosuppressive drugs, such as glucocorticoids, disease-modifying drugs (DMARDs) and various biological agents. Registry data suggest approximately a doubling of the risk of a serious infection with anti-TNF therapy (van Dartel et al, 2013). The most common sites of infection are the respiratory tract and the skin. The risk of septic arthritis is also increased in patients with RA and it can be extremely challenging to differentiate between an acute flare of monoarthritis secondary to RA and a septic arthritis. It is therefore critical to urgently aspirate the joint and to organise a Gram stain and culture of the synovial fluid.

2.4.7.6 Cancer

There is a slightly increased risk of malignancy in patients with RA, especially lymphoma in certain patient subsets, such as those with longstanding disease and seropositive patients. It has been clearly shown that this risk is related to the severity and inflammatory activity of the disease (Baecklund et al, 2006). The anti-TNF agents do not appear to increase the overall rate of malignancy, except for skin cancers (melanoma and non-melanoma), where the risk is about doubled (Raaschou et al, 2013). Consequently, regular clinical examination for lymph nodes and dermatological review are important.

2.4.7.7 Haematological abnormalities

The majority of patients with RA have a mild normocytic hypochromic anaemia that correlates with elevation of the acute phase reactants and the activity of the disease. A few of these patients respond to treatment with iron. Folate and B12 deficiency may also be a cause of anaemia in RA. Thrombocytosis is frequent in RA and is related to disease activity. Leucopenia (particularly neutropenia) and thrombopenia in association with splenomegaly suggest Felty's syndrome.

2.4.7.8 Vasculitis

One of the initial pathological changes in RA includes inflammatory changes in small blood vessels. However, when considering vasculitis as a complication, the focus is more on the arteries or arterioles. Typical

manifestations include purpuric lesions on the skin that can subsequently develop into cutaneous ulceration (figure 29), peripheral neuropathy or involvement of internal organs. Vasculitis is fortunately rather uncommon. The presence of vasculitis is associated with disease severity, although it does not necessarily parallel the activity of the joint manifestations. A form of localised RA vasculitis with small periungual lesions is generally benign and does not require additional immunosuppressive therapy.

Figure 29 Cutaneous vasculitis. (Source: Cofer, <http://www.lecofer.org>.)



The two common neurological manifestations are a mild distal sensory neuropathy and a severe sensory motor neuropathy (mononeuritis multiplex). The latter form is characterised by severe arterial damage on nerve biopsy specimens. Symptoms of the milder form include paraesthesias or burning in a stocking and glove distribution, in association with decreased touch and pin-prick sensation. Organ-specific vasculitis can lead to organ infarctions. Neurovascular disease may be the only manifestation of vasculitis and establishing the diagnosis is often challenging. Severe organ-threatening vasculitis must be managed aggressively with high-dose glucocorticoids and immunosuppressive agents.

2.4.7.9 Renal disease

The kidney is rarely affected directly in RA but membranous nephropathy, vasculitis and secondary amyloidosis have been described. However, both analgesics such as the non-steroidal anti-inflammatory drugs (NSAIDs) as well as some DMARDs (eg, gold, ciclosporin) can affect renal function, resulting in raised serum creatinine and/or proteinuria.

2.4.7.10 Pulmonary disease

RA-associated lung disease has become recognized as a relatively frequent extra-articular disease manifestation, with a prevalence within the range between 5% and 30% (Chansakul et al, 2015; Cavagna et al, 2013), reaching even 67% (Bilgici et al, 2005). The rather wide range of estimated prevalence is a result of differences in study designs and studied populations, as well as lacking diagnostic and classification criteria for lung affection in patients with RA. Nevertheless, it is widely accepted that lung disease in RA patients may be caused by the disease itself, by infections or by drugs used to treat the disease.

The disease itself may affect the pleura, the lung parenchyma, large and small airways, as well as – less commonly – the pulmonary vasculature (Chansakul et al, 2015). All of these presentations may be asymptomatic and occasionally precede the articular features of RA (Lee et al, 2005). Pleural disease in RA presents as pleuritis with or without secondary pleural exudative effusion and fibrosis, and – less frequently – as bronchopleural fistula and pneumothorax due to ruptured subpleural rheumatoid nodules (Chansakul et al, 2015).

Parenchymal affection comprises interstitial lung disease (RA-ILD) and the relatively uncommon pulmonary rheumatoid nodulosis. Interstitial lung disease (ILD) is rather common in longstanding RA, with an estimated prevalence of up to 67% (Bilgici et al, 2005). However, ILD-related HRCT features were identified in almost 30% of RA patients within two years from disease onset (Habib et al, 2011). RA-ILD is more common in men, aged over 60 years, in smokers and in those with high titres of RF (Cavagna et al, 2013). The description of RA-ILD follows the American Thoracic Society/European Respiratory Society international consensus classification of idiopathic interstitial pneumonias (American Thoracic Society and European Respiratory Society, 2002) and its recent update (Travis et al, 2013), given the lack of a dedicated classification. About 50% of patients with RA with ILD have the usual interstitial pneumonia (UIP) subtype with bilateral subpleural predominantly basal reticulation, with honeycombing on HRCT, about a third, the non-specific interstitial pneumonia (NSIP) subtype with predominant ground-glass abnormalities, followed by organising pneumonia (OP) with patchy areas of consolidation. Organising pneumonia, in particular, responds well to glucocorticoid treatment, while the patients with usual interstitial pneumonia usually far worse. Less common patterns observed in the context of RA-ILD are desquamative interstitial pneumonia (DIP), lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia (AIP) and diffuse alveolar damage (DAD) (Yunt and Solomon, 2015). HRCT is the initial method of choice to determine the ILD subset, especially for UIP and NSIP where its accuracy compared to histological diagnosis has been reported to be about 70% (Cavagna et al, 2013). Biopsy should still be performed in cases of less typical HRCT findings to exclude infection and to discern between UIP and other RA-ILD subtypes in patients not responding to treatment (Lee et al, 2005).

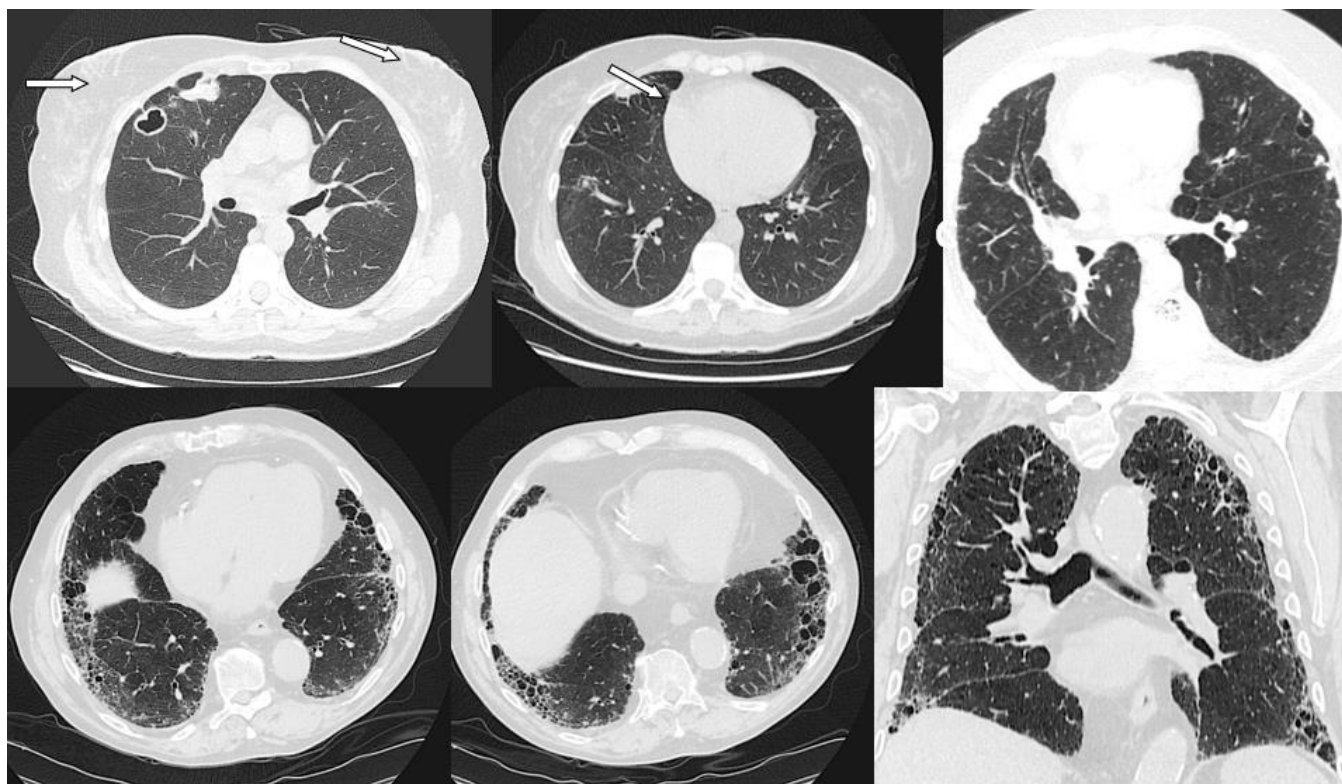
Nodular lung disease is an uncommon feature, more frequent in patients with subcutaneous rheumatoid nodules and in patients with a high RF titer (Capobianco et al, 2012)(figure 30). Pulmonary rheumatoid nodules are usually asymptomatic and the prognosis is generally good, although complications may occur. They may pose a diagnostic challenge, especially when presenting as a single nodule, which may mimic malignancy or infection. Calcified pulmonary nodules are a feature typical for Caplan's syndrome – pulmonary nodulosis in patients with pneumoconiosis.

Both the large and small airways may be affected in RA. Lung function tests and HRCT are essential to determine the nature and extent of airway involvement. Bronchiectasis is the most common disease of the airways in RA, affecting up to 50% of patients (Junt and Solomon, 2015). Their significance lies in the increased risk of infections.

Patients with RA are prone to respiratory infections owing to their use of immunosuppressive medication. Pneumonia due to opportunistic infection can mimic ILD, which can be challenging, especially in the context of previously known ILD (Cavagna et al, 2013).

Last but not least, the possibility of drug-related lung disease must always be taken into account in any patients with RA who present with new-onset cough or shortness of breath (Amital et al, 2011). Drugs associated with the occurrence of lung disease are methotrexate, TNF-alpha inhibitors, leflunomide, rituximab, sulfasalazine and tocilizumab (Yunt and Salomon, 2015). New-onset pulmonary disease including various ILD subtypes have been described in the context of their use. However, the mechanism and causality of these relationships still remains to be clarified (Shaw et al, 2015).

Figure 30 Pulmonary disease in rheumatoid arthritis. Upper left: excavated pulmonary nodule; upper centre: calcified pleural nodule; upper right: bronchiectasis; lower left: usual interstitial pneumonia (UIP); lower centre: honeycombing; lower right: coronal image of UIP.



2.4.7.11 Cardiac complications

Pericarditis can be seen as part of the inflammatory activity with RA and is often present concurrently with pleuritis. Inflammation of the myocardium and endocardial inflammation may also be present. These manifestations generally resolve as disease activity is controlled. Conduction defects and haemodynamically significant valvular lesions are uncommon.

2.4.7.12 Arteriosclerosis

Several studies have shown that patients with RA have an increased risk of clinical coronary heart disease (CHD) compared with age- and sex-matched subjects without RA and that this risk is maintained after controlling for traditional CHD risk factors (diabetes mellitus, hypertension, dyslipidaemia, body mass index and smoking). One study suggested that the risk of CHD in patients with RA even precedes the ACR criteria-based diagnosis of RA (Maradit-Kremers et al, 2005).

Some studies support the view that atherosclerosis correlates with the level of systemic inflammatory activity over time and that the inflammatory process affects cardiovascular morbidity and mortality and accelerated coronary and extra coronary atherosclerosis (Chung et al, 2007). The therapeutic consequence is that anti-

inflammatory therapy may reduce the cardiovascular risk and some studies have supported this by showing that treatment with methotrexate (Choi et al, 2002) and anti-TNF agents (Jacobsson et al, 2005) may reduce cardiovascular morbidity and mortality. Several biological agents such as tocilizumab (anti-IL-6R monoclonal antibody) and tofacitinib (anti-JAK) tend to increase serum levels of low-density lipoprotein cholesterol. However, the clinical relevance of these changes to cardiovascular outcomes is unknown.

2.4.7.13 Gastrointestinal manifestations

RA does not affect the gastrointestinal tract directly. Gastro-duodenal ulcers are, however, rather frequent owing to the use of NSAIDs, which is why proton-pump inhibitors are routinely prescribed to patients with RA receiving chronic NSAID therapy. Liver disease may also be secondary to drugs commonly used in RA, such as methotrexate, NSAIDs and paracetamol. Liver involvement may be present in up to two-thirds of patients with Felty's syndrome. Liver biopsies are now rarely required, although abdominal ultrasound and fibro-scans may be of some use in monitoring patients with liver function test abnormalities.

2.4.7.14 Secondary amyloidosis

Secondary amyloidosis is an increasingly uncommon complication of RA. This is thought to be related to the implementation of more effective treatment strategies in RA. Amyloidosis results from the deposition in various organs (such as the kidneys) of an autologous protein in an insoluble fibrillar form. In patients with RA, excess serum amyloid A protein production is stimulated by the cytokines of the inflammatory response. Previously, renal amyloidosis was a rather frequent complication, leading to renal failure, dialysis and renal transplantation, but this should now primarily be regarded as treatment failure of RA itself.

Although the diagnosis of amyloidosis may be suspected on the basis of history and clinical manifestations, a tissue biopsy should be used to confirm the diagnosis. An abdominal fat pad biopsy is recommended for patients with more than one organ affected. In patients with just one organ involved, biopsy of the clinically affected organ is suggested as fat pad biopsy has a low sensitivity for amyloidosis in these patients.

2.4.8 Functional disability and its consequences

RA is associated with significant pain and joint destruction, as well as progressive loss of mobility and the ability to care for oneself (figure 31). Pain is the area of health in which most patients would like to see improvement (Heiberg and Kvien, 2002). Important correlates of functional disability in patients with RA include female sex, age, disease duration and disease activity measures, such as the Ritchie articular index and ESR, which can be considered predictors of a poorer functional status.

Figure 31 X-ray picture of a right hand in longstanding erosive rheumatoid arthritis with arthrodesis of the wrist, Z-shaped deformity of the thumb and subluxation of the metacarpophalangeal joints, resulting in significant functional impairment.



In addition to indicating a requirement for more aggressive treatment, high levels of disability have a negative impact on the psychological and social functioning of a patient, the consequences of which include mental distress, depression and fatigue. Pain and disability are the two variables most consistently related to mental distress, and high levels of disability with a consequently decreased ability to cope are commonly associated with depression, even in the early stages of the illness. This association of RA with depression has important implications for the overall healthcare burden of the disease and points to the need to deal with depression as part of a patient's comprehensive treatment plan.

Fatigue is also a significant and frequently debilitating problem for people with RA, as it contributes to work difficulties, reduced ability to participate in rehabilitation programmes and strained personal relationships. The FACIT (Functional Assessment of Chronic Illness Therapy) measurement system is a collection of health-related quality-of-life questionnaires that can be used to measure fatigue. Fatigue scores are significantly higher in patients with RA than in healthy individuals, and patients with RA with a history of affective disorder have higher levels of fatigue than those without such a history. The fatigue experienced by the patients with RA is strongly associated with disease severity measured by DAS28 and Clinical Disease Activity Index scores and is independent of anaemia.

2.4.9 Mortality

While RA has traditionally been regarded as a chronic, painful, disabling condition with an essentially non-fatal outcome, numerous studies conducted over the past four decades have found that it is associated with an increased mortality in comparison with the general population of the same age and gender. Standardised mortality ratios (ie, the ratio of deaths among patients with RA compared with the age-matched general population) have been reported to range from 1.16 to 3.0 in studies conducted in various countries. Some studies show a more pronounced increase in mortality in women. Disease severity, activity and disability are strongly linked to mortality in patients with RA, and other independent predictors include age, level of education, comorbidity and use of glucocorticoids. However, whether glucocorticoid use is a marker of disease severity or is in itself deleterious remains unclear.

The major causes of death among patients with RA are cardiovascular and cerebrovascular diseases. Male sex and age at disease onset have been found to predict both the occurrence of cardiovascular events and death. However, it is uncertain whether the results from these previous studies correctly reflect the current mortality risk. Some studies have indicated that RA is now a milder disease than it was several decades ago and also that the disease on average starts later than before. It is also assumed that the advances in treatment strategies and access to new treatments have improved the health of patients with RA. However, it is still important to consider RA as a severe disease with a potential reduction in life expectancy.

2.4.10 Has the disease improved?

To examine changes in disease severity over time potential outcomes include survival, the need for joint replacement surgery, health status and employment. Decreased disease mortality has been reported from Sweden. Data from 47 000 patients were collected from the Swedish Hospital discharge registry. The patients were followed up after 5 and 10 years and this was then linked to the cause of death registry. Compared with patients discharged in the 1960s and early 1970s, patients with RA discharged in the 1980s and 1990s had a significantly reduced mortality rate (Bjornadal et al, 2002). Nevertheless, compared with a matched population, mortality in RA was still doubled, mainly owing to cardiovascular disease. Interestingly, a decreasing mortality for patients in the past two decades was observed.

Despite being considered the most important advance in the management of rheumatic diseases back in the 1980s (Fries, 1989), joint replacement surgery is today an undesirable disease outcome that can be postponed by early administration of disease modifying therapy (Moura et al, 2015). This is based on the notion that early treatment may significantly lower the rate of radiological progression, possibly targeting pathogenetic mechanisms still reversible during the existence of the early therapeutic “window of opportunity” (Kyburz et al, 2011). It is noteworthy that joint surgery other than joint replacement was also delayed in patients from a population-based cohort treated early with DMARDs (Verstappen et al, 2006). These non-joint-replacement

interventions include rheumatoid nodule removal, arthroscopy, carpal tunnel decompression, arthrodesis, synovectomy and resection arthroplasty. In the multivariate analysis, factors associated with risk of joint surgery were higher joint scores (as measures of disease activity) and radiographic progression early within two years following diagnosis (Verstappen et al, 2006).

Several studies demonstrated a decline or at least no change in rates of RA-related joint surgery in the 2000s compared to previous decades, which is in contrast to increasing rates of joint surgery in the general population (mainly due to osteoarthritis)(Jämsen et al, 2013; Sokka et al, 2007; Louie and Ward, 2010). The observed contrast may be ascribed to the increasing use of DMARDs among RA patients – primarily conventional synthetic DMARDs, since data on the role of biologicals in preventing joint surgery still remain scarce. Other plausible explanations may be patient selection towards milder RA cases and natural evolution of RA towards a milder disease (Sokka et al, 2007).

Data from the National Database of the German Collaborative Arthritis Centres show a decrease in disease activity scores for the period between 1997 and 2007, with the number of patients with low disease activity (DAS28 <3.2) having increased from 23% to 49%. At the same time, the intensity of drug treatment increased, with 23% of patients being treated with combinations of DMARDs in 2007 as compared with only 8% a decade earlier. Importantly, this development was paralleled by a strong decrease in the number of annual days of sick leave for each employed person (Ziegler et al, 2010).

A shift to an older age at RA onset has also been reported during the past few years. If patients nowadays develop RA at an older age than previously and if we assume that disease progression is the same, then today's average patient with RA would be spared several years of disease severity in comparison with patients several decades ago. Documentation of improved long-term outcome requires long-term observational data over 10–20 years. Repeated cross-sectional data from the Oslo RA registry in 1994 and 2004 suggest an improved overall health status. For example, the average Modified HAQ score improved from 1.68 in 2001 to 1.58 in 2004. Similar findings were obtained for other dimensions of health status (Heiberg et al, 2005).

Summary Points

- ➔ Joint involvement with a symmetrical small-joint polyarthritis dominates the clinical picture of RA, but extra-articular manifestations may be present both at disease onset and in established disease.
- ➔ The new 2010 ACR/EULAR classification criteria recognise the need to diagnose and treat RA early in order to prevent joint damage and preserve normal functional status.
- ➔ Identification of prognostic markers are as important as the diagnosis of the disease. Elevated acute phase reactants, presence of ACPA and rheumatoid factor, and erosive disease at disease onset, predict persistent erosive arthritis.
- ➔ Several differential diagnoses need to be considered. RA frequently starts after the age of 50, thus generalized osteoarthritis with finger involvement will often be an important consideration. In younger age groups, reactive arthritis and connective tissue diseases need to be considered.
- ➔ RA may result in joint deformities, particularly in the hands and feet. Hand and feet radiographs remain the gold standard in RA imaging, although the use of ultrasonography and MRI is becoming increasingly frequent.
- ➔ Osteoporosis and premature arteriosclerosis are common in RA and are probably related to the inflammatory activity. More data are needed to clarify whether active anti-inflammatory treatment will reduce the frequency of these manifestations.
- ➔ The overall health of RA patients and the burden of disease has improved over the past few decades, which is most likely due to better and more aggressive treatment strategies, and access to better diagnostic, monitoring and treatment modalities.

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module

EULAR on-line course on Rheumatic Diseases

Pathogenesis and clinical aspects of rheumatoid arthritis

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IN-DEPTH DISCUSSION I

**Measuring disability and health-related quality of life
(HRQoL) in rheumatoid arthritis (RA)**

Summary

Rheumatoid arthritis (RA) can cause severe disability and reduce health related quality of life, aspects that are important to the patients. Thus, it is important to measure disability and health related quality of life in clinical practice and in clinical trials. The aim of this summary is to present an overview of the most important patient self-report instruments that are used to assess disability and health-related quality of life (HRQoL) in patients with RA.

The concepts

Several definitions of disability have been presented. In a recent review, (Leonardi et al, 2006) the following definition has been proposed: "Disability is a difficulty in functioning at the body, person or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors". HRQoL is a broader concept which can be defined as the impact of health on an individual's ability to function as well as the perceived well-being in physical, mental and social domains of life (Coons et al, 2000). Disability is a subset of HRQoL.

The measurement tools

Questionnaires are used to assess disability and HRQoL. Visual analogue scales (VAS) are widely used to measure pain and fatigue, as well as the patients' global assessment of their disease. Generic instruments with several items have been developed for use in patients regardless of disease. One of the major advantages of such instruments is the opportunity to compare results between disease groups and to compare patients with healthy individuals (Kvien and Uhlig, 2006). Disease specific instruments have typically been developed for use in patients with RA or other arthritic diseases.

Instruments measuring disability

The Stanford Health Assessment Questionnaire (HAQ) (Bruce and Fries, 2005) was introduced in the 1980's and is now widely used in evaluation of patients with RA. It was initially developed for use in rheumatology, but has later also been applied to other diseases. Some investigators will therefore argue that HAQ can be considered a generic instrument.

The disability index includes questions about the ability of patients to perform 20 activities of daily living, and is most commonly referred to as the HAQ-questionnaire, and sometimes as the HAQ-disability index (HAQ-DI). Four response categories are available for each question; without any difficulty (score 0), with some difficulty (score 1), with much difficulty (score 2) or unable to do (score 3). The 20 activities are classified into eight categories with two or three activities each. A score is then assigned to each of the eight categories based on the highest score of the items within the category. Patients are also asked about use of aids and devices, and if

they need help from another person for activities in any of the eight categories. If category score is lower than two, it is increased to two within any category in which the patient uses a device or help from another person, so that the underlying disability is more accurately represented. It is important to note that HAQ scores without this adjustment will be lower than the scores obtained with the original scoring system. The total HAQ score, with range 0-3, is the mean of the scores for the eight categories (Bruce and Fries, 2005).

The Modified Health Assessment Questionnaire (MHAQ) (Pincus et al 1983) keeps one question from each of the eight categories in the HAQ and reduces the number of items to eight. No adjustment of scores is possible. The total MHAQ score is the mean of the scores for each activity. MHAQ can easily be administered in clinical practice, but will provide lower scores than HAQ, especially for patients with high disease activity.

A multidimensional health assessment questionnaire (MDHAQ) (Pincus et al, 1999) includes more items, such as demanding physical activities, pain, fatigue, anxiety and depression. The aim of this instrument is to be able to measure disability in patients with healthier conditions and avoid the ceiling effect of HAQ and MHAQ in patients with limited disability. Furthermore, the MDHAQ was developed as a comprehensive measure of disability in a short and user-friendly format and also included questions on other dimensions of health, including stress, anxiety and depression.

Profiles and utility instruments measuring Health Related Quality of Life

There are two main groups of instruments measuring Health Related Quality of Life (HRQoL): Profiles and Utility instruments. A profile contains separate scores for several dimensions. A utility score provides only one sum score for each patient on a scale from 0.0 (a health state similar to death) and 1.0 (perfect HRQoL). Some of the instruments also allow values below 0.0, representing health states that are considered worse than death.

SF-36 (Ware and Sherbourne, 1992) is the most widely used generic health status measure. It is used in health surveys in the general population as well as in various disease populations. The 36 items in the questionnaire are grouped into eight multi-item subscales measuring physical functioning (10 items), role limitations due to physical health (4 items), bodily pain (2 items), general health (5 items), vitality/energy/fatigue (4 items), social functioning (2 items), role limitations due to emotional problems (3 items), mental health (5 items), plus one item on reported health transition. Each scale is expressed with values from 0-100 and a low score indicates poor health. One particular advantage of SF-36 is that it also includes a scale on energy/vitality, a dimension which is considered important by patients. The domain concerning physical functioning is based on 10 items regarding limitations in physical activities because of health problems, but none of these items directly addresses dexterity, which is important in RA.

The EQ-5D (Brooks, 1996) is the most widely used utility instrument and captures five health dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression), with three response categories within each of these dimensions; no problems, some or moderate problems and extreme problems (Brooks, 1996). EQ-5D encompasses 243 different health states (Rasanen et al, 2006). One reason for the widespread use may be that EQ-5D is easy to use with only five questions.

SF-6D is a relatively new utility instrument where some of the answers from SF-36 and SF-12 can be recalculated into a utility score (Brazier et al, 2002). The opportunity to recalculate answers from SF-36, which is already measured in many clinical trials, makes it possible to reduce the amount of questionnaires in studies.

Disease specific profiles

The Arthritis Impact Measurement Scales (AIMS) was developed in 1980 to measure the health status of patients with arthritis (Meenan et al, 1980) with 7 demographic items and 55 health status items. It was later revised into the AIMS2 which is an expanded version of AIMS with 78 items capturing information in 12 areas of health (mobility level, walking and bending, hand and finger function, arm function, self-care tasks, household tasks, social activity, support from family and friends, pain, work, level of tension, mood) (Meenan et al, 1992). These twelve scales can be aggregated into 5 major dimensions (physical functioning, social interaction, pain, work and affect). The score is from 0 to 10 (10 being worst possible health).

The Rheumatoid Arthritis Quality of Life questionnaire (RAQoL) is a RA-specific quality of life measure that comprises 30 statements about unfulfilled needs related to activities relevant to patients (de Jong et al, 1997). Each question is answered with Yes or No. Possible scores range from 0 to 30, the higher score representing worse quality of life.

Clinical meaning of disability and HRQoL in RA

Disability is one of the most important outcomes in RA. Decreased functional status (disability) assessed by HAQ has been identified as the most important predictor of mortality in two studies carried out for over two decades in patients with RA (Wolfe et al, 2003; Yelin et al, 2002). Disability is also associated with work incapacity, representing an important burden for the RA patient and the society (Callahan et al, 1992).

RA-related disability comprises two components: a reversible activity-related component and an irreversible component depending on the extent of damage accrual (Aletaha et al, 2006). The activity-related component is driven by pain and stiffness (Smolen and Aletaha, 2009), whereas the irreversible component, interestingly, is primarily a consequence of cartilage destruction (radiologically detected as joint space narrowing) rather than of bone erosions (Aletaha et al, 2011). According to this model, irreversible disability should equal the level of disability determined after achieving a defined treatment target such as low disease activity or, ideally,

remission. However, improvement of physical function over time has been observed even if the target was achieved and maintained thereafter (Radner et al, 2015). Although this effect may seem contradictory to the “floor effect” of irreversible disability persisting after achieving remission, it might be a consequence of improved residual activity over time and, possibly, recovery of joint mobility, muscle strength and fatigue.

RA is responsible for only a portion of overall disability in patients with RA. At least three other determinants have been identified as contributors to disability in RA: comorbidities, mental health and age (Smolen and Aletaha, 2009). In a study by Radner et al., comorbidities influenced disability independent of RA activity and other disease characteristics (Radner et al, 2010). After achieving remission, a “floor effect” was described, i.e. a residual level of irreversible disability ascribed not only to RA-related damage but also to comorbidities. The observed effect was independent of the instrument used, i.e. the HAQ as a measure of disability or SF-36 as a HRQoL measure (Radner et al, 2010). Furthermore, a higher burden of comorbidities led to increased disability in each domain of the HAQ and to decreased HRQoL as determined by the physical component score of the SF-36. On the other hand, the mental component score of the SF-36 was not influenced by comorbidities (Radner et al, 2011).

Of note, comorbidities were identified in 32% of patients with recently diagnosed RA in an inception cohort from the UK, while their 15-year cumulative incidence was 81% (Norton S et al, 2013). Comorbidities have been associated with an increased risk of all-cause and cardiovascular mortality, as well as a 10-year decline in functional status. Given the association of disability with increased mortality, and the fact that disability is – to a large extent – driven by comorbidities, comorbidities may be the link between disability and increased mortality in RA (Smolen and Aletaha, 2009; Radner et al, 2010). According to a recent systematic review and meta-analysis (Matcham et al, 2014), RA negatively affects overall HRQoL measured by SF-36, as well as its physical (to a greater extent) and mental health components (to a lesser extent). Both of these components are lower in patients with RA compared to the general population, but also - even more strikingly – lower compared to patients with some of the most important causes of morbidity: hypertension, congestive heart failure, type 2 diabetes mellitus and myocardial infarction. Higher age has been associated with lower physical functioning and, interestingly, with a higher score in the mental health domain. The latter effect may be a consequence of a greater impact of the disease on self-realization at a younger age.

Due to their clinical importance and prognostic implications, disability and HRQoL should be regularly assessed throughout the follow-up of patients with RA. They should be taken into account when making clinical decisions, in addition to assessment of disease activity (Smolen et al, 2016).

In summary,

- Questionnaires assessing health have been shown to be useful and important in clinical trials as well as to monitor disease course in clinical practice and to predict important outcomes.
- The choice of instrument should be based on the situation and the goals of the use. Instruments that have been validated should be chosen to optimize the results.
- Disability is comprised of a reversible portion associated with RA disease activity and an irreversible portion resulting from accrued damage and comorbidities.
- Both disability and comorbidities have been described as important predictors of mortality in patients with RA.
- The physical and mental health components of HRQoL are lower in RA than in other important causes of morbidity in the general population, such as myocardial infarction, congestive heart failure and type II diabetes mellitus.

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3

module

EULAR on-line course on Rheumatic Diseases

Pathogenesis and clinical aspects of rheumatoid arthritis

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IN-DEPTH DISCUSSION II

Cytokines and rheumatoid arthritis

Cytokines are small molecular weight mediators of cell-cell communication and include interleukins (ILs), interferons, growth factors, colony-stimulating factors, and other groups. These molecules are released by a variety of cells and usually act locally in a tissue to affect adjacent cells in a paracrine manner. Cytokines also may act inside a cell (intracrine), affect the same cell after release (autocrine), or travel through the circulation to act at a distance in an endocrine manner (i.e. IL-6 and the activation of acute-phase proteins by hepatocytes). Extensive data has been accumulated over the last 20 years to implicate various cytokines in the pathophysiology of rheumatoid arthritis and other rheumatic diseases. Abnormalities in cytokine production are not the cause of these diseases, but reflect continuous production by immune and inflammatory cells.

An important principle to emerge is that chronic inflammatory disease may result from the excess production of pro-inflammatory cytokines and/or the inadequate production of anti-inflammatory cytokines or factors (Mateen et al, 2014). Amongst other cells, macrophages and CD4-positive T lymphocytes play a major role in the production of pro-inflammatory cytokines within the inflamed synovial membrane (Szekanecz, 2007). Pro-inflammatory cytokines with the most prominent role in the inflammation of RA, also serving as targets of successfully used biological therapies, are tumour necrosis factor (TNF)- α and IL-6. They mediate processes inherent to the innate immune response: endothelial activation, migration of leukocytes towards the synovial tissue, activation of fibroblast-like synoviocytes (FLSs) and chondrocytes, angiogenesis and nociception. Furthermore, they are responsible for RA-associated structural damage by activation of osteoclasts (McInnes et al, 2016). IL-6 is directly involved in the acute phase response, it is considered the main driver of anemia of chronic disease (Raj, 2009) and might be associated with an increased cardiovascular risk (McInnes et al, 2015). Additionally, IL-6 has a prominent role in adaptive immunity, regulating the differentiation of naïve T cells towards proinflammatory Th17 cells or anti-inflammatory T regulatory (Treg) cells (McInnes et al, 2016). TNF- α is also involved in adaptive immunity, stimulating proliferation and differentiation of lymphocytes and inducing pro-inflammatory cytokines and other molecules (Mateen et al, 2016).

Members of the IL-1 cytokine family also have a prominent place in inflammation and osteoclast activation in RA, with their role overlapping with the role of TNF- α in innate immunity (Kay and Calabrese, 2004). However, contrary to the clinically effective inhibition of TNF- α and IL-6 receptor, targeting IL-1 has not shown to lead to meaningful clinical results.

GM-CSF and its receptor have been identified as novel targets in the treatment of RA. Granulocyte-macrophage colony stimulating factor (GM-CSF) promotes activation, differentiation and survival of macrophages and neutrophils, promoting their pro-inflammatory activity (Cornish et al, 2009). Mavrilimumab, a monoclonal antibody against GM-CSF receptor has shown to significantly reduce disease activity and improve disability in a phase 2 randomized double-blind study (Burmester et al, 2013).

Several other cytokines present in the rheumatoid synovium are also likely to contribute to the pathogenesis of RA (Table 1 and Figures 1 and 2). The IL-23/IL-17 pathway is potentially involved in the pathogenesis of arthritis (reviewed in Gabay, 2009; Lubberts, 2015; Roeleveld and Koenders, 2015; Mateen et al, 2016). IL-23 is a heterodimeric protein that belongs to the IL-12 family of cytokines. In addition to its specific subunit, p19, it shares a common p40 unit with IL-12. IL-23 stimulates the polarization of Th17 cells and the production of IL-17. It also directly stimulates osteoclastogenesis. Activated synovial macrophages represent a source of IL-23. IL-17, on the other hand, may induce the production of IL-23 by synovial fibroblasts, thus activating a positive feedback loop. Furthermore, IL-17 stimulates the production of IL-1, TNF α , and IL-6 by human monocytes and of IL-6 by rheumatoid synovial fibroblasts. The combination of IL-17 and TNF- α exhibits synergistic stimulation of IL-1 β , IL-6, and IL-8 (also termed CXCL8) production in rheumatoid synovial fibroblasts. The broad effects of IL-17 include promoting persistent disease and supporting angiogenesis by stimulating fibroblast like synoviocytes to produce vascular endothelial growth factor (VEGF). IL-17 also promotes tissue damage by inducing the production of matrix metalloproteinase in human monocytes and their derivatives in synovial tissue, as well as the differentiation of osteoclasts leading to bone degradation. In addition to Th17 cells, IL-17 is also produced by lymphocytes, neutrophils and mast cells within arthritic synovial tissues. Th17 cells also secrete TNF- α and GM-CSF, therefore playing a role in both the innate and adaptive immunity. Blocking IL-23 and IL-17 ameliorates the severity of collagen-induced arthritis.

Serum and synovial fluid IL-17 levels correlate with markers of acute phase response, disease activity and structural damage. However, clinical trials of agents targeting the IL-23 or IL-17 have not shown sufficient clinical efficacy in patients with RA (Lubberts, 2015). One IL-17A inhibiting antibody – ixekizumab – exerted only a limited effect on disease activity, symptoms and acute phase parameters, while the other – secukinumab – did not achieve an effect in the short term, despite slightly better results noted in the prolonged treatment course. Even more disappointingly, brodalumab, an anti-IL-17 receptor (IL-17RA) antibody, as well as ustekinumab and guselkumab – monoclonal antibodies targeting IL-23, failed to show a clinically relevant effect in RA (Semerano et al, 2016). These findings may be explained by the existence of specific disease subtypes responding specifically to IL-17 targeting, but also by a redundancy in the effects mediated by different cytokines involved in RA. To that end, since TNF- α and IL-17 seem to act synergistically, concomitant blockade of both cytokines may prove to be therapeutically useful (McInnes et al, 2016). It is noteworthy that biological agents already successfully used in the treatment of RA – abatacept, tocilizumab, tofacitinib and rituximab - have been associated with a decline in the number of Th17 cells and, in turn, of IL-17 levels (Roeleveld and Koenders, 2014).

IL-22 is another proinflammatory cytokine produced by Th17 cells. Its levels positively correlate with RF and ACPA titers. Furthermore, its presence is significantly associated with erosive arthritis (Roeleveld and Koenders, 2015; Lubberts E, 2015).

IL-12 released by macrophages or dendritic cells through innate immune mechanisms regulates the polarization of Th1 cells and the production of IFN- γ by Th1 and NK cells (reviewed in Mateen et al, 2012). Results of studies including paired synovial fluid and serum samples showed that IL-12 is produced in inflamed joints. In addition, IL-12 levels correlate with disease activity, and decrease in serum and synovial fluid following DMARD therapy. IL-18 is also produced by macrophages and dendritic cells and acts in synergy with IL-12 to stimulate IFN- γ production by Th1 and NK cells. IL-18 is also produced by synovial fibroblasts in response to IL-1 and TNF- α , thus contributing to a positive feedback loop. IL-18 acts as a chemo attractant for T cells and as an angiogenic factor. It has a natural antagonist, IL-18 binding protein (IL-18BP). Administration of recombinant IL-18BP inhibited the development and severity of collagen-induced arthritis, thus supporting the role of IL-18 in experimental arthritis. IL-15 is present in high concentrations in rheumatoid synovial fluid and can also be found in the synovial membrane where it appears to be produced by macrophages, T cells and NK cells. IL-15 activates T cells to induce TNF- α production in macrophages through cell-cell interactions, and stimulates synovial fibroblasts to proliferate and resist apoptosis. Thus, the effects of IL-15 in the rheumatoid synovium result in the activation of T cells, macrophages and fibroblasts (Yang et al, 2015). In addition to proinflammatory cytokines, the rheumatoid synovium is also a source of Th2 and regulatory cytokines including IL-4, IL-10, IL-1 receptor antagonist (IL-1Ra) and transforming growth factor (TGF)- β (Mateen et al, 2016; Alunno et al, 2015). The latter also has positive effects on tissue repair. However, the production is insufficient to counterbalance the effect of pro-inflammatory cytokines, leading to the perpetuation of the inflammatory process. Strikingly, recent evidence revealed a potential anti-inflammatory role of TNF- α , mediated via its RII receptors (unlike its inflammatory actions mediated via RI receptors). One of the most important anti-inflammatory actions mediated by TNF- α is differentiation of Treg cells from its precursors - naïve T helper cells (Alunno et al, 2015).

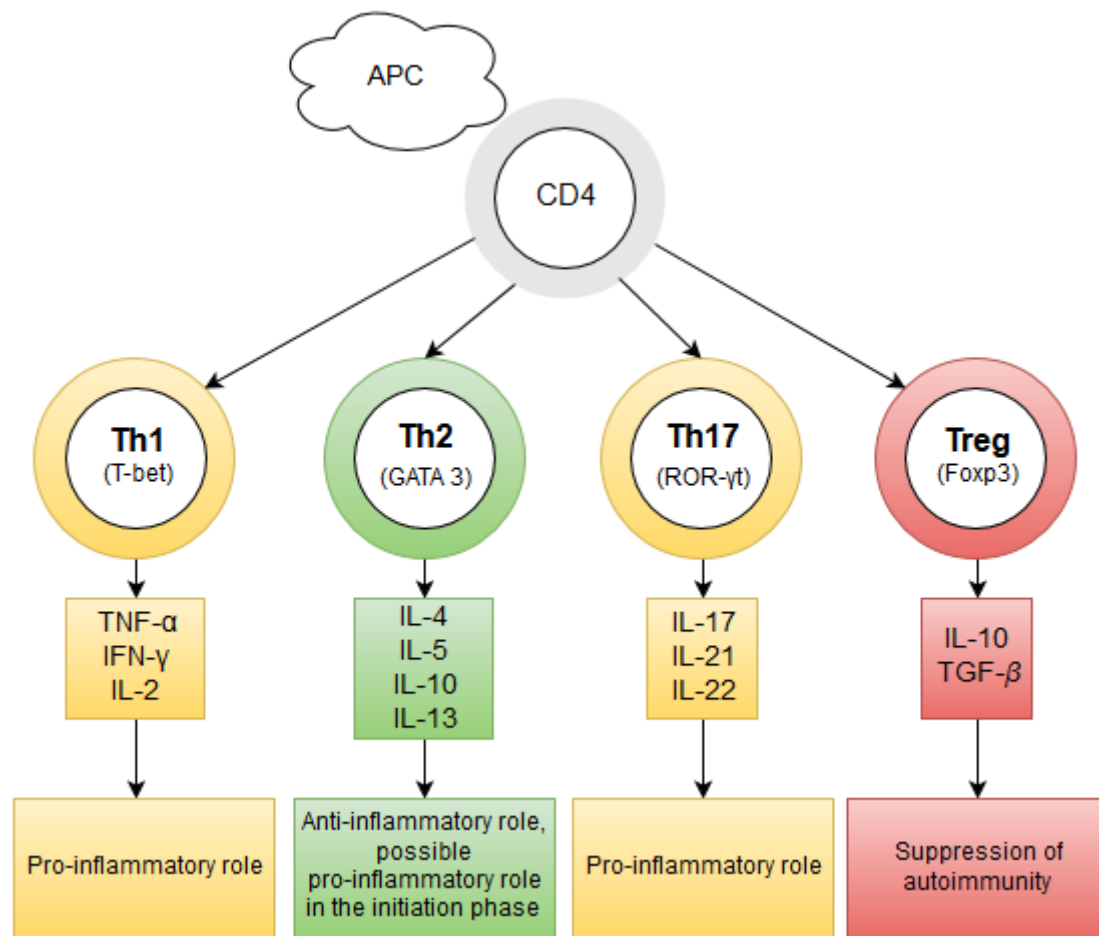
The profile of cytokines present in the rheumatoid synovial tissue varies according to the stage of the disease. Notably, patients with early arthritis (symptom duration less than 3 months) that progressed to RA exhibited a different synovial cytokine profile than patients that remitted or developed other arthritides (Raza K, 2005). The absence of the Th1-cytokine interferon (IFN)- γ and the presence of Th2-cytokines IL-4 and IL-13 together with (presumably) Th17-derived IL-17 in early RA, favour an important role for T cells – in particular Th2 and Th17 cells, in the initiation phase of RA.

Finally, it is important to mention that distinct cytokine profiles were found to correlate with subtypes of lymphocyte infiltration in active RA. The major histological pattern of diffuse synovitis was marked by low-level transcription of genes for IFN γ , IL-4, IL-1 β , and TNF α . Follicular synovitis was the next most common pattern with the presence of abundant IL-10. Lastly, granulomatous synovitis was characterized by high levels of transcription of IFN γ , IL-4, IL-1 β , and TNF α (Klimiuk PA, 1997).

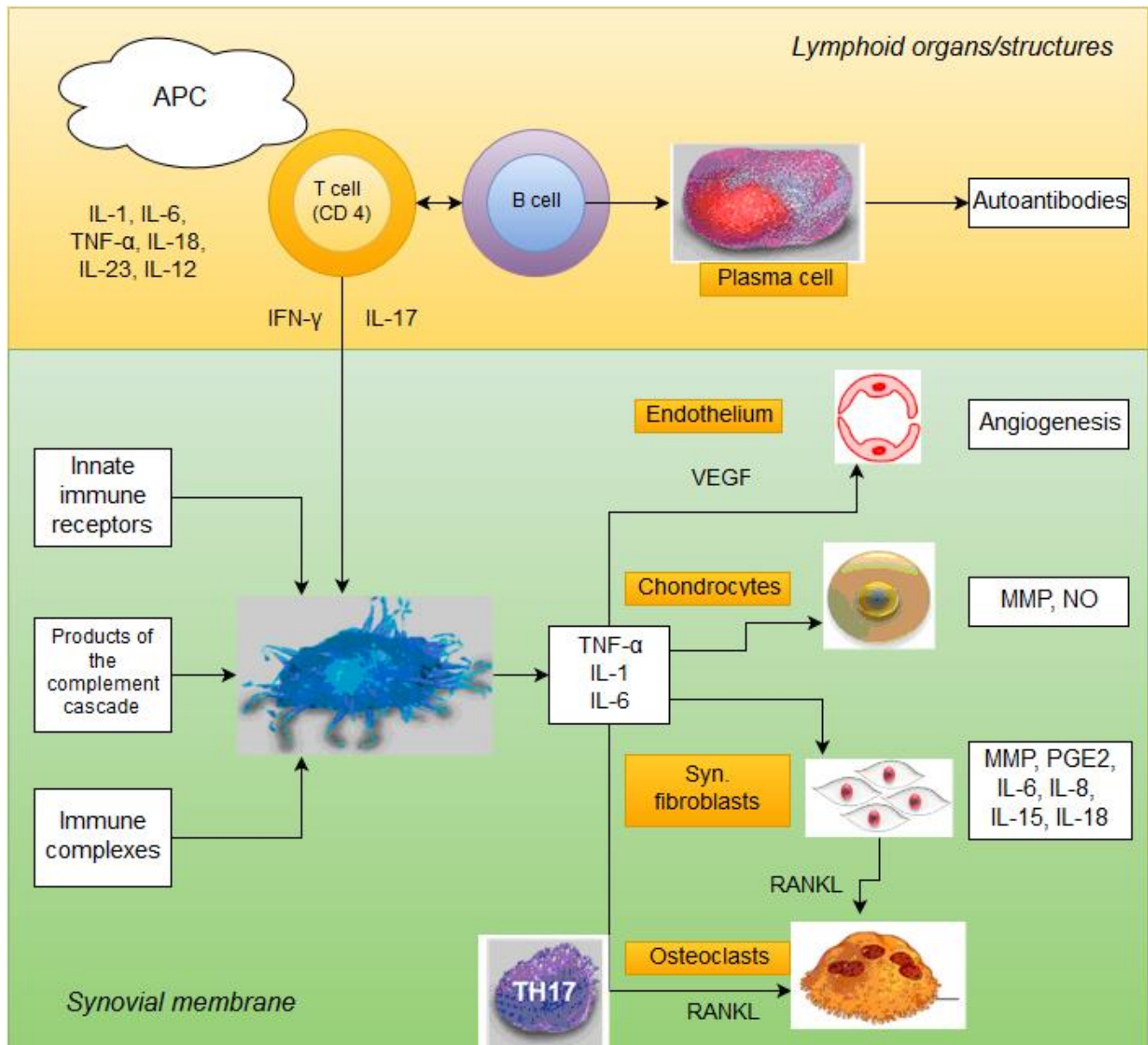
Table 1. Cellular source and functions of cytokines

Cytokines	Main cellular source	Function
TNF- α	macrophages/T cells	Pro-inflammatory, recruitment of inflammatory cells, endothelial, chondrocyte and synovial cell activation, cartilage and bone degradation (Th1 response)
IL-1	macrophages	Similar to the role of TNF- α
IL-1Ra	macrophages	Anti-inflammatory (inhibitor of IL-1)
IL-6	macrophages/stromal cells	Pro-inflammatory, stimulates T cells (Th17) and B cell activator, induces acute phase response and anemia of chronic disease
IL-8 (CXCL8)	macrophages/stromal cells	Pro-inflammatory/recruitment of neutrophils, pro-angiogenic
GM-CSF	lymphocytes	Pro-inflammatory, activation of macrophages and neutrophils
IL-23	macrophages/dendritic cells	Stimulates Th17 responses (see IL-17 below), osteoclastogenesis
IL-17	T cells/mast cells/neutrophils	Pro-inflammatory, support of disease persistency and perpetuation of the inflammatory state, angiogenesis, bone damage (Th17 responses)
IL-22	T cells	Osteoclast activation
RANK ligand	synovial fibroblasts/T cells	Osteoclast activation
IL-12	macrophages/dendritic cells	Stimulates Th1 (IFN- γ) responses
IL-18	macrophages/dendritic cells	Pro-inflammatory/stimulates Th1 (IFN- γ) responses and NK cells
IL-15	macrophages/stromal cells	Pro-inflammatory, activates T and NK cells
Interferon (IFN)- γ	T cells/NK cells	Th1 responses/activation of macrophages
IL-4	T cells/basophils	Promotion of humoral immunity and inhibition of the Th1 response (Th2 responses)/anti-inflammatory in models of arthritis
IL-10	macrophages/T cells	Anti-inflammatory
TGF- β	macrophages/stromal cells	Anti-inflammatory, Treg expansion (but Th17 in presence of IL-6), tissue repair, fibrosis

This table represents some of the main cytokines involved in the pathogenesis of arthritis as demonstrated in animal models and/or in human RA.

Figure 1. Major subsets of CD4⁺ T lymphocytes involved in the pathogenesis of RA

Naïve CD4 cells are activated by antigenic peptides presented by HLA II molecules by antigen presenting cells (APC). Activated CD4 T cells differentiate into at least four different phenotypes depending on the local cytokine milieu: Th1, Th2, Th17 and regulatory T cells (Treg). Distinct markers of each cell phenotype are indicated in parentheses. Each cell type produces a set of signature cytokines and has a specific role in the autoimmunity of RA. While Th1 and Th17 responses have a pro-inflammatory role, Th2 and the regulatory T cell responses play a counter-regulatory role, with the Th2 response counterbalancing Th1 and the Treg counterbalancing the Th17 response (Th1/Th2 and Th17/Treg dichotomy).

Figure 2. Dissecting the immune response in RA

The activation of adaptive immune responses take place primarily in lymphoid organs or lymphoid structures within the rheumatoid synovium. T cells are activated by antigen presenting cells (APC) which release cytokines inducing the polarization of T cells into T helper 1 (Th1) or Th17 cells producing interferon-gamma (IFN- γ) and IL-17, respectively. T helper cells contribute to the maturation of B cell responses and autoimmune responses leading to the production of autoantibodies, including rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA). In the synovial membrane, macrophages can be activated by different stimulants including immune complexes, products of the complement cascade (via complement receptors), activated T cells, and innate immune receptor ligands, leading to the release of pro-inflammatory cytokines such as TNF- α , IL-1 and IL-6. These cytokines stimulate 1) endothelial cells leading to enhanced expression of adhesion molecules and angiogenesis (this effect is also mediated by vascular endothelial growth factor (VEGF) and some chemokines), 2) articular chondrocytes to release matrix metalloproteinases (MMP) and nitric oxide (NO) leading to cartilage breakdown, 3) synovial fibroblasts to release cytokines, prostaglandin E₂ (PGE₂), and other inflammatory agents as well as MMP, and 4) directly and indirectly the maturation and activation of osteoclasts leading to

bone erosions. Synovial fibroblasts and T cells secrete also RANK ligand (RANKL) and contribute to the stimulation of osteoclasts.

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4

module

EULAR on-line course on Rheumatic Diseases

Treatment of rheumatoid arthritis

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LEARNING OUTCOMES

- To know the general approach to the patient with rheumatoid arthritis (RA).
- To know the concepts of window of opportunity, treatment to target and tight control.
- To know the range of agents available to treat RA and to be familiar with the major indications for, and toxicities of, conventional synthetic and biological disease-modifying antirheumatic drugs.
- To know the emerging role of targeted therapies in the treatment of RA.
- To know the optimal strategic approaches to disease management aiming at early remission or low disease activity states
- To know the main clinical studies that have contributed to RA care improvement (*Appendix 1*)
- To know how to adjust RA treatments before and during pregnancy and lactation (*Appendix 2*)
- To be familiar with the vaccination recommendations in RA (*Appendix 3*)
- To be able to detail the role played by allied health professionals in the treatment of RA (*In-Depth Discussion 1*)
- To be familiar with the major indications for, and toxicities of, analgesics, Non-Steroidal Anti-Inflammatory drugs (NSAIDs) and steroids (*In-Depth Discussion 2*).
- To be able to explain the concept of “bridging therapy” for steroids, and to be familiar with their structural effect (*In-Depth Discussion 2*).
- To be familiar with the local and non-pharmacological therapeutics (local steroid injections, radioisotopic synoviorthesis, rehabilitation, splints, orthoses, and braces, surgery, cervical spine management) (*In-Depth Discussion 3*).

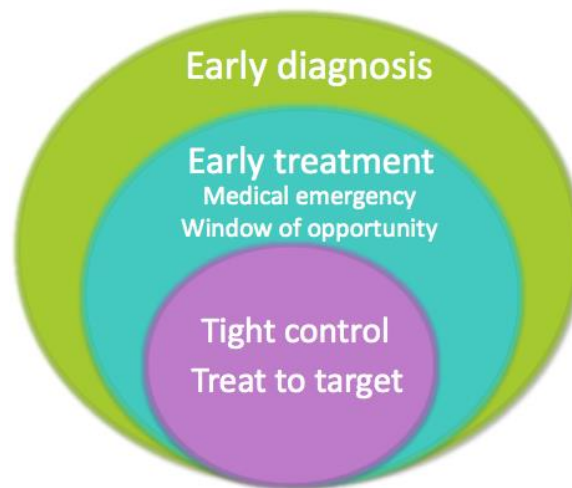
Introduction

The treatment of rheumatoid arthritis (RA) has remarkably evolved over the past 20 years. Indeed, for many decades, the therapeutic approach was to adopt a cautious “wait and see” strategy at the initial steps of the disease to keep the most effective – or the least ineffective – therapies for more advanced stages. The pyramidal strategy proposed at that time (Fries et al. 1990) placed first non-pharmacological (physiotherapy, occupational therapy, rest and rehabilitation, education) and symptomatic treatments (painkillers and non-steroidal anti-inflammatory drugs or NSAIDs), with use of steroids for intense flares. Disease Modifying Anti-rheumatic Drugs (DMARDs) – mainly Gold salts or D-penicillamine at that time – or other immunosuppressant drugs were to be introduced later in the disease course. In addition, the decision to change therapy was generally driven by either physician (occasionally patient) perception of efficacy or by toxicity, without any formal assessment of disease activity due to the lack of validated composite measures. Thus, this approach is clearly identified as non-optimal nowadays since it did not address the 3 main disease consequences:

- Severe disability due to progressive and extensive joint damage,
- Substantial morbidity related to disease-related cardiovascular disorders or drug side effects (infections, drug allergy, osteoporosis)
- Increased mortality due to cardiovascular events or infections.

During the 1990s, RA care has evolved as the results of the implementation of 3 main paradigms (**Figure 1**):

- 1/ Improvements in the diagnosis of RA at an early stage, which has been facilitated by the development of new classification criteria (ACR/EULAR 2010, Aletaha ARD 2010);
- 2/ The demonstration of a need for early treatment as soon as RA diagnosis – “RA is a medical emergency”, as diabetes mellitus or hypertension (T Pincus 1994) – and the identification of “window of opportunity” for RA treatment (P Emery 2002);
- 3/ The development of the notion of RA “tight control” in which therapeutic adjustments have to be based on an validated composite measure of RA disease activity – somehow equivalent to blood pressure in hypertension or glycosylated haemoglobin in diabetes mellitus – (J Smolen, 2010) and the definition of remission or low disease activity as ultimate goal (J Smolen, 2013 et 16);

Figure 1: The 3 main paradigms of RA care

In addition, there was a substantial increase in the number of therapeutic agents (DMARDs) able to modify the natural evolution of RA, either at the joint level (inflammation and damage) or at the systemic level (reduction in cardiovascular morbidity and mortality).

1/ Early RA diagnosis

The first challenge for the physician is to make an early diagnosis. This one should be ideally made by the rheumatologist: patients presenting joint swelling associated with pain and morning stiffness of at least one joint should be referred to and seen by a rheumatologist, ideally within six weeks after the onset of symptoms (Combe, 2007). Making the diagnosis of RA is a quite difficult task and should include:

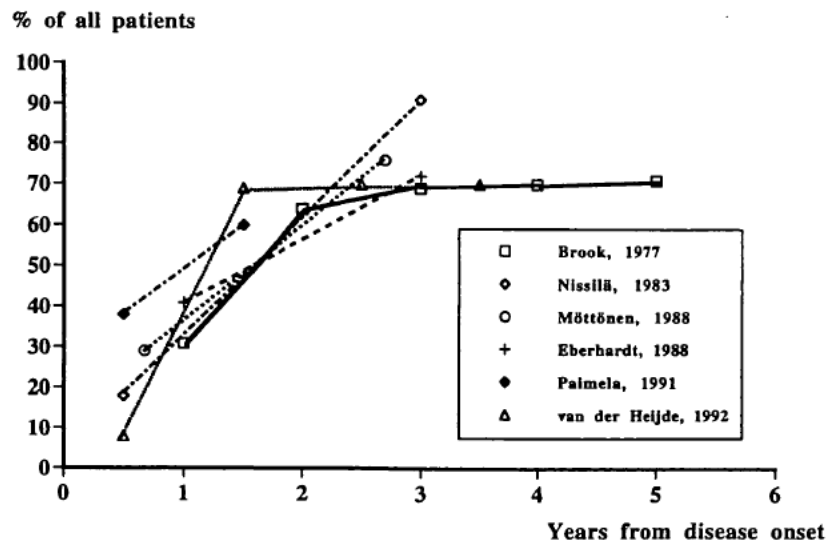
- the recognition of a rheumatic inflammatory disorder compatible with RA (the ACR/EULAR 2010 classification criteria might be of help, Aletaha ARD 2010)
- the exclusion of differential diagnoses, which differ in patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis or gout (Aletaha ARD 2010);
- the identification of patients at risk of developing persistent and/or erosive arthritis (Combe, 2007).

2/ RA as a medical emergency and the notion of a “window of opportunity”

The better understanding of the RA pathogenesis, as well as RA joint and systemic consequences, has led to recommend an as early as possible therapeutic intervention. RA became a “medical emergency” (T Pincus, 1995) as diabetes or hypertension, indicating that treatments have to be started as soon as the diagnosis and not when the first consequences of the diseases occur (stroke, renal insufficiency or visual loss for example). One of the most convincing elements to support such a recommendation was the demonstration that joint damage starts as soon as the first weeks or months of the disease: the majority of patients (75%) develop erosive disease within the first two years of the disease, and the rate of progression (expressed as newly eroded joints or increase in radiographic damage) is the highest during the early years of the disease (Van Der

Heijde, 1995) (figure 2).

Figure 2: Rapidity of erosive disease onset in patients with early RA (van der Heijde 1995).



The development of such erosions constitutes the basis of RA-induced “irreversible damage”, as opposed to synovial inflammation which remains accessible to modern therapies throughout RA course. To start treatment in the early phase of the disease represents a unique **window of opportunity** for an efficacious treatment in order to completely block synovial inflammation and prevent the development of synovial hypertrophy and joint damage (**Figure 3a**). Delaying DMARD therapy for as little as 8 or 9 months after initial diagnosis appears to directly contribute to functional and radiographic deterioration in patients with RA (Smolen, 2002). The existence of this window of opportunity was attested by a work on the results of the Leiden Early Arthritis Clinic (LEAC) and ESPOIR cohorts, in which the start of the treatment within the first 12 weeks of the disease is associated with a higher chance to achieve RA drug-free remission (Van Nies et al. 2015) (**Figure 3b**).

Figure 3a: Relation between delay of the therapeutic intervention and the effect on inflammation and joint damage/loss of function (Emery P, 2002).

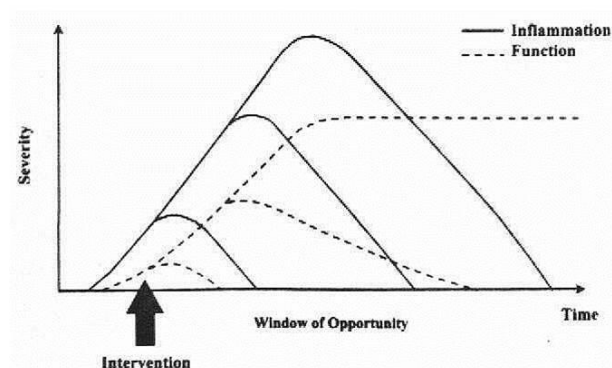
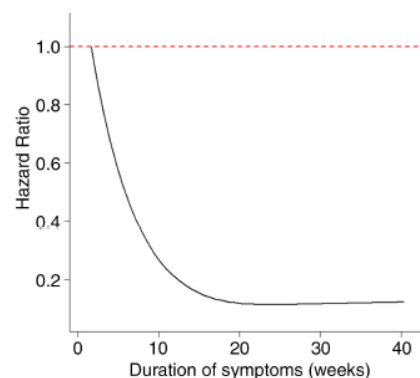


Figure 3b: Relation between the probability of achieving drug-free remission in early RA patients and the delay of DMARD initiation after RA onset in the ESPOIR cohort (Van Nies et al. 2015).



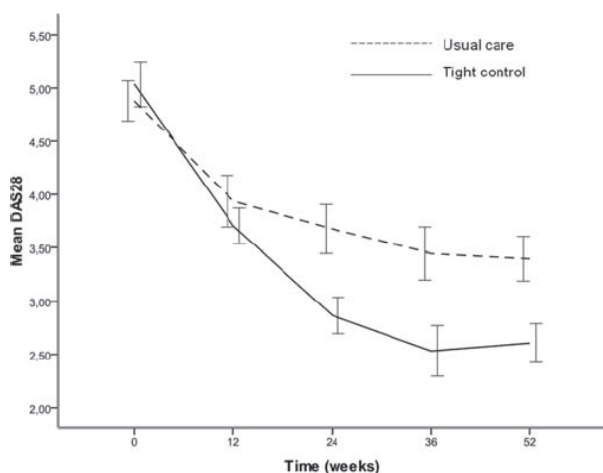
3/ “Tight control” and “treat to target (T2T)”

During the last 2 decades, several disease activity measures have been proposed: the Disease Activity Score (DAS) 28, which is a disease activity score using 28 joint counts along with other components in a complex calculation (MLL Prevoo, 1995); the simplified disease activity index (SDAI, JS Smolen, 2003) and clinical disease activity index (CDAI, D Aletaha, 2005) which provide continuous numerical scales reflecting disease activity (higher is worse) (**Table 1A & B**). These measures can classify disease activity states (high, moderate, low and remission). Thanks to these tools, EULAR as well as ACR guidelines recommended to use composite measures to assess RA patient disease activity in daily care in order to make regular adjustment of DMARDs – i.e., disease tight control – and be able to achieve the optimal and consensual therapeutic goal: remission or at least low disease activity – i.e., treat to target (*Felson DT, 2011).

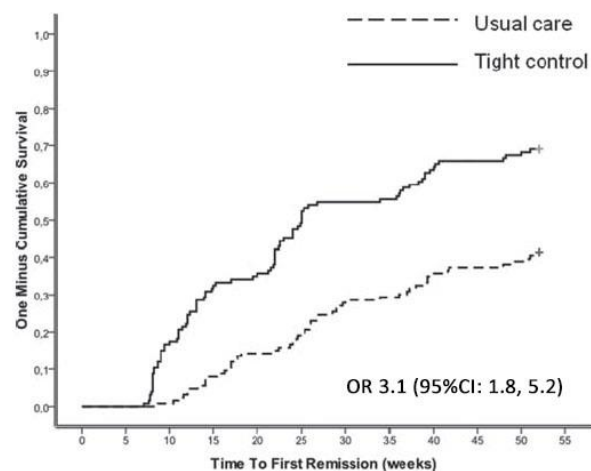
These statements were based on several randomized controlled trials and a metaanalysis that demonstrated that dynamic strategies based on these 2 notions were more effective than usual care, i.e., not disease activity-driven (Schipper LG et al. 2010; Schipper et al, 2012) (**Figure 4**).

Figure 4: Benefit of a DAS28-driven dynamic strategy (tight-control) over usual care in a 1-year randomized controlled trial (Schipper et al. 2012)

a. Evolution of mean DAS28 in the 2 arms



b. Time to achieve DAS28 remission in the 2 arms



The wide implementation of such principles have been associated with RA prognosis improvement, with less overall disability, reduction in the need of orthopaedic surgery, reduction of sick day as well as improvement in cardiovascular morbidity and mortality.

Table 1A: Composite measures of disease activity including joint counts, and ACR-EULAR remission criteria

Components		Cutpoints			
		Remission	Low disease activity	Moderate disease activity	High disease activity
DAS28-ESR*	Tender joint count (of 28)	< 2.6	2.6 to	> 3.2 to ≤ 5.1	> 5.1
	Swollen joint count (of 28)		3.2		
	Erythrocyte sedimentation rate (in mm)				
	Patient global assessment (0-100 VAS)				
DAS28-CRP†	Tender joint count (of 28)	< 2.6	2.6 to	> 3.2 to ≤ 5.1	> 5.1
	Swollen joint count (of 28)		3.2		
	C-reactive protein (in mg/dL)				
	Patient global assessment (0-100 VAS)				
SDAI‡	Tender joint count (of 28)	≤ 3.3	> 3.3 to	> 11 to ≤ 26	> 26
	Swollen joint count (of 28)		11		
	Patient global assessment (0-10 VAS)				
	Physician global assessment (0-10 VAS)				
CDAI§	Tender joint count (of 28)	≤ 2.8	> 2.8 to	> 10 to ≤ 22	> 22
	Swollen joint count (of 28)		10		
	patient global assessment (0-10 VAS)				
	physician global assessment (0-10 VAS)				
ACR-EULAR remission	SDAI	SDAI ≤ 3.3			
	CDAI	CDAI ≤ 2.8			
	Boolean: swollen joint count (of 28), tender joint count (of 28), patient global assessment (0-10 VAS), C-reactive protein (in mg/dL)	Boolean all ≤ 1			

Patient global assessment reflects global health in DAS 28; mm in DAS 28; cm in CDAI, SDAI, Boolean.

ACR=American College of Rheumatology. EULAR=European League against Rheumatism. DAS28=disease activity score using 28 joint counts. SDAI=simplified disease activity index. CDAI=clinical disease activity index. TJC28=tender joint count (of 28). SJC28=swollen joint count (of 28). ESR=erythrocyte sedimentation rate (in mm). GH=global health. CRP=C-reactive protein (in mg/dL); *DAS28-ESR calculated according to the following equation: $0.56 \times \sqrt{TJC28} + 0.28 \times \sqrt{SJC28} + 0.70 \times \log_e(ESR) + 0.014 \times GH$. †DAS28-CRP calculated according to the following equation: $0.56 \times \sqrt{TJC28} + 0.28 \times \sqrt{SJC28} + 0.36 \times \log_e(CRP+1) + 0.014 \times GH + 0.96$ ‡SDAI calculated according to the following equation: $TJC28 + SJC28 + PtGA + EGA + CRP$.

§CDAI calculated according to the following equation: $TJC28 + SJC28 + PtGA + EGA$

Table 1B: ACR response criteria and ACR-EULAR remission criteria

	Components	Definition
ACR-EULAR remission	Index: SDAI, CDAI; Boolean: swollen joint count (of 28), tender joint count (of 28), patient global assessment, C-reactive protein (in mg/dL)	SDAI ≤ 3.3 CDAI ≤ 2.8 Boolean all ≤ 1
ACR20 Response	Tender joint count, Swollen joint count, ESR or C-reactive protein (in mg/dL), Pain on VAS, Patient global assessment, Physician global assessment, functional capacity on HAQ	Improvement of 20% of - TJC - SJC - AND of 3 of the 5 others
ACR50 Response	Tender joint count, Swollen joint count, ESR or C-reactive protein (in mg/dL), Pain on VAS, Patient global assessment, Physician global assessment, functional capacity on HAQ	Improvement of 50% of - TJC - SJC - AND of 3 of the 5 others
ACR70 Response	Tender joint count, Swollen joint count, ESR or C-reactive protein (in mg/dL), Pain on VAS, Patient global assessment, Physician global assessment, functional capacity on HAQ	Improvement of 70% of - TJC - SJC - AND of 3 of the 5 others
ACR Non response	Tender joint count, Swollen joint count, ESR or C-reactive protein (in mg/dL), Pain on VAS, Patient global assessment, Physician global assessment, functional capacity on HAQ	Absence of ACR20 response

*It is worthy of note that ACR (American College of Rheumatology) distinguish a change from baseline of several defined variables by at least 20% (ACR20, minimal response), 50% (ACR50, moderate response) or 70% (ACR70, major response) (Felson, 1995) (Table 1b). However, the ACR criteria have been developed to differentiate active therapy from placebo in clinical trials (in particular, ACR20), but cannot be used in practice (on the contrary of ACR-EULAR criteria) because they are not based on a continuous scale (improvement is related to baseline values of the respective variable, which differ between individual patients or within patients at different treatment starts) (*Smolen, 2016).*

1. Pharmacological treatment in RA

1.1 Overview of Disease-Modifying Antirheumatic Drugs (DMARDs)

DMARDs constitute the backbone of RA pharmacological treatment, and all patients with RA are candidates for DMARD therapy. These agents are commonly characterised by their capacity to:

- reduce or reverse RA signs and symptoms as well as acute phase response,
- slow down or stop joint damage progression,
- reduce consequences of systemic inflammation and physical limitation, mainly cardiovascular diseases.

By these actions, they limit long-term disability, improve quality of life and ability to work, and thus interfere with the entire disease process (Smolen et al. 2007).

DMARDs form two major classes: synthetic chemical compounds (sDMARDs) and biological agents (bDMARDs). In light of the recent emergence of new therapeutics (such as kinase inhibitors and biosimilars), a new nomenclature was recently proposed, and adopted by the EULAR Task Force in the 2013 and 2016 recommendations (Smolen et al, 2014; *Smolen et al, 2014; Smolen et al, 2016). Consequently, the term conventional sDMARDs (csDMARDs) are now used to include chemical agents such as methotrexate (MTX), sulfasalazine and leflunomide, whereas tofacitinib, a new sDMARD specifically designed to target janus kinases (JAKs), is designated as a targeted sDMARD (tsDMARD). The five available tumour necrosis factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the T cell costimulation inhibitor, abatacept, the anti-B cell agent, rituximab, and the interleukin (IL)-6 receptor (IL-6R)-blocking monoclonal antibody, tocilizumab, as well as the IL-1 inhibitor, anakinra, are subsumed as biological originator (bo) DMARDs, while biosimilars (bs), such as bs-infliximab, recently approved by the European Medicines Agency (EMA), are named bsDMARDs (table 2).

Table 2. Nomenclature of disease-modifying antirheumatic drugs, proposed by Smolen et al., and adopted by the EULAR Task Force in the 2013 recommendations (Smolen et al. 2014, *Smolen et al. 2014).

Disease Modifying Antirheumatic Drugs (DMARDs)			
Synthetic DMARDs (sDMARDs)		Biological DMARDs (bDMARDs)	
Conventional synthetic DMARDs (csDMARDs)	Targeted synthetic DMARDs (tsDMARDs)	Biological originator (boDMARDs)	Biosimilar (bsDMARDs)
Methotrexate (MTX)	Tofacitinib	TNF blockers	TNF blockers
Leflunomide (LEF)		- Adalimumab (HUMIRA)	- Etanercept (BENEPALI)
Sulfasalazine (SSZ)		- Certolizumab (CIMZIA)	- Infliximab (REMSIMA, INFLECTRA)
Hydroxychloroquine*		- Etanercept (ENBREL)	
		- Golimumab (SIMPONI)	
		- Infliximab (REMICADE)	
		Anti-IL6R	
		- Tocilizumab (ROACTEMRA)	
		LcT co-stimulation blocker	
		- Abatacept (ORENCIA)	
		Anti-CD20 (LcB targeting)	
		- Rituximab (MABTHERA)	
		IL-1Ra	
		- Anakinra (KINERET)†	

TNF=tumour necrosis factor; IL6R=Interleukine 6 Receptor; LcT= T lymphocyte; CD20, cluster of differentiation 20; LcB=B lymphocyte; IL-1Ra=interleukine 1 antagonist;

* Usually used in combination with MTX. † Anakinra is exceptionally used for the treatment of rheumatoid arthritis, because it is less effective and of more constraining use (see below).

1.2 Conventional synthetic DMARDs (csDMARDs)

The discovery of synthetic DMARDs as effective antirheumatic drugs has traditionally been based on empirical data, in contrast with recently introduced biological DMARD agents, which were developed from bench to bedside. The synthetic DMARDs most commonly used include methotrexate (MTX), sulfasalazine (SSZ), leflunomide (Table 3). Hydroxychloroquine (HCQ) is usually used in combination with MTX, and rarely alone.

Older molecules (azathioprine (AZA), gold salts, minocycline, cyclosporine A or D-penicillamine) are now rarely used, either because they did not demonstrate the same level of efficacy – especially on structural damage – or because their risk/benefit ratio appears less interesting than the previous one.

Glucocorticoids, although they may have a DMARD effect, have a specific positioning as bridging therapy, i.e., as short-term therapy aiming to rapidly control disease activity before getting the full efficacy of DMARDs. This will be discussed in In-Depth Discussion 2 (www.eular-onlinecourse.org).

Conventional synthetic DMARDs are therefore considered the first step in the pharmacological treatment of RA and should be started in all patients as soon as possible after diagnosis, to reduce disease activity, control joint damage and prevent disability (Smolen et al, 2010; Smolen et al, 2014*, Smolen et al, 2016*). This concept will be detailed in the strategies section and in Appendix 1.

1.2.1 Methotrexate

MTX is the anchor drug in the treatment of RA, both in monotherapy and combination therapy, due to a favourable efficacy/toxicity ratio. It is effective over long periods of time and it has a better toxicity profile and a slightly faster onset of action than other synthetic DMARDs. It was one of the first conventional DMARDs with proven efficacy on radiographic progression.

➡ Mechanism of action

MTX resembles folic acid and is a competitive inhibitor of folate-dependent enzymes, such as dihydrofolate reductase (DHFR). These enzymes are involved in the pyrimidine (DNA) synthesis and the de novo purine synthesis of DNA and RNA. DHFR inhibition by MTX leads to depletion of tetrahydrofolates that are essential for DNA, RNA and protein synthesis (figure 5).

Figure 5: MTX mechanism of action. After being taken into the cell both methotrexate (MTX) and polyglutamated forms of MTX inhibit dihydrofolate reductase, an enzyme that catalyses the conversion of dihydrofolate into tetrahydrofolate, which is the active form of folic acid. Tetrahydrofolate is involved in many single-carbon transfer reactions, including the synthesis of pyrimidines. Inhibition of dihydrofolate reductase causes depletion of intracellular tetrahydrofolate, which has a cytotoxic effect, especially on rapidly dividing cells. MTX-polyglutamate (MTX-PG) also inhibits *de novo* purine synthesis and thymidylate synthase, which contribute to its cytotoxic effects. AICAR, amino imidazole-4-carboxamide ribonucleotide; AMP, adenosine monophosphate; ATIC, AICAR transformylase; DHF, dihydrofolate; DHFR, dihydrofolate reductase; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; IMP, inosine monophosphate; PG, polyglutamate; THF, tetrahydrofolate; TYMS, thymidylate synthetase.

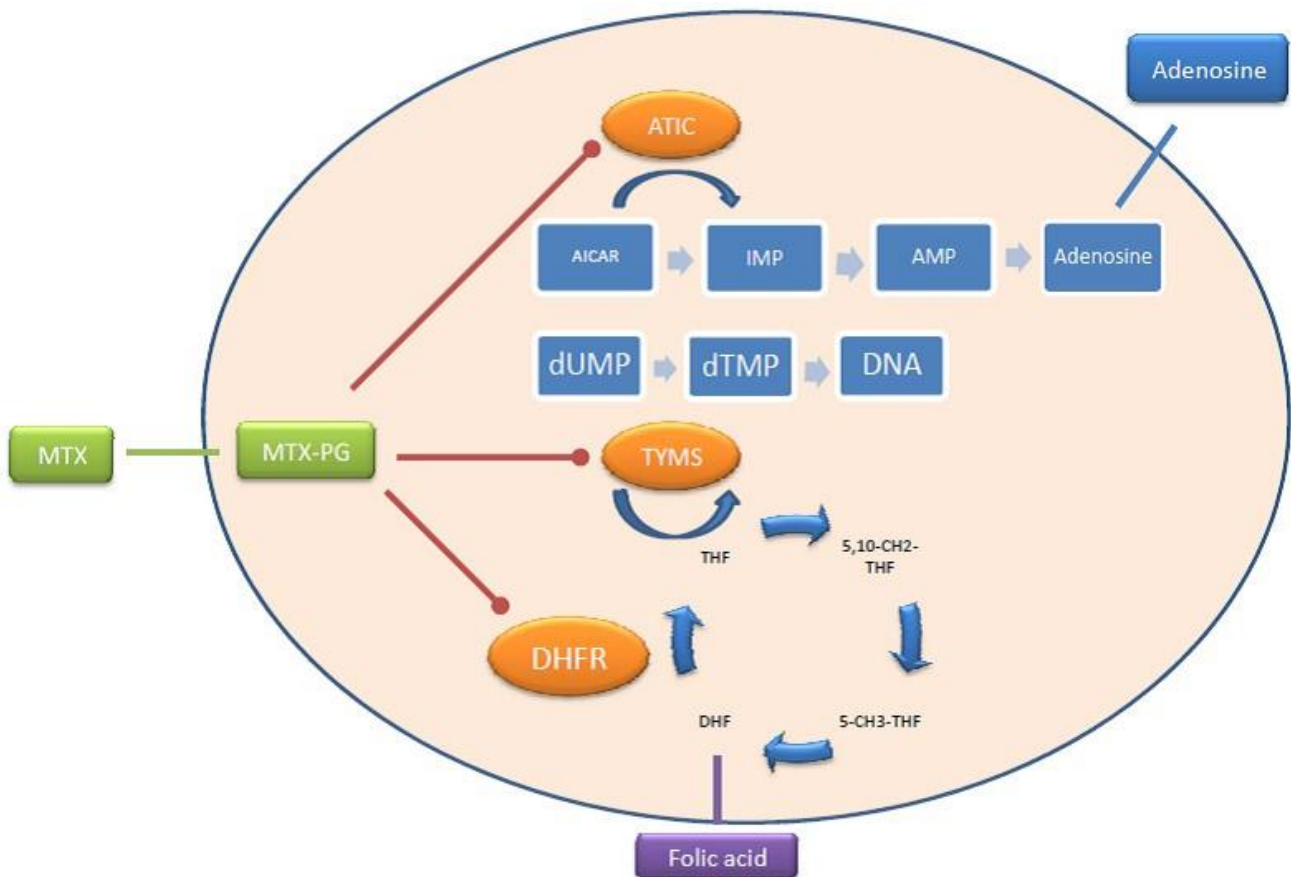


Table 3.A: main conventional synthetic DMARDs: mechanism of action, contraindications, precaution of use and main adverse effects.

	Methotrexate	Leflunomide	Sulfasalazine	Anti-malarial*
Mechanism of action	Reversible competitive inhibitor of DHFR (Folic acid analogue)	Isoxazole derivative (inhibits de novo pyrimidine synthesis)	5-aminosalicylic acid derivative, metabolised to sulfapyridine (active drug) and 5-ASA	4-aminoquinoline derivatives
Contraindications	<ul style="list-style-type: none"> - Pregnancy (teratogenic) - Concomitant use of trimethoprim-sulfamethoxazole (bone marrow suppression) - Severe chronic kidney failure - HIV or severe chronic infection - Anaemia, thrombocytopenia 	<ul style="list-style-type: none"> - Pregnancy (teratogenic) - Breast-feeding 	<ul style="list-style-type: none"> - G6PD deficiency - Hypersensitivity to sulfamides or salicylic acid - Porphyria 	<ul style="list-style-type: none"> - Retinopathy - Hypersensitivity to 4-aminoquinoline derivatives
Precaution of use	<ul style="list-style-type: none"> - Chronic liver disease† - Chronic pulmonary disease‡ 	<ul style="list-style-type: none"> - Hypertension - Renal and hepatic diseases 	<ul style="list-style-type: none"> - Haematologic problems - Renal and hepatic diseases 	<ul style="list-style-type: none"> - Impaired renal or hepatic function (↑risk of retinopathy)
Main adverse effects	<ul style="list-style-type: none"> - Mild GI complaint, nausea, vomiting, - Elevated transaminases (tolerated if <3N) - Hypersensitivity pneumoniaφ - Haematologic toxicity (leukopenia, thrombocytopenia, megaloblastic anaemia, pancytopenia) - Skin rash, hair loss - Subcutaneous nodules - Infections (viruses, opportunistic) 	<ul style="list-style-type: none"> - Diarrhoea - Hypertension - Hair loss - Elevated transaminases, cytolytic hepatitis - Rare: pancytopenia, peripheral neuropathy, vasculitis, interstitial pneumopathia, cutaneous lupus 	<ul style="list-style-type: none"> - GI complaints (nausea, pain) - Headaches, dizziness - Skin rash, - Lyell syndrome, DRESS syndrome - Leukopenia, agranulocytosis, thrombocytopenia - Haemolysis (G6PD deficiency) - Reversible oligospermia - Rare: cytolytic hepatitis, eosinophilic pneumonia or pulmonary fibrosis, ANA, anti-DNA Ab or drug induced lupus 	<ul style="list-style-type: none"> - Retinopathy - Anorexia, nausea, vomiting, GI complaints - Headaches, dizziness - Skin rash, pruritus - Skin pigmentation - Alopecia - Neuromyopathy - Leukopenia, thrombocytopenia, anaemia

DHFR, dihydrofolate reductase; MTX, methotrexate; GI, gastrointestinal; HIV, Human Immunodeficiency Virus; 5-ASA, 5-aminosalicylic acid; G6PD, glucose-6-phosphate dehydrogenase; ANA, antinuclear antibody; Ab, antibody; SSZ, salazopyrine; GFR, glomerular filtration rate; † The patient should be referred to a specialised hepatic consultation to ask for authorization; ‡ the patient should be referred to a specialised pulmonary consultation to ask for authorization; § requires to stop definitely the treatment

Table 3.B: modalities of prescription of the main conventional synthetic DMARDs.

	Methotrexate	Leflunomide	Sulfasalazine	Anti-malarial*
Mode of administration	Oral or SC	Oral	2g-3g/day in two divided doses	Hydroxychloroquine 2x200mg/day (≈6mg/kg/day) Chloroquine 2 100mg/day (≈3-4mg/kg/day)
Dose	≈ 10 to 25 mg/week** (3 mg/kg/week) Folic acid 5 to 10 mg/week, given 48 hours after MTX	If not well tolerate, can be decreased to 10 mg/day	(Gradual increase: 500mg a week)	Ideally in combination with other DMARD (no structural effect)
Mean half life	10 hours	15-18 days, but long persistence (enterohepatic circulation)	6-10 hours	40 days
Screening investigations	Please refer to table 4	<ul style="list-style-type: none"> Full past medical history and clinical examination to exclude a contraindication. Take into account the precautions of use (see table 3.A) CBC, liver enzymes, creatinine 		
Monitoring	CBC, liver enzymes, albuminemia, creatinine: Per week during the first 3 months, then/3 months	Avoid to use in patients with hypertension Blood pressure, CBC, liver enzymes, creatinine: Per 15 days during 6 months, then/2 months	Exclude G6PD deficiency CBC, liver enzymes, creatinine: Per month during the first 6 months, then space out	Ophthalmologic assessment at baseline (within the 1 st year of starting) - Ophthalmologic assessment at baseline, then annual after 5 years or earlier according to risk factors of retinopathy¶ - Electrocardiogram before and after treatment start; CBC and renal function - For some centres: HCQ serum levels (compliance check)
Mean time to be active/therapeutic response evaluation	6-8 weeks/3 months	6-8 weeks/3 months	3-4 months	2-4 months
Interruption before scheduled surgery†	- No need if scheduled orthopaedic surgery - Necessary to stop if septic surgery (15 days before)	- Not adequate (long half-life) - For some authors, wash out if high septic risk surgery	- Not systematic - If risk of interference with other drugs, hepatotoxicity or reduction of GFR, SSZ can be stopped 1-2 days before surgery.	Not necessary
Interruption before pregnancy‡	3 months	2 years or do a wash-out (cholestyramine 3x8g/day during 11 days)	Not necessary (but use with caution if breast feeding)	Can be continued throughout pregnancy Compatible with breast feeding

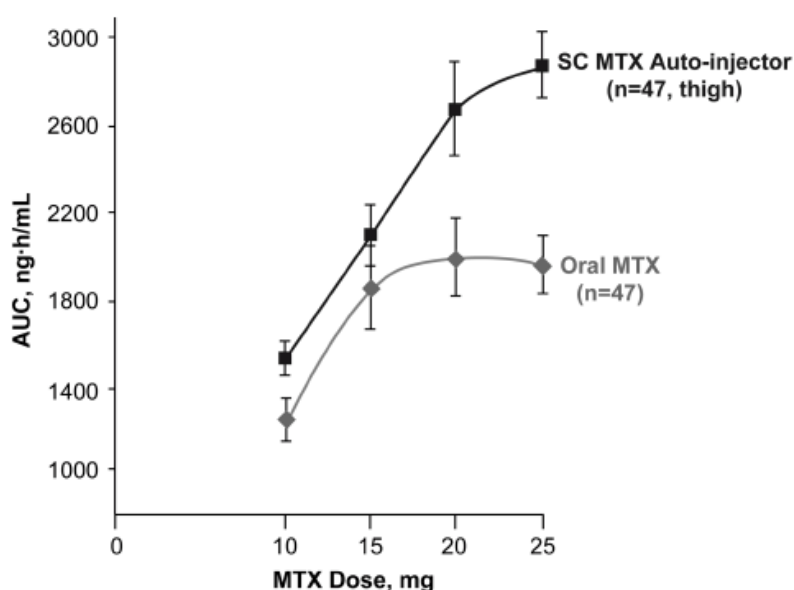
* Hydroxychloroquine and chloroquine; ** the same day of the week; ¶ Risk factors of retinopathy: long-term use (1% after 5-7 years or 1000 mg of cumulative dose), impaired renal or hepatic function, age >60 years, obesity, retinal or macular disease, cytochrome P450 gene polymorphisms or a prior history of antimalarial drug use. Assessment should include visual fields and SD OCT (spectral-domain optical coherence tomography), and multifocal electrinogram (mfERG) and/or fundus auto fluorescence. † Perioperative management of csDMARDs is detailed in In-Depth Discussion 3. ‡ Periconceptional management of cs DMARDs is detailed in Appendix 2.

The mechanisms by which MTX exerts its effects are complex and yet not fully known. Several mechanisms have been proposed: inhibition of T cell proliferation due to the effects of MTX on purine and pyrimidine metabolism, inhibition of transmethylation reactions required for the prevention of T cell cytotoxicity, interference with glutathione metabolism leading to alterations in recruitment of monocytes and other cells to the inflamed joint, and promotion of the release of the endogenous anti-inflammatory mediator adenosine (Cronstein et al. 2005). The probable anti-inflammatory effect of MTX is suggested clinically by the rapid clinical response to treatment as well as the equally rapid flare of disease once it is stopped.

➡ Metabolism

The bioavailability varies according to the administration form. The bioavailability of doses superior to 15mg/week administered orally is highly variable, and represents on average two-thirds of that of subcutaneous (SC) or intramuscular (IM) administration (Jundt et al. 1993; Schiff et al. 2014) (Figure 6). This conducted authors to recommend oral administration with 2 MTX intakes on the same day for patients receiving doses > 15 mg/week.

Figure 6: Bioavailability of MTX after oral or parenteral administration. There is a consistently greater bioavailability of subcutaneous (SC) MTX compared with oral MTX. Mean oral MTX exposure plateaus at doses ≥ 15 mg/week. AUC, area under the concentration versus time curve; MTX, methotrexate; SC, subcutaneous; SEM, standard error of the mean (adapted from Schiff et al. 2014 with permission).



After absorption, 50–70% is bound to plasma proteins, mainly albumin. In case of hypoalbuminemia, quite frequent in severe RA, plasmatic free-MTX levels can be elevated. Serum and synovial fluid concentrations of MTX are approximately equal. MTX is principally (80–90%) excreted by the kidneys: hence, in case of kidney failure, MTX excretion is decreased and thus toxicity increased.

➡ Efficacy in RA

Many randomised controlled trials versus placebo or versus other DMARDs (leflunomide, azathioprine, gold, cyclosporine, penicillamine)) have demonstrated MTX clinical and structural efficacy (*Gaujoux-Viala et al. 2013). The percentage of responders to MTX is high, between 50 and 60%. The onset of action is about 4 to 8 weeks, with a maximal clinical efficacy usually obtained during the 6 first months. MTX also improves the quality of life evaluated through functional indexes, and could allow steroids interruption in 12 to 33 % of patients (Bannwarth 1994). MTX is considered as the optimal 1st line agent in RA and is used as an anchor therapy on which other csDMARDs, tsDMARDs or bDMARDs can be added in case of inadequate response.

➡ MTX prescription in practice

The strategy of prescription has been adopted by several countries as a result of the 3E (Evidence, Expertise, Exchange) initiative (Visser et al. 2008). The clinical, biological and imaging screening tests are detailed in table 4.

MTX can be administered orally or parenterally (subcutaneously or intramuscularly) at an optimal dose of 0.3 mg/kg/week. When high doses are used, splitting the dose can increase bioavailability (Hoekstra et al, 2006). Although the oral route is used most frequently, the parenteral route may be preferred in patients with inadequate clinical response or gastrointestinal intolerance. Furthermore, as seen previously (figure 6), for doses ≥ 15 mg/day, the biodisponibility is better with parenteral administration. Hence, several authors have compared the efficacy and safety of SC versus oral MTX. Initial treatment with SC was associated with lower rates of treatment changes, no difference in toxicity, and some clinical improvements (lower DAS-28 or better ACR20 and ACR70 responses) in disease control versus oral MTX over the first year in patients with early RA (Braun et al. 2008; Hazlewood et al. 2016). Lower doses are recommended in elderly people or in case of renal insufficiency. To ensure compliance and avoid administration errors, it is recommended to prescribe MTX on a specific weekday, which should be noted on the prescription form. The time of onset of action of MTX ranges from 2 to 6 weeks. Regular biologic monitoring is recommended: hemogram, serum creatinin, liver function tests and albuminemia every 1–3 months (Table 3).

MTX should be combined with folic acid to reduce gastrointestinal side effects (26% relative risk reduction) and the incidence of adverse events due to transaminase elevations (77% relative risk reduction), without loss of efficacy. In a literature systematic review a trend towards a reduction in mucosal side effects was reported,

but no conclusions could be drawn about haematological outcomes owing to poor reporting (Shea et al, 2013). Folic acid given at a dose of 5 to 10 mg/week is recommended usually 24–48 h after MTX to avoid counteractions. Higher doses of folic acid can be used in parallel with increases in MTX, but in the latter case, folic acid should not be prescribed within 24 h of MTX intake. Folinic acid (reduced folate), the form of the vitamin found before the metabolic reduction to tetrahydrofolate by dihydrofolate reductase, at 1 mg/day may be more potent than folic acid to combat acute MTX toxicity.

Table 4: Clinical, laboratory and imaging screening before starting methotrexate (MTX) and the general approach to the patient with rheumatoid arthritis

Clinical	<ul style="list-style-type: none"> ▪ Patient education: oral and written information ▪ Assess risk factors for toxicity: alcohol intake, hepatotoxic drugs, obesity, NASH... ▪ Assess contra-indications: <ul style="list-style-type: none"> ○ Absolute: pregnancy, haematologic disease (hypoplasia, thrombocytopenia, anaemia), chronic kidney or liver disease, alcoholism, chronic infectious disease, AIDS ○ Relative (require specialised assessment for authorization): chronic pulmonary disease, viral B or C hepatitis, diabetes, obesity ▪ Check compliance with vaccination plan. Vaccination according to recommendations*
Laboratory	<ul style="list-style-type: none"> ▪ Complete blood count, transaminases and liver function, creatinin, albuminemia, fasting glucose, lipid profile ▪ Serology for HIV, HBV, HBC ▪ Serum protein electrophoresis ▪ Pregnancy test (for women)
Imaging/ Other Para clinical examination	<ul style="list-style-type: none"> ▪ Chest X-rays ▪ If chronic pulmonary disease: pulmonary function testing and diffusing capacity of the lung (useful for reference)

NASH, non-alcoholic steatohepatitis; CBC, complete blood count; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis virus.

**For the vaccination plan and recommendations, please refer to the corresponding section of this course in Appendix 3*

➡ Adverse events

Adverse reactions to MTX are frequent and occur in more than half of patients. Some patients can develop several clinical or biological side effects. However, these adverse reactions tend to be minor and can often be managed without stopping the drug. The potentially serious side effects are listed in table 5, and the management of daily problems described in table 6. Predisposing factors for toxicity are high dose, long exposure, advanced age, renal insufficiency, hypoalbuminaemia, viral or alcoholic hepatitis and concomitant use of other antifolate treatments.

- o Hepatic adverse effects

Although MTX has a documented hepatotoxicity at high doses (especially those used in cancerology), MTX-induced liver fibrosis is very rare at low doses used in Rheumatology (Walker, et al. 1993). Thus, liver biopsies are not routinely needed, and regular monitoring of liver enzymes is sufficient. Risk factors for drug-induced fibrosis include: age > 60 at first prescription, renal failure, long duration of treatment, viral hepatitis, alcoholism, fatty liver.

Transaminase elevation is frequent (12 to 48 %), and dependent on the dose. An increase up to 2 fold the upper limit of normal is tolerated. When alanine aminotransferase and/or aspartate amino transferase (ALT/AST) increase to more than three times the upper limit of normal, it is recommended that MTX is stopped, but introduction later at a lower dose can be considered. If transaminases are persistently high despite interruption of MTX, other causes should be considered such as viral hepatitis, hepatotoxic drugs, hypoalbuminemia, fatty liver, alcohol intake, and appropriate diagnostic procedures should be performed, including a hepatological assessment (and a liver biopsy if needed). In case of pre-existing B or C hepatitis prior to MTX introduction, a hepatological assessment is essential, to consider viral activity and the benefit/risk ratio of prescribing the drug.

- o Hypersensitivity pneumonia

Hypersensitivity pneumonia is a rare – but serious and potentially fatal- adverse event that presents as an acute syndrome, usually early in the course of MTX treatment (<0.5% cases within 3 years of follow-up in a review by Salliot and van der Heijde, 2009). Risk factors that contribute to its occurrence are probably idiosyncratic as for other hypersensitivity reactions. Pre-existing lung disease is reported to be the most consistent risk factor, but it has not been related to MTX dose. There is no consensus about the data for age, disease duration, smoking and diabetes. Cough, dyspnoea and fever are the most common symptoms. Chest X-rays and scannography show an interstitial syndrome. The differential diagnosis includes severe infectious pneumonia, particularly *Pneumocystis jirovici* pneumonia. A bronchoscopy for bronchoalveolar lavage (BAL) is essential for diagnosis (the BAL will show an alveolitis rich in TCD4 lymphocytes). When the diagnosis of hypersensitivity pneumonia is suspected, MTX should be stopped, and if confirmed, the patient should be treated by high doses of methylprednisolone and MTX should be definitively contra indicated. The fatality rate has been reported to be as high as 17% and the reaction tends to occur early in the course of treatment (50% of cases in the first 32 weeks). Progression to fibrosis is rare. Hence, the patient and his general practitioner should be systematically informed of this risk prior to MTX introduction. Furthermore, a chest X-ray is systematic in the screening before treatment, and a pulmonary assessment is essential in case of pre-existing chronic pulmonary disease.

Table 5: Potential serious side effects of low dose MTX, with clinical expression and predisposing factors

Toxicity	Clinical expression	Predisposing factors
Hepatopathy	<ul style="list-style-type: none"> ▪ ↑ transaminases (low progression) 	<ul style="list-style-type: none"> ▪ Pre-existing B or C hepatitis ▪ Alcoholism ▪ Obesity, NASH ▪ Diabetes ▪ Age > 60 years-old ▪ Renal or cardiac failure
Hypersensitivity pneumonia	<ul style="list-style-type: none"> ▪ Cough, fever, dyspnoea (progressive or acute, unpredictable apparition, potentially lethal) 	<ul style="list-style-type: none"> ▪ Chronic pulmonary disease ▪ Old age ▪ Diabetes ▪ Smoking
Medullar aplasia	<ul style="list-style-type: none"> ▪ Infectious syndrome ▪ Bleeding ▪ Aphtha, mucosal inflammation 	<ul style="list-style-type: none"> ▪ Malnutrition, hypoalbuminemia ▪ Renal failure ▪ Methotrexate overdosage ▪ Multiple taking during the week
Infections (communal or opportunistic)	<ul style="list-style-type: none"> ▪ Pneumococcal pneumonitis ▪ Pulmonary pneumocystosis ▪ Aspergillosis ▪ Nocardiosis 	<ul style="list-style-type: none"> ▪ Malnutrition, hypoalbuminemia ▪ Lymphopenia, leukopenia ▪ Renal failure ▪ High doses of glucocorticoids ▪ Methotrexate overdosage
Lymphoma*	<ul style="list-style-type: none"> ▪ Adenopathy ▪ Fever, night sweat 	<ul style="list-style-type: none"> ▪ Viral reactivation (EBV)

EBV, Epstein-Barr virus. * Sometimes regressive when the treatment is stopped

Table 6: Medical attitude to daily problems under methotrexate (MTX) treatment.

Medical problem	Medical response
Transaminases elevation	<ul style="list-style-type: none"> Exclude another medicinal cause (analgesics, NSAIDS*) If the elevation is > 2-fold the upper limit and the responsibility of methotrexate is suspected: consultation of a specialist
Cough, with or without fever, with or without dyspnoea	<ul style="list-style-type: none"> Consult a rheumatologist and (or) a pulmonologist Exclude a hypersensitivity pneumonia methotrexate-induced <p>Two mistakes that should not be made:</p> <ul style="list-style-type: none"> Avoid methotrexate reintroduction without sufficient para-clinical examination Avoid to incriminate and stop methotrexate for good without sufficient evidence
Aphtha, mucosal inflammation	<ul style="list-style-type: none"> CBC** to rule out agranulocytosis or aplasia <p>If CBC normal: antiseptic mouthwash +/- try SC administration if previously oral</p>
Fever > 39°C	<ul style="list-style-type: none"> Antibiotic treatment according to the suspected infection type and microbe In case of pulmonary infection or slow evolution (> 48-72h): CBC* and consultation of a specialist
Apparition of an adenopathy or splenomegaly	<ul style="list-style-type: none"> Necessity of para-clinical exploration to search for a lymphoma Consultation of a specialist
Apparition of a malignancy other than lymphoma	<ul style="list-style-type: none"> The link between methotrexate and cancer has not been demonstrated
Pregnancy†	<ul style="list-style-type: none"> Information of the patient (high risk of spontaneous abortion or malformation) <ul style="list-style-type: none"> Stop immediately methotrexate and consult a rheumatologist Obstetrical consultation MTX should not be used for at least 3 months for men and 1 month for women before planned pregnancy, and should not be used during pregnancy or breast feeding

* NSAIDS, Non-Steroidal Anti-Inflammatory Drugs; **CBC, complete blood count. † Periconceptional management of MTX is detailed in Appendix 2.

o Haematological toxicity

Haematological toxicity (leukopenia, thrombocytopenia, megaloblastic anaemia, pancytopenia) occurs in about 3% of patients treated with MTX. The frequency is increase in patients > 65 and in case of chronic kidney failure (which increases the MTX concentration in serum). Although concomitant use of NSAIDs seems to be safe, anti-inflammatory doses of aspirin (> 1g/j) should be avoided, especially in case of chronic kidney disease, because it decreases the tubular excretion of the drug. Cases of bone marrow suppression with concomitant use of trimethoprim-sulfamethoxazole have also been reported, and this antibiotic should thus be avoided in case of MTX prescription.

- o Infections

Their frequency seems higher in MTX-treated patients, although it is not known with exactitude. They might be viral (especially herpes zoster, cytomegalovirus), bacterial community or opportunistic (*Pneumocystis carinii*, *Aspergillus*, *Cryptococcus* or *Nocardia*). In case of scheduled orthopaedic surgery, low-dose MTX can be continued during the elective perioperative period without an increased risk of complications and this minimises postoperative RA flares (Pieringer et al, 2007; Loza et al, 2009; Harle et al, 2010). However, it is essential to stop it at least 15 days before the intervention in case of septic surgery (Table 3).

- o Malignancies and lymphoma

The link between MTX and cancer has not been demonstrated. The link between MTX and lymphoma is complex. RA patients, independently of MTX use, are at higher risk of developing a lymphoma, especially a non-Hodgkin type. However, B-lymphoma have been reported in RA patients treated with MTX (Mariette et al, 2002). Epstein-Barr virus seems to play a role, as the serology is positive in 50 % of the patients. These lymphoma are sometimes regressive after MTX discontinuation.

- o Other side effects

Rash

Dermal toxicity include rash, hair loss (often regressive when MTX is stopped or folinic acid increased), localised skin reaction (pruritus, red patch, haematoma) with subcutaneous administration. Subcutaneous nodules related to RA may worsen during MTX treatment, or appear under treatment if not existing previously. These nodules can sometimes be located inside the lungs.

Mild gastrointestinal complaints

They are very frequent (20 to 60% of patients), and even more frequent when MTX is used orally and at high doses. They include nausea, vomiting, anorexia, and diarrhoea or stomach ache. To minimise these non-serious gastrointestinal side effects switching from oral to parental (preferentially subcutaneous). MTX might be helpful, based on studies that demonstrate better tolerability with intramuscular formulations. Splitting the dose, although commonly performed, is mainly supported by expert opinion.

Teratogenicity

MTX is teratogenic, and should not be given to pregnant or breast-giving women. More details about the periconceptional management of MTX can be found in Appendix 2.

1.2.2 Leflunomide

➡ Mechanism of action

Leflunomide is an isoxazole derivative and a prodrug whose active metabolite is malononitrilamide A77 1726. It inhibits de novo pyrimidine synthesis, resulting in diverse antiproliferative and anti-inflammatory effects such as suppression of TNF-induced cellular responses and inhibition of matrix metalloproteinases and osteoclasts.

➡ Metabolism

The half-life of the active compound is 15 days. Leflunomide and its active metabolite are extensively protein bound and undergo further metabolism before excretion, which at the same time hepatic and renal. Leflunomide persistence in the organism can reach two years, because the molecule is reabsorbed through an enterohepatic cycle. The absorption can be interrupted through the use of cholestyramine or activated charcoal.

➡ Efficacy in RA

Leflunomide has demonstrated to be as efficacious and safe as MTX, and is currently the best alternative in this indication. Leflunomide monotherapy is not inferior to MTX in controlling disease manifestations in both early and established RA and in slowing radiographic damage (Cohen et al. 2001; Sharp et al. 2000; Smolen et al. 2004). Combination therapy of leflunomide and TNFi might also be as effective as its combination with MTX, but adequate randomised controlled trials have not been undertaken. Interpretation is based on small cohort studies and is not completely consensual (Finckh et al, 2009; De Stefano et al, 2010; Benucci et al, 2011). The two-year therapeutic maintenance level of leflunomide is not significantly different from MTX (\approx 85% versus 79 %, Cohen et al. 2001).

➡ Leflunomide prescription in practice

The screening investigations are detailed in table 3. Because of its slow onset of action (approximately 6–8 weeks) a loading regimen of 100 mg daily for 3 days was initially advocated to rapidly achieve clinically active serum concentrations. Most clinicians, however, do not now use this regimen owing to toxicity, and results from the LEADER study confirmed that in DMARD-naïve patients, a loading dose does not increase efficacy at 3 months, in comparison with a fixed regimen of 20 mg/day, and is associated with a higher rate of adverse events (Cutolo et al, 2010). The dose can be decreased to 10 mg/day but, owing to the long half-life of the active metabolite, a prolonged period may be required before plasma levels decline after dosage reduction.

➡ Side effects and contraindications

Leflunomide may increase the risk of foetal death and have teratogenic effects and should only be started if pregnancy is excluded and is not planned for the near future. Because of a lack of data, it is safer not to use leflunomide in lactating women (Götestam Skorpen et al. 2016). In view of its long half-life, a course of cholestyramine (3×8 g daily for 11 days) can be given to facilitate clearance of the active compound. Without washout, elimination of leflunomide may take 2 years but even with washout, pregnancy should be avoided within 6 months of stopping the drug. Women taking leflunomide who wish to conceive must discontinue the drug and undergo cholestyramine washout before attempting conception. Other contraindications to the use of leflunomide include liver disease, severe renal impairment, severe immunodeficiency and rifampicin therapy. Adequate monitoring of side effects, including raised liver enzymes, diarrhoea, alopecia, high blood pressure, rash and leukopenia, is required (Table 3). Cases of leflunomide-induced pneumonitis and reversible axonal sensory motor peripheral neuropathy have also been described.

1.2.3 Sulfasalazine

➡ Mechanism of action and metabolism

SSZ is a 5-aminosalicylic acid derivative which is metabolised via the colonic intestinal flora to sulfapyridine and 5-aminosalicylic acid (5-ASA) and, after absorption, it is metabolised further. Sulfapyridine is the active moiety in RA and rheumatic diseases, although its mechanism of action has not been identified. It is mainly excreted in the urine, either as unchanged drug or as its metabolites, with a relatively short half-life (<10 h). 5-ASA has an action on the digestive mucosa, by decreasing IgAs, explaining its role in inflammatory bowel diseases.

➡ Efficacy in RA

In randomised double-blind placebo controlled trials, SSZ was associated with statistically significant benefits for various measures of disease activity according to the results of individual trials and/or meta-analysis (Weinblatt et al. 1999). It had similar efficacy to that of various other synthetic DMARDs in several randomised double-blind comparative trials. Although SSZ has a structural effect similar to leflunomide (Scott et al. 2001), and in spite of the absence of clear clinical differences in the rare head-to-head controlled studies of SSZ versus MTX, SSZ is often considered to be less efficient than MTX. This might also be related to limited compliance to high-dose SSZ owing to the large number of daily pills (four to six) that has to be taken continuously.

➡ SSZ prescription in practice

SSZ is prescribed at doses of 2–3 g/day in two divided doses. A gradual increase in dose (500 mg a week, for instance) should be performed to minimise potential toxicity when beginning SSZ treatment. The dose should

be adapted in case of renal or liver insufficiency. Hypersensitivity to sulfa drugs or salicylates or glucose-6-phosphate dehydrogenase deficiency should be assessed, and the drug should not be given if present. The screening investigations and monitoring are detailed in table 3.

➡ Side effects and contraindications

SSZ was generally well tolerated in clinical trials, although approximately 20–25% of patients withdrew because of intolerable side effects—two-thirds of which result from gastrointestinal symptoms or central nervous system toxicity (headache, dizziness) and about 4–5% are due to rash. Most adverse effects occur in the first months of treatment (table 3). Myelopoiesis inhibition can also occur at any time and periodic laboratory screening is therefore recommended, particularly in patients with impaired renal or hepatic function or blood dyscrasia. Patients should be informed of the risk of severe drug reaction: bullous dermatosis such as Lyell syndrome or DRESS (drug reaction with eosinophilia and skin syndrome) characterised by fever, rash and markedly abnormal liver function tests may be induced by SSZ, resembling a viral illness, which should lead to prompt discontinuation of the drug. Patients with known hypersensitivity to sulfa drugs or salicylates and those with glucose-6-phosphate dehydrogenase deficiency (risk of haemolysis) should not be given SSZ. Some patients receiving SSZ may develop orange-coloured urine, tears or skin. It is one of the few DMARDs (together with HCQ and low-dose glucocorticoids) that are relatively safe in pregnancy, although it should be used with caution in women who are breast-feeding. In men, SSZ may cause reversible oligospermia.

1.2.4 Antimalarial agents

➡ Mechanism of action and metabolism

The antimalarial agents - mainly hydroxychloroquine (HCQ), because chloroquine (CQ) is not used in common practice for RA treatment- are 4-aminoquinoline derivatives. Their mechanism of action is imperfectly known. They concentrate inside cells within acidic cytoplasmic vesicles, resulting in changes in acidity, and interfere with the processing of auto antigenic peptides. It was shown that antimalarial agents can interact with nucleic acids and inhibit endosomal Toll-like receptor activation, suggesting a potential mechanism to modulate activation of the innate immune system (Kuznik et al, 2011). Furthermore, antimalarial agents exert in vitro protective effects against the disruption of annexin A5 by antiphospholipid antibodies, improve lipid profile and reduce the risk of diabetes in patients with RA (Bili et al, 2011; Morris et al, 2011; Solomon et al, 2011).

HCQ is absorbed from the gastrointestinal tract and have extended serum half-lives due to tissue depot effects. It takes 2–4 months for antimalarial agents to become effective. Excretion of HCQ is mainly by renal clearance and its dose should be reduced in patients with renal insufficiency.

➡ Antimalarial drug prescription in practice

HCQ did not demonstrate significant efficacy in joint damage prevention and is therefore recommended in combination with MTX, as it may contribute to a higher peak and area under the curve concentrations of MTX in blood, or in association with other DMARDs (Smolen et al, 2010; Smolen et al, 2014*). The doses recommended are detailed in table 3.

Monitoring should include proper eye management. Recent recommendations of the American College of Ophthalmology propose a baseline assessment, within the first year of starting the drug, then at 5 years and annually afterwards to exclude maculopathy (Marmor et al. 2016). This assessment should include: fundus examination, visual fields, multifocal electrinoqram (mfERG) and/or fundus auto fluorescence, plus and spectral-domain optical coherence tomography (SD OCT) if maculopathy is present. At recommended doses, the risk of toxicity up to 5 years is under 1%.

Many centres also regularly control serum levels of HCQ: these measures could help to adapt the doses and thus to limit retinal toxicity, but are especially useful to check out patient compliance, as the serum elimination is long. The therapeutic levels for HCQ are commonly estimated to be higher than 500-1000 ng/mL.

➡ Adverse effects

Antimalarial drugs are generally well tolerated and serious adverse events are rare. The most feared adverse event is retinopathy, which is less common with HCQ than with CQ, and occurs only infrequently with low doses (HCQ < 5 to 6.5 mg/kg/day or CQ 2.3 to 3 mg/kg/day) (Marmor et al. 2016). The risk of retinal toxicity increases with long-term use (1% after 5–7 years or 1000 mg of cumulative dose), impaired renal or hepatic function, age >60 years, obesity, tamoxifen use, retinal and macular disease, genetic polymorphisms in the cytochrome P450 gene, or a prior history of antimalarial drug use (Marmor et al. 2016). HCQ and CQ retinopathy are not reversible, and cellular damage may progress even after the drugs are stopped. When retinopathy is not recognized until a bull's eye appears, the disease can progress for years, often with foveal thinning and an eventual loss of visual acuity. However, when retinopathy is recognized early, before retinal pigment epithelium damage, there is only limited progression after discontinuing the medication and the fovea will not be involved. Thus, screening may not “prevent” damage, but if conducted properly it enables the detection of toxicity before vision is significantly affected (Marmor et al. 2016). Headaches, dizziness, rash, pruritus, mild gastrointestinal complaints (anorexia, nausea, vomiting, abdominal cramps and diarrhoea) sometimes require its discontinuation, but no routine laboratory monitoring is required. Skin pigmentation and alopecia can occur. Neuromyopathy, haematological side effects (leukopenia, thrombocytopenia, anaemia) atrioventricular block due to antimalarial drugs (less common with HCQ) are rare complications.

1.2.5 Glucocorticoids

Although glucocorticoids do have a structural effect and can thus be considered as DMARDs (Kirwan et al, 2007), they also have a lot of side effects which might reduce their chronic use. Hence, most authors nowadays consider that their prescription should be, when possible, limited to “bridging therapy” in the initial treatment strategy, in combination with one or more csDMARDs, for up to 6 months, but should be tapered as rapidly as clinically feasible (Smolen et al. 2013). In practice, they can be useful to manage disease flares. These concepts and the modalities of prescription and monitoring will be detailed in In-Depth Discussion 2 (www.eular-onlinecourse.org).

1.2.6 Other DMARDs

Gold salts are the oldest group of synthetic DMARDs used in the treatment of RA, yet their mode of action remains poorly understood. Gold affects macrophage and B cell function and can modify matrix metalloproteinase (collagenase) production and antibody production. Some gold preparations can only be administered by intramuscular injection (gold sodium thiomalate and gold sodium thioglucose), starting at 10 mg/week followed by weekly dose increments up to 50 mg/week. Noticeable clinical effects are usually not achieved until after 4–6 months of treatment, making its onset of action the longest of all the DMARDs. If there is no response after a cumulative dose of 1 g has been given, gold treatment should be discontinued. If there is a favourable response, however, treatment can be tapered over a period of several months until an effective monthly maintenance dose has been found. The oral version (auronofin) is usually started at 6 mg/day in two split doses and then increased to 9 mg/day after 3 months. Injectable gold is more effective than oral gold, especially on progression of joint damage. Gold is generally well tolerated but can lead to severe allergic reactions (skin rash), stomatitis, proteinuria, neuropathy, thrombocytopenia and potentially life-threatening bone marrow aplasia requiring prompt discontinuation. Although rarely used nowadays because of the frequency of adverse effects, gold as monotherapy or in combination with prednisone or MTX remains an alternative for patients with refractory disease. AZA, cyclophosphamide, cyclosporine, D-penicillamine, tacrolimus and tetracycline derivatives (minocycline, doxycycline) are sometimes used in the treatment of RA. AZA and cyclophosphamide use is declining because of their side effects (myelosuppression, increased risk of infection and malignancies with long-term use, and hepatotoxicity). Cyclosporine is an effective DMARD, especially in combination with MTX, but its toxicities (hypertrichosis, tremor, gum hyperplasia, hypertension and dose-related loss of renal function), though reversible in most cases, have prevented its widespread use. Tetracycline derivatives inhibit metalloproteinase activity involved in joint destruction and are sometimes used as adjunctive treatment early in the disease (Gaujoux-Viala et al, 2010 and 2013).

Given the wide array of more effective and safer DMARDs and with the introduction of effective biological agents, these DMARDs are mainly reserved for patients with refractory RA, intolerant to previously described DMARDs and biological agents.

1.2.7 Combinations of cs DMARDs

This point will be detailed further in the strategy section.

Summary points: conventional synthetic (cs) DMARDs

- ➔ csDMARDs should be started in every patient upon diagnosis.
- ➔ Methotrexate (MTX) is the preferred first-line DMARD owing to its good efficacy/safety ratio.
- ➔ Leflunomide or SSZ should be considered as an alternative when MTX fails or is not tolerated.
- ➔ Antimalarial drugs are weak DMARDs when used as monotherapy, but they can be used in association with other DMARDs and may have additional benefits in patients with RA and a high risk of cardiovascular disease.
- ➔ Glucocorticoids in low to moderate doses have an important role as bridging treatment in early disease or during flares, in addition to csDMARDs, due to their high efficacy and rapid onset of action. This concept will be detailed in In-Depth Discussion 2.
- ➔ In DMARD-naïve patients, csDMARD monotherapy with or without glucocorticoids should be preferred to csDMARD combination therapy (2016 EULAR recommendations update, please see the strategies section below).

1.3 Biological DMARDs (bDMARDs)

Numerous biological agents that target inflammatory cytokines, cytokine receptors or cells within the synovium and immune system have been developed during the last 20 years.

Owing to the broad information and scientific literature on this topic, the text given in *italic* is only informative for the student and no assessment questions will be asked on it. Further information can be found through small clinical vignettes of the main randomised controlled trials in Appendix 1.

1.3.1 Targeting cytokines or cytokine receptors using biological agents

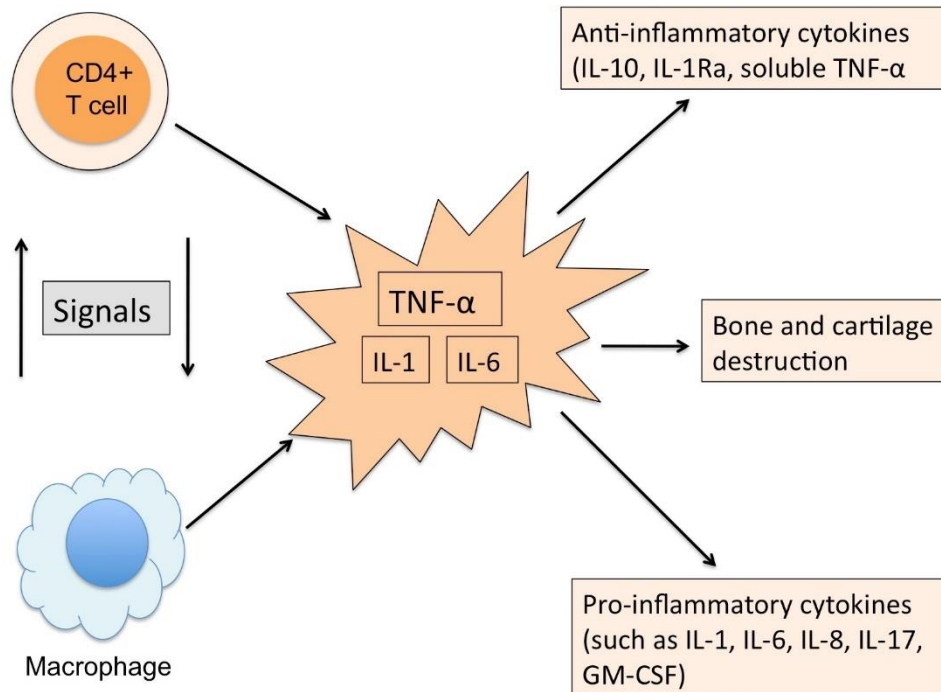
A broad range of cytokine pathways are activated in RA synovitis, especially pro-inflammatory cytokines such as TNF α (Tumour Necrosis Factor α) and interleukine (IL)-1 and IL-6 (McInnes and Schett, 2007*) (Figure 7).

More details on RA pathophysiology can be found in the dedicated course (www.eular-onlinecourse.org).

Cytokines are peptides that exist in families of related molecules. They function by binding to a specific receptor on a target cell and thereby facilitate communication within the immune system between cells that may be required to operate together but which may be situated some distance apart. For instance, the biological effect of TNF α and the activation of the target cell require the binding of the cytokine with the membrane receptors p55 or p75. These membrane receptors also exist in a soluble circulating form, and are

currently considered as natural inhibitors of TNF, because they can decrease its bioavailability while binding it (Singh et al. 2009).

Figure 7: Simplified representation of the cytokine cascade in the pathophysiology of rheumatoid arthritis.



TNF-α mediates diverse activities in RA, including local activation of synovial leucocytes, endothelial cells, platelets, synovial fibroblasts, chondrocytes and osteoclasts. It also mediates systemic effects, in part via driving IL-6 and hence acute phase responses, or IL-1 and joint destruction. TNFα acts as a critical checkpoint cytokine in the inflammatory cascade and, thus agents that block its activity have, in general, been associated with marked clinical improvement and prevention of joint destruction.

TNF-α, Tumour Necrosis Factor α; IL, interleukin; Ra, Receptor antagonist; GM-CSF, granulocyte macrophage colony stimulation factor.

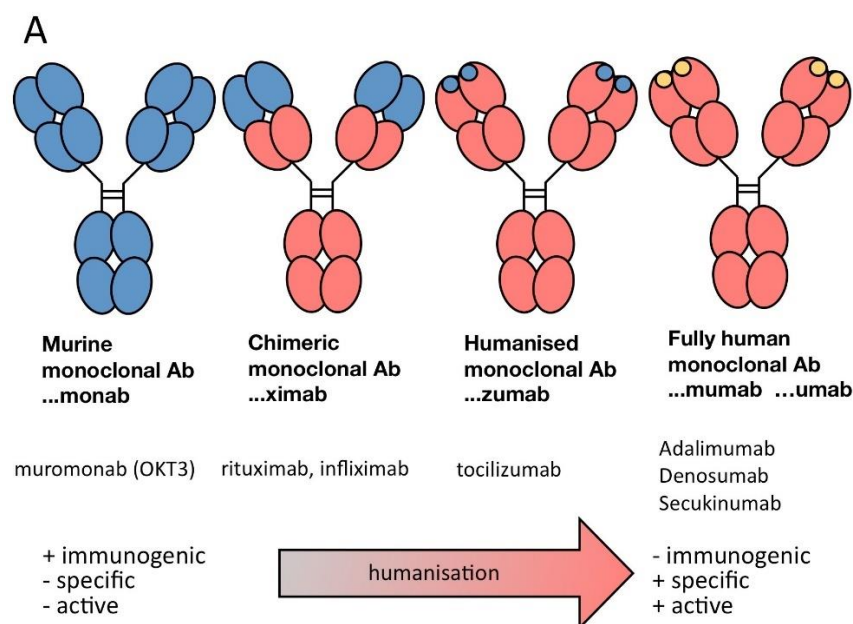
Nomenclature

The advent of sophisticated molecular technology has allowed the generation of highly specific molecular antagonists to cytokines or cytokine receptors (Hueber et al, 2010).

These targeted treatments may be:

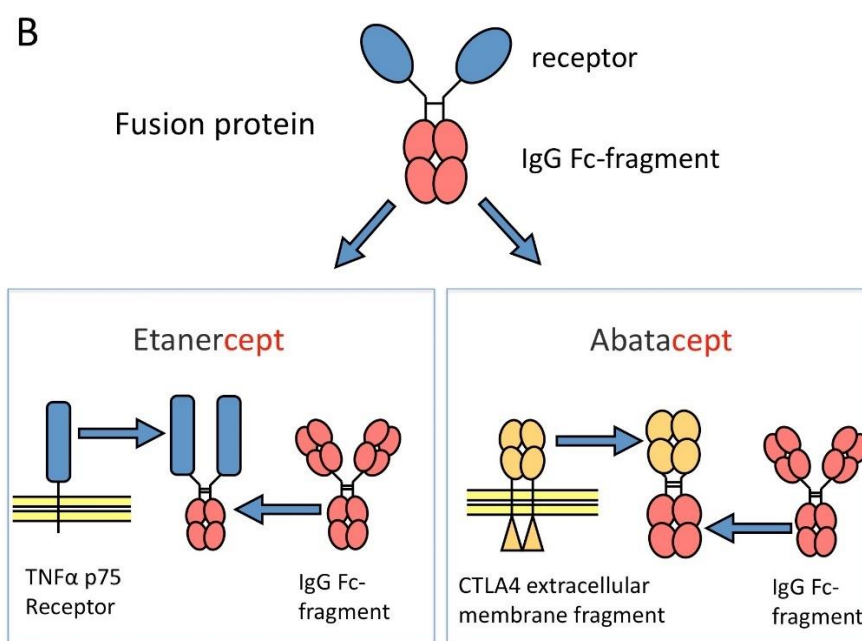
1. monoclonal antibodies, with usually as suffix “mab” (“ximab” for chimeric antibodies, “mumab” for fully human, “zumab” for humanised, e.g., infliximab, adalimumab, certolizumab, golimumab, tocilizumab),
2. native cytokine receptors coupled to the Fc component of human immunoglobulin, with suffix “cept” (e.g., etanercept)
3. recombinant antagonists that closely resemble the cytokine structure but deliver no signal when bound by receptor (e.g., anakinra) (figure 8).

Figure 8: schematic illustration of the different mechanisms of action of biological treatments. A. Monoclonal antibodies (Ab).

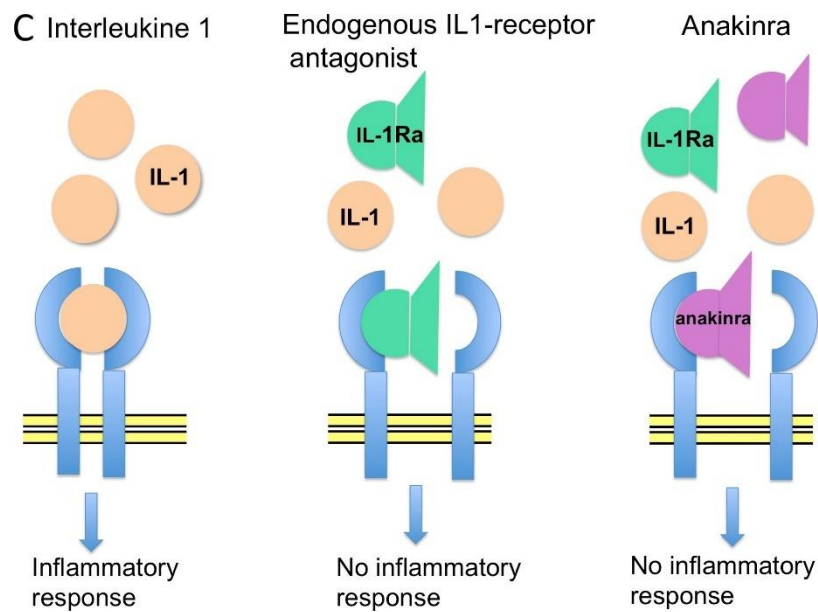


Monoclonal antibodies (Ab) can be murine, chimeric, humanised or fully human, according to the suffix used. Humanisation decreases the risk of immunisation, thus increasing tolerance and therapeutic maintenance. Monoclonal Ab can be directed against a cytokine (TNF α for infliximab and adalimumab, IL-17 for secukinumab), a receptor (IL6-R for tocilizumab) or the membrane of a cellular type (CD20 of B lymphocytes for rituximab). Muromonab is a monoclonal Ab directed against CD3 used in prevention of graft reject. Denosumab is an Ab directed against receptor activator of nuclear factor kappa-B ligand (RANKL) used in osteoporosis. Secukinumab is an Ab in development in RA, spondylarthritis and psoriasis, directed against IL17.

Figure 8: schematic illustration of the different mechanisms of action of biological treatment (continued). B. Fusion proteins.



Fusion proteins couple a receptor and an IgG Fc-fragment, and usually have the suffix –cept. Etanercept is a soluble receptor aiming at TNF α . Abatacept inhibits T cell co-stimulation.

Figure 8.C. Recombinant antagonists.

Recombinant antagonists closely resemble the cytokine structure but deliver no signal when bound by receptor. Anakinra is a recombinant form of the natural endogenous IL-1 receptor antagonist called IL-Ra.

1.3.2 TNF inhibitors in RA

Five TNF inhibitors (TNFi) are currently available for the treatment of RA (**table 7**).

1.3.2.1 Anti-TNF antibodies in RA

➡ Infliximab

Infliximab is a human murine chimeric antibody that defined the fundamental importance of TNF in the pathogenesis of RA by the landmark studies of Feldman and Maini in the early 1990s (Feldmann and Maini, 2001). It binds both soluble and membrane-bound forms of TNF.

Infliximab and low-dose MTX promote benefit at the American College of Rheumatology 20% (ACR 20) level in around 60% of recipients within 8–12 weeks, with fewer patients achieving ACR 50 and ACR 70 responses. *The pivotal phase III study (ATTRACT study) compared MTX/placebo with MTX/infliximab combinations (four dose regimens) in patients with established RA with an inadequate response to MTX therapy. MTX/infliximab recipients showed significantly greater improvement after 1 year than MTX/placebo recipients judged by higher ACR 20, ACR 50 and ACR 70 response rates and reduced progression of the Sharp score (Maini et al, 1999).* Several studies have replicated and extended these data and a robust dataset indicates that infliximab is a well-tolerated and efficacious treatment for established RA.

Three studies indicate that infliximab may exhibit better efficacy if used in earlier disease. *In the ASPIRE study, recruitment of patients with early RA led to higher response rates at each ACR category level as compared with*

the results previously obtained in established disease, and prevented erosive progression. Improved responses are particularly evident compared with placebo when those patients presenting with high CRP levels were considered as a subset (Smolen et al, 2006). Additionally, the BeSt study—in which a variety of strategic approaches to RA treatment were compared—showed that infliximab added to MTX at an early disease stage can lead to significant improvements in clinical disease activity and prevent erosive progression. More importantly, this strategy can induce remission in a proportion of patients, which is maintained when infliximab is stopped and, in a small number of patients, even after stopping all treatments (Goekoop-Ruiterman et al, 2007). The pathophysiological mechanism for such better results in early intervention is not yet clear. Interestingly, infliximab can induce the generation of regulatory T cell subsets, which may promote reinstitution of immune tolerance in the presence of synovitis, and this may contribute to better results when this drug is used early on in the course of the disease.

Infliximab should be given as an infusion over 2 h, which can be decreased to 1 h after the third infusion if well tolerated. Infliximab should be prescribed together with MTX (at least 10 mg/week) or an equivalent csDMARDs (higher efficacy and less development of anti-drug antibodies). The drug is given on weeks 0, 2 and 6 and then 8-weekly thereafter. The licensed dose for use in RA is 3 mg/kg, although, in some patients, higher doses and/or increased frequency of administration may be required (e.g., increase up to 5 mg/kg every 6 weeks), depending upon local healthcare provider recommendations or when response is lost, to overcome neutralising antibodies. Plasma concentrations of infliximab and the formation of human antichimeric antibodies (HACAs) are known to be good predictors of response to infliximab at the individual level. Secondary failure has also been shown to be dependent, at least in part, on HACA synthesis, which is increased when infliximab is used in monotherapy.

➡ Adalimumab

Adalimumab was the first human monoclonal antibody against TNF to be licensed for use in RA. Several randomised controlled datasets support the use of adalimumab in RA, and indicate that it is better than placebo in controlling signs and symptoms and in retarding progressive erosive disease. *Two pivotal studies deserve specific mention. The ARMADA study was a phase III study in established RA, in which adalimumab/MTX was shown to be better than placebo/MTX as measured by ACR responses and erosive progression (Weinblatt et al, 2003). Response rates were broadly similar to those seen with other TNF blocking agents, with about 69% of patients achieving ACR 20 response. This clinical response was globally maintained over 4 years of open follow-up, with a safety profile similar to that of the first 6 months. Reduction of glucocorticoid and/or MTX dosages did not adversely affect long-term efficacy. Adalimumab has also been tested in patients with early RA. The PREMIER study examined patients with RA of <3 years' duration and compared adalimumab/MTX with MTX alone and with adalimumab alone (Breedveld et al, 2006). The*

combination was significantly better than either agent used alone in the generation of ACR 50 improvements and also in retarding erosive progression

Adalimumab is given as a 40 mg subcutaneous (SC) injection every other week. It should be used in combination with MTX (at least 10 mg/week) or an equivalent csDMARD, which decreases immunogenicity and improves efficacy, but in patients intolerant to MTX it can be used as monotherapy and the dose increased to 40 mg every week, if necessary. However, for reasons of safety and cost, this dose increase is rarely used.

➡ Certolizumab

Certolizumab is a humanised antibody, in which the recombinant Fab' fragment that recognises TNF has been conjugated with a polyethylene glycol chain. The pegylation of the Fab' fragment increases its half-life and can also reduce its immunogenicity, without affecting the affinity and specificity of the antibody.

Certolizumab was found to be better than placebo in patients who were MTX incomplete responders in two phase III trials (RAPID 1 and RAPID 2) (Keystone et al, 2008; Smolen et al, 2009a). Either 400 mg (RAPID 1) or 200 mg or 400 mg (RAPID 2) of SC certolizumab plus MTX were given at weeks 0, 2 and 4, followed by 200 mg or 400 mg every 2 weeks, for a total of 52 weeks (RAPID 1) or 24 weeks (RAPID 2), in parallel with a regimen of placebo plus MTX. In both studies, at week 24, a significantly higher percentage of patients receiving certolizumab (57% up to 61%) achieved ACR 20 as compared with those in the placebo arm (13.6% and 8.7%), with no differences in efficacy between the 200 or 400 mg doses, at any time. Clinical benefits were noted 1 week after treatment, achieved their maximum at weeks 16–20 and were maintained through weeks 52 (RAPID 1) and 24 (RAPID 2). A greater inhibition of radiographic progression, as evaluated by the mean change in the modified Total Sharp Score, was also identified in the certolizumab-treated group at the end of the studies. Furthermore, in patients who were forced to withdraw at 16 weeks owing to lack of response at weeks 12 and 14, effects on radiographic scores at this early time were also demonstrated, indicating that certolizumab may reduce joint damage even when ACR 20 is not achieved. Similarly, 400 mg of certolizumab given monthly as monotherapy when DMARDs have failed (FAST4WARD), is clinically efficacious, although with lower rates of patients achieving ACR 20/50/70 as compared with those receiving regimens in association with MTX (Fleischmann et al, 2009).

Table 7: summary table of the five TNF inhibitors available.

	Infliximab	Etanercept	Adalimumab	Certolizumab pegol	Golimumab
Mode of action	Chimeric monoclonal Ab	IgG-Fc-receptor construct (fusion protein)	Human monoclonal Ab	Humanised monoclonal Ab (Fab' fragment conjugated with PEG chain)	Human IgG1 monoclonal Ab (specific for both circulating and membrane bound TNF)
Mode of administration	IV	SC	SC	SC	SC
Dose	3 (to 5) mg/kg W0-W2-W6, then /6 to 8 weeks Mandatory association to MTX or other DMARD (Prevention of ADA)	50mg/week	40 mg every 2weeks	Induction regimen of 400mg at 0, 2 and 4 W, then maintenance dose of 200 mg/2weeks	50 mg/month
Mean half life	≈ 10 days	≈ 3-4 days	≈ 15 days	≈ 10-15 days	≈ 12-15 days
Contraindications	<ul style="list-style-type: none"> Active and/or chronic infections. Past history of severe or bad/untreated infection (tuberculosis +++) Hypersensitivity to the active substance or to an excipient Demyelinating diseases and/or retro-orbital optic disease 			<ul style="list-style-type: none"> Neoplasia* or hemopathia < 5 years Congestive heart failure (NYHA class III/IV and ejection fraction ≤ 50 %) Pregnancy and/or breast feeding Live attenuated vaccines¶ 	
Pre-treatment screening	<ul style="list-style-type: none"> Clinical examination**: exclude infections, malignancy < 5 years, congestive heart failure Patient education Exclude pregnancy Check for compliance with vaccination plan. Vaccination according to recommendations¶ Laboratory tests for CBC, liver function, creatinine, fasting glucose and lipid profile 			<ul style="list-style-type: none"> Serology for HIV, HBV and HVC (for some countries only if risk factors) Serum protein electrophoresis Antinuclear antibodies, and if positive, anti-DNA antibodies Exclude active or latent tuberculosis and treat according to local guidelines Chest X-ray examination Oral hygiene/stomatology assessment (for some centres) 	
Biologic monitoring	CBC, liver enzymes, creatinine, CRP before each infusion	CBC, liver enzymes, creatinine, CRP every three months	CBC, liver enzymes, creatinine, CRP every three months	CBC, liver enzymes, creatinine, CRP every three months	CBC, liver enzymes, creatinine, CRP every three months
Therapeutic response evaluation	4 th infusion	3 months	3 months	3 months	3 months If weight > 100 kg, possibility to increase dose to 100mg/months, after evaluating benefits/risks ratio
Interruption before scheduled surgery required (medium-high septic risk) [†]	4-8 weeks	2-4 weeks	8-10 weeks	8-10 weeks	8-10 weeks

Ab, antibody; ADA, anti-drug antibody; Fab', fragment antigen-binding; W, week; MTX, methotrexate; DMARD, Disease-Modifying Anti-Rheumatic Drug; IV, intravenous; SC, subcutaneous; CBC, complete blood count; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; NYHA, New York Heart

*Association; CRP, C-reactive protein. *Other than non-melanoma skin cancer that was removed completely with disease-free margins** Detailed clinical examination and pre-treatment screening, for TNFi and other bDMARDs can be downloaded in English version on www.cri-net.com; ¶ Detailed information and vaccination guidelines are given in Appendix 3. †Perioperative management of bDMARDs is detailed in In-Depth Discussion 3*

The safety profile of certolizumab was comparable to that seen with other anti-TNF therapies. From a pooled analysis of 4065 patient-years in randomised and open-label trials, the most common side effects were infections, with respiratory tract infections and tuberculosis being the most common serious infectious events. Pain at the site of injection was referred in 1.8% and injection site reactions occurred in 7.9% of patients (lower than with other subcutaneous biological drugs). Of interest, a prolonged activated partial thromboplastic time was seen in about 5% of patients in RAPID 2, which reflects an interference of polyethylene glycol with phospholipids used in commercial assays and does not seem to translate into any effect on coagulation in vivo (Fleischmann, 2010).

Certolizumab is approved for the treatment of moderate to severe RA by the Food and Drugs Administration (FDA) and by the European Medicines Agency (EMA) with an induction regimen of 400 mg at 0, 2 and 4 weeks, followed by a maintenance dose of 200 mg every other week, with subcutaneous administration in association with MTX

➡ Golimumab

Golimumab (Singh et al, 2010), a fully human IgG1 monoclonal antibody specific for both circulating and membrane-bound TNF, has been developed upon TNF immunisation of genetically modified mice (Zhou et al, 2007). Three pivotal randomised placebo-controlled clinical trials demonstrated the efficacy and safety of golimumab in MTX-naïve (GO-BEFORE), MTX inadequate responder (GO-FORWARD) and anti-TNF failure (GO-AFTER) patients with RA. The GO-BEFORE study, which included patients with <3 years' disease duration, did not detect significant differences in ACR 50 responses (primary end point) between the combination therapy groups of golimumab (50 or 100 mg) every 4 weeks plus MTX and MTX as monotherapy, but a difference would have been seen if the ACR 20 responses had been considered. A decrease in joint damage was shown at week 52 in the active treatment arm plus MTX in comparison with MTX monotherapy (Emery et al, 2009b). Using the same study design, GO-FORWARD showed significantly higher ACR 20 responses at week 14, in patients with active disease despite MTX therapy, treated with golimumab 50 and 100 mg, in combination with MTX (56%), compared with MTX and placebo (33%). The ACR 20 responses were detected as early as 4 weeks and in general increased until week 24 (Keystone et al, 2009). The follow-up analysis of the GO-FORWARD study, including the subgroup of patients who entered early escape at week 16 combined with those who crossed over from placebo to active treatment, showed that efficacy was sustained up to 52 weeks (Keystone et al, 2010).

In the GO-AFTER study, patients for whom TNFi had failed or been discontinued were assigned to one of three arms: placebo, golimumab 50 mg or golimumab 100 mg SC every 4 weeks, with concomitant DMARDs being allowed. A significantly greater proportion of patients in the golimumab combination groups (37%) achieved ACR 20 as compared with placebo (18%) (Smolen et al, 2009b). Both the GO-BEFORE and GO-FORWARD included a golimumab monotherapy arm and although 100 mg golimumab was associated with some clinical benefit, this was not better than with MTX alone. Similarly, there was no clear difference in the efficacy of the two golimumab doses, and golimumab 100 mg plus MTX was associated with higher rates of serious adverse events. Therefore 50 mg once a month in combination with MTX is the regimen approved both in the USA and Europe. The safety profile of golimumab is identical to that of other anti-TNF drugs.

1.3.2.2 TNF blocking agents in RA: soluble receptor

➡ Etanercept

Etanercept is a recombinant TNF receptor fused to a human Fc molecule creating a bivalent TNF binding agent. It has a shorter “on and off” binding rate to TNF than the antibodies noted above, which may account for its distinct pharmacodynamics and, perhaps also, mode of action.

Several randomised controlled double-blind trials provide the core evidence for its benefit in RA. Monotherapy with etanercept promotes benefit at the ACR 20 level in around 60–70% of recipients within 8–12 weeks. Etanercept reduces clinical inflammation, improves physical function and quality-of-life indices and reduces radiographic progression. In general, studies show that withdrawal rates with etanercept are lower than with placebo. The pivotal phase III study for early RA compared MTX with etanercept monotherapy in patients with RA of <3 years’ duration (Bathon et al, 2000). Both therapeutic arms improved significantly as measured by clinical response criteria and by reduced radiographic progression. Etanercept recipients exhibited marginal, but nevertheless significantly greater, improvement after 1 year than MTX recipients judged by ACR and Sharp erosion scores. Symptomatic control was evident at an earlier stage.

In a further study, clinical benefit was also shown in partial or non-responders to MTX when etanercept was used in combination with MTX (Weinblatt et al, 1999). However, the critical trial demonstrating the superior benefits of etanercept with MTX is the TEMPO study (Klareskog et al, 2004). In this large study etanercept alone, MTX alone or the two in combination were compared. Etanercept + MTX was superior in improving clinical signs and symptoms and also in suppressing radiographic progression; indeed, some patients even appeared to have an improved Sharp score. However, in this TEMPO study, most of the patients were MTX naïve, which might explain the superiority of the combination. In a recent study (ADORE) of patients with true MTX resistance, a combination of MTX with etanercept was not better than etanercept alone, which suggests that monotherapy with etanercept is possible in true MTX-resistant patients (van Riel et al, 2008). The COMET study has recently added information, determining high levels of efficacy in patients with early RA and high

disease activity (DAS28>5.1) in whom etanercept was added as initial treatment. Fifty per cent of patients receiving combination therapy and 28% of those receiving MTX monotherapy achieved clinical remission. Outcomes were particularly improved as measured by prevention of radiographic progression over 1 year, with a percentage of non-progressors of 80% in the combination arm and 59% in the MTX monotherapy group. This was translated into additional benefits in productivity gains, with less work absenteeism. Clinical and radiographic benefits were maintained at 2 years of follow-up (Emery et al, 2008a; Emery, 2009c).

Etanercept is given as an SC injection in a dose of 25 mg twice a week or 50 mg once a week.

1.3.2.3 TNF inhibitors and cardiovascular risk

There is increasing interest in the ability of TNF blocking agents to modify cardiovascular risk, which is increased in RA. Data suggest that patients with RA have a higher incidence of atherogenesis, coronary artery calcification, increased rates of myocardial infarction, cardiac-related death and reduced survival after a vascular event in comparison with the general population. This increased risk may be related to cytokine activity and it has been predicted that TNF blocking agents may reverse or retard the vascular morbidity noted above (Sattar and McInnes, 2005). TNF blocking agents reduced the risk of myocardial infarction in patients who respond to this treatment compared with those treated with a synthetic DMARD. This study had, however, a limited follow-up (maximum 1.66 years) and long-term follow-up will be necessary to confirm these results (Dixon et al, 2007).

However, TNFi can induce cardiac decompensation, and are therefore contraindicated in severe cardiac failure (please see below in the safety section).

1.3.2.4 Safety of TNF inhibitors

The safety of TNFi has now been analysed for over 10 years, and solid data from various metaanalyses and registries exist. It will be further treated in a specific section about the safety of all bDMARDs, including TNFi and non-TNFi.

1.3.3 Other biologic DMARDs (non-TNFi)

Four non-TNFi bDMARDs exist (Table 8 A. & B.) in the therapeutic arsenal, although anakinra is not commonly used for the treatment of RA.

Table 8.A: Main non-TNF inhibitors biological DMARDS used in RA

	Rituximab	Abatacept	Tocilizumab	Anakinra
Mode of action	Chimeric monoclonal Ab, anti-CD20 (B lymphocytes)	Recombinant fully human protein CTLA4-Ig Inhibits lymphocyte co-stimulation	Humanised monoclonal Ab that inhibits IL-6 receptor (membrane bound and soluble form)	Recombinant IL-1 antagonist (binds to type I IL-1 receptor)
Mode of administration	IV	IV	IV	SC
Dose	1g, repeated 14 days later Or for some centres: 500mg, repeated 14 days later With premedication: Paracetamol 1g Methylprednisolone 100 mg Dexchlorpheniramine 1 phial If relapse, to be repeated after at least 6 months Associated to MTX or other DMARD	10 mg/kg D0, D15, D30, then every 30 days SC 125 mg/week Associated to MTX or other DMARD	8mg/kg/4 weeks (min 480 mg and max 1.2g) (Dose adaptation if receiving other treatments metabolized through CYP 450 enzymes §) SC 162 mg, once/week Associated to MTX (or other DMARD), or monotherapy if MTX not tolerated	100mg/day Associated to MTX
Mean half life	20-22 days (depends on the dose and regimen)	15 days (IV)	12-15 days (8 mg/kg IV)	4-6 hours
Contraindications	- Hypersensitivity to rituximab or excipient - Severe and uncontrolled infection - Congestive heart failure (NYHA class III/IV and ejection fraction ≤ 50 %) or uncontrolled CV disease - Pregnancy (relative) and breast feeding	- Hypersensitivity to abatacept or excipient - Severe and uncontrolled infection - Pregnancy (relative) and breast feeding	- Hypersensitivity to TCZ or excipient - Severe and uncontrolled infection - Pregnancy (relative) and breast feeding	- Hypersensitivity to anakinra or excipient - Severe kidney failure (CrCl<30 mL/min) - Pregnancy and breast feeding
Precaution of use	- IgG below laboratory levels - Lymphopenia T and/or B - Hepatitis - HIV	- Past history of recurrent or chronic infection or risk factors for infection	- Diverticulitis - Active liver disease and liver failure - Neutropenia , thrombocytopenia - Dyslipidaemia	- Past history of recurrent or chronic infection or risk factors for infection - Neutropenia <1500/mm ³ - Dyslipidaemia - Cardiovascular disease

- neutropenia < 1500/mm ³	- Recent or scheduled vaccination - Diabetes mellitus (abatacept therapy can interfere with blood glucose measurements) - MGUS - Malignancy within the last 5 years*	- Cardiovascular disease - Demyelinating disease - Malignancy within the 5 last years*	- Active liver disease and liver failure
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Ab, antibody; CD, cluster of differentiation; W, week; MTX, methotrexate; DMARD, Disease-Modifying Anti-Rheumatic Drug; IV, intravenous; SC, subcutaneous; CV, cardiovascular; CrCl, creatinine clearance rate; Ig, immunoglobulin; CBC, complete blood count; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; NYHA, New York Heart Association; TCZ, tocilizumab; RTX, rituximab; CRP, C-reactive protein; MGUS, Monoclonal gammopathy of undetermined significance

*§Full list available on <http://medicine.iupui.edu/clinpharm/ddis> *Other than non-melanoma skin cancer that was removed completely with disease-free margin.*

Table 8.B: Main non-TNF inhibitors biological DMARDs used in RA (continued)

	Rituximab	Abatacept	Tocilizumab	Anakinra
Screening before treatment	<ul style="list-style-type: none"> Clinical examination: exclude infections, malignancy < 5 years, congestive heart failure, diverticulitis (TCZ) Patient education Exclude pregnancy Check for compliance with vaccination plan. Vaccination according to recommendations¶ Laboratory tests for CBC, liver function, creatinine, fasting glucose and lipid profile Serology for HIV, HBV and HCV (for some countries only if risk factors) Serum protein electrophoresis Antinuclear antibodies, and if positive, anti-DNA antibodies Exclude active or latent tuberculosis and treat according to local guidelines Chest X-ray examination Oral hygiene/stomatology assessment (for some centres) For TCZ, abatacept and RTX: lymphocyte typing and immunoglobulin assays by weight in patients previously treated with RTX, or before treatment with RTX 			
Biologic monitoring	CBC, liver enzymes, creatinine, CRP: every three months	CBC, liver enzymes, creatinine, CRP: every three months	-Hemogram (neutropenia), liver enzymes, creatinine, CRP/month during the first 3-6 months, then/3 months - Lipid profile 8 weeks after the first infusion/injection	- Hemogram (neutropenia), liver enzymes, creatinine, CRP/month during the first 6 months, then/3 months - Lipid profile/6 months
Therapeutic response evaluation	Between 4 and 6 months	Between 3 and 6 months	Between 3 and 6 months	Between 3 and 6 months
Interruption before scheduled surgery required (medium-high septic risk)†	20-24 weeks	8-12 weeks (IV)	8-10 weeks (8mg/kg)	1-2 weeks

Ab, antibody; CD, cluster of differentiation; W, week; MTX, methotrexate; DMARD, Disease-Modifying Anti-Rheumatic Drug; IV, intravenous; SC, subcutaneous; CV, cardiovascular; CrCl, creatinine clearance rate; Ig, immunoglobulin; CBC, complete blood count; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; NYHA, New York Heart Association; TCZ, tocilizumab; RTX, rituximab; CRP, C-reactive protein; MGUS, Monoclonal gammopathy of undetermined significance

¶ Detailed information and vaccination guidelines are given in Appendix 3. †Perioperative management of bDMARDs is detailed in In-Depth Discussion 3.

1.3.3.1 Cell targeting agents in RA (anti-CD20)

The concept that directly targeting and depleting or functionally modulating circulating leucocyte subsets and/or within the target tissues, was one of the first strategies to be tested. Initial efforts focused on T cells, so agents such as anti-CD4 antibody and Campath-1H were administered, but had limited benefits in RA. The success of this approach was first achieved through the use of rituximab, an anti-CD20 chimeric monoclonal antibody that induces B cell and plasmablast depletion.

➡ Rituximab

Rituximab is a chimeric monoclonal antibody containing humanised and murine sequences in its protein structure. It is a potent cell lytic antibody developed initially for the treatment of B cell lymphoma. On binding to cells expressing CD20, rituximab induces cell death through a variety of mechanisms that include complement-mediated lysis, antibody-dependent cellular killing and apoptosis induction. The rationale for the use of rituximab in the treatment of RA is based in its potential to reduce synthesis of autoreactive antibodies, such as RF and ACPA, and impair antigen presentation to T cells as well as cytokine production. Rituximab has been shown to be efficacious in comparison with placebo in a variety of clinical studies. This has been translated into reproducible results in daily practice with a reasonable safety profile.

An initial study compared rituximab in combination with MTX or cyclophosphamide and comprised intravenous preinfusions of methylprednisolone and concomitant oral glucocorticoids (Edwards et al, 2004; Cohen et al, 2006; Emery et al, 2006). The DANCER study (Dose-Ranging Assessment International Clinical Evaluation of Rituximab in RA) established that rituximab was superior to placebo when administered to MTX refractory patients for whom other DMARDs, including biological agents, might have failed, again together with different glucocorticoid regimens (Emery et al, 2006). In the REFLEX study (Randomized Evaluation of Long-term Efficacy of rituximab in RA) inadequate responders or patients intolerant to at least one TNF blocking agent were enrolled to receive rituximab or placebo on a background of MTX (Cohen et al, 2006). In these studies the rate of ACR 20 responders at week 24 for those receiving 1000 mg of rituximab, given as two infusions 2 weeks apart on a MTX background, was variable: 73% (Edwards et al, 2004), 54% (DANCER) and 51% (REFLEX) in comparison with placebo (38%, 28% and 18%, respectively), probably owing to different inclusion criteria and allowance of various glucocorticoids regimens.

Clinical responses to rituximab may be delayed by up to 3 months and the duration of efficacy varies, with most patients experiencing a relapse after 6 and 8 months, but some remain well up to more than 15 months (Popa et al, 2007; Roll et al, 2008). Rituximab administration is followed by peripheral B cell depletion, usually assessed by the number of circulating CD19+ cells, on average 2 weeks after administration, and its serum levels fall below the limit of detection at week 16–20. This is generally associated with a gradual recovery of B cell counts and with clinical relapse in some, but not all, patients. Although there is no direct correlation between the degree and duration of B cell depletion and clinical response, repopulation generally occurs before the development of flares (Breedveld et al, 2007; Popa et al, 2007). Patients who are seropositive for RF and/or IgG ACPA have a higher probability of responding to rituximab, with better control of disease manifestations and radiographic progression (Dorner et al, 2009).

The decision as to which patient should be re-treated and when this should occur is of utmost importance. Both the SERENE (Study Evaluating Rituximab's Efficacy in methotrexate iNadequate rEsponders) and MIRROR

studies, despite different study designs, confirmed that re-treatment with a second course of rituximab (either 2×500 mg, 2×1000 mg or dose escalation) was associated with maintenance or improvement of ACR responses at week 48, as compared with week 24, and a further increase in the number of MTX inadequate responders achieving low disease activity ($\text{DAS28-ESR} \leq 3.2$) (Emery et al, 2010a; Rubbert-Roth et al, 2010). No significant differences were found between the different treatment arms, although a higher percentage of patients receiving 2×1000 mg, achieved a good or moderate EULAR response and ACR 50 and ACR 70 responses. Examining radiographic progression in MTX naïve patients with RA, the IMAGE study suggests that the 2×1000 mg regimen is better than 2×500 mg for the inhibition of joint damage during the first 24 months but after this time and up to 2 years the radiographic damage was minimal and similar between groups (Tak et al, 2011). These studies also support the efficacy of rituximab in MTX naïve (IMAGE) and MTX inadequate responders (SERENE and MIRROR).

The need for re-treatment in responders (partial or complete) should be assessed at least by 24 weeks but should not be performed before 16 weeks since there are no data informing shorter interval spacing of therapeutics. A fixed schedule regimen still lacks formal evaluation and might be associated with overtreatment of some patients (Emery et al, 2009a).

Global assessment of rituximab safety in patients treated in clinical trials, with a total of 5013 patient-years, indicated that rituximab was generally well tolerated and that the rate of serious adverse events did not increase with re-treatment or with the duration of exposure. The most common adverse events were infusion-related reactions, which decreased with successive re-treatments. The overall rate of serious infections (4.3 per patient-year, 7% of patients) was similar to that reported with other biological agents; pneumonia, cellulitis and urinary tract infection were the most common. Two cases of tuberculosis were registered in clinical trials safety databases and also six cases of progressive multifocal leukoencephalopathy. Hepatitis B reactivation has been reported in one patient, highlighting the importance of screening for HBV, including antibodies against core antigen (anti-HBc), vaccination and HBV prophylactic treatment when indicated. Immunoglobulin levels should be quantified before and during treatment as hypo-IgG (present in 5% of patients) is a predictor of severe infections (Gottenberg et al, 2010). In contrast, although IgM is the most common subtype of immunoglobulin to decrease with treatment, this effect has not been related to a higher risk of infections (van Vollenhoven et al, 2010a). Immunological response to vaccination might be less effective in patients receiving rituximab, therefore required vaccinations (HBV, tetanus and pneumococcus) are recommended at least 4 weeks before starting treatment. Human antichimeric antibodies (HACAs) were detected in 11% of patients but this does not seem to increase the risk of infusion-related reactions or loss of efficacy and indeed secondary failure to rituximab in patients who respond is uncommon. Preliminary reports also indicate that in patients who have discontinued rituximab and started other biological DMARDs the rate of serious adverse events is not increased even when the majority of patients (83%) had B cell counts below

the lower limit of normal (Genovese et al, 2010). The first reports of combination of rituximab with other biological agents have been published. Safety was the major concern. Rates of serious adverse events were similar or lower than in the non-combined trials but as yet no clear advantage in efficacy was seen (Greenwald et al, 2011; Rigby et al, 2013).

Rituximab, licensed for patients who have intolerance or inadequate response to TNFi, has therefore become an important therapeutic option for patients with RA and an update consensus has been published (Buch et al, 2011). In spite of this, better predictors of treatment outcome and a clearer insight into the mechanism of action of rituximab in patients with RA are still required, in order to provide a rational treatment schedule. Moreover, registry data will be helpful in determining the overall safety of repeated dosing in clinical practice.

➡ Other B cell targeting therapies

Other anti-CD20 antibodies that are humanised such as ocrelizumab and veltuzumab and the fully human ofatumumab, are in phase II/III trials. Neutralisation of the B cell survival and activation cytokines BLyS (or B cell activating factor (BAFF)) and APRIL is an approach that is in development. Atacicept (which blocks both the B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) and might therefore reversibly suppress B cell function across maturation stages) has completed phase I studies and appeared to be well tolerated. However, phase II trials do not seem to support a future role for atacicept in the treatment of RA (van Vollenhoven et al, 2010b).

1.3.3.2 Costimulation blockade in RA: abatacept

Optimal activation of T lymphocytes requires signalling via the T cell receptor (signal 1) and by costimulatory molecules—the so-called ‘second signal’. The dominant pathway to provide signal 2 involves CD28 on T cells and CD80 and CD86 on antigen-presenting cells (e.g., macrophages, dendritic cells). CTLA4, which is structurally similar to CD28, can bind to CD80/CD86 with higher affinity, and can prevent the CD28-mediated delivery of signal 2 to T cells. Abatacept is a soluble recombinant fully human protein that comprises the extracellular domain of CTLA4 and the Fc portion of an IgG1 molecule that has been modified to prevent complement activation. The T cell therefore receives one single signal which tends to switch off the cell—the so-called ‘anergy’ response. The principle of costimulatory blockade is therefore to effectively switch off the T cell compartment, including naïve T cells both systemically and locally in the joint, inducing immunomodulation and downstream events, such as blocking cytokine production (TNF, IL-1 and IL-6) and B cell activation (Platt et al, 2010).

Several randomised placebo controlled clinical trials have been conducted that demonstrated significantly higher clinical responses rates after abatacept administration than with placebo in patients with active RA despite previous treatment with DMARDs (Kremer et al, 2006; Schiff et al, 2008), anti-TNF therapies (Genovese

et al, 2005; Weinblatt et al, 2007; Genovese et al, 2008a) and DMARDs or biological agents (Weinblatt et al, 2006). The most commonly used dose was approximately 10 mg/kg given at days 0, 15, 29 and every 28 days thereafter, in association with DMARDs. *The AIM study, focusing on patients with active RA despite MTX treatment, yielded 68% ACR 20 responders in abatacept recipients compared with 40% in placebo-treated patients after 6 months, rising to 73% and 40% ACR 20 responders, respectively, after 1 year; the ACR response was maintained up to 5 years. The rate of radiographic progression was reduced with a sustained pattern over the years and nearly half of the patients had no additional damage at 5 years (Kremer et al, 2006; Genant et al, 2008; Westhovens et al, 2009b). The ATTAIn study similarly demonstrated significantly higher response rates in patients treated with abatacept compared with placebo recipients, this time in an RA population for whom at least one TNF blocking agent had failed, confirming that abatacept can be used successfully in non-responders to TNFi (Genovese et al, 2005). In the ATTEST study, the first head-to-head trial between biological agents, patients were treated with abatacept + MTX, or infliximab 3 mg/kg + MTX or placebo + MTX, and although abatacept had a similar efficacy at short term (6 months), it showed better efficacy in the long term (1 year), and had an overall better safety profile. It is important to highlight that infliximab was given at a fixed dose of 3 mg/kg every 8 weeks, as the design of the trial did not allow an increase in the frequency and/or dose (Schiff et al, 2008).*

There is particular interest in the effects of abatacept in early disease. Abatacept in combination with MTX showed higher efficacy than MTX alone (ACR 70 43% vs 27%) and superior inhibition of radiographic damage in patients with early RA and poor prognostic factors who were MTX naive at 2 years (Westhovens et al, 2009a). More recently, abatacept also proved to be able to delay the progression to RA, at 1 year, in a subgroup of patients with undifferentiated/early RA. This exploratory study (ADJUST) showed that besides delaying radiographic progression, ACPA levels were reduced, supporting the concept that abatacept can modulate T cell function in early phases of the disease (Emery et al, 2010b). Furthermore, data from the French Registry ORA (Orencia and Rheumatoid Arthritis) highlighted that positivity for ACPA is associated with a better response to abatacept and a higher retention rate at 6 months (Gottenberg et al, 2012).

Approval of the abatacept subcutaneous formulation was based on a trial programme that included three randomised controlled trials and two open-label studies: ACQUIRE (MTX inadequate responders (MTX-IRs), with an MTX background); ACCOMPANY (patients who were MTX naive or MTX intolerant/failures, with or without a MTX background); ATTUNE (switching from long-term IV to SC abatacept, in patients receiving MTX or anti-TNF-IRs); ALLOW (effects on immunogenicity and safety of withdrawing and reintroducing abatacept) and AMPLE (head-to-head trial comparing SC abatacept with adalimumab, with an MTX background). The conclusion from these studies was that SC abatacept is not inferior to the IV formulation and that similar efficacy is observed with or without an IV loading dose, both at 6 months and follow-up. Furthermore,

preliminary data from AMPLE suggest that abatacept in combination with MTX has comparable efficacy to adalimumab plus MTX at 12 months (Solomon, 2012; Schiff, 2013).

Abatacept is approved by the FDA and EMA for patients with moderate to severe RA who are non-responders to DMARDs or anti-TNF therapies, both in combination with non-biological DMARDs or in monotherapy.

Abatacept is available for administration as an infusion (loading dose at 0, 2 and 4 weeks followed by monthly administration), according to a weight-tiered dosing regimen (<60 kg = 500 mg; 60–100 kg = 750 mg; >100 kg = 1000 mg); and as an SC formulation with one induction dose weight-base as above, followed by a fixed weekly 125 mg dose. Although the approved SC regimen includes a single IV loading dose, this has not been commonly used in clinical practice.

The safety profile of this agent is satisfactory. From a pooled analysis, excluding the abatacept plus etanercept trial, the number of serious infections was slightly increased compared with placebo but the overall total number of serious adverse events was similar. Higher rates of headaches and infusion reactions were also reported (Maxwell and Singh, 2010). Recently, a Cochrane review based on a meta-analysis of adverse events registered in clinical trials suggested that abatacept has a better safety profile than other biological DMARDs (Singh et al, 2011a). Concerns about a possibly increased risk of cancer, taking into account the mechanism of action of the drug, have not been confirmed in the safety data base from phase 3 trials or in registries. An additional study compared the combination of abatacept plus etanercept with etanercept plus placebo showing no benefit of this association and an increased risk of serious adverse events (Weinblatt et al, 2007). Safety data from SC abatacept trials have highlighted lower serious infectious rates than with the IV formulation, without significant differences in other adverse events with the exception of injection site reactions (3.5%). Cases of tuberculosis and psoriasis have been described. The risk of immunogenicity might be slightly lower with SC abatacept, and switching from IV to SC administration does not seem to be associated with a significant increase in immunogenicity (Schiff, 2013).

1.3.3.3 IL-6 blockade: Tocilizumab

Several lines of evidence support the role of IL-6 in RA pathogenesis. This encouraged the development of tocilizumab, the first humanised monoclonal antibody that inhibits IL-6 receptor signalling through both its membrane bound (mIL-6R) and soluble (sIL-6R) forms. IL-6 expression is greatly increased in the synovial tissue of patients with RA and a correlation between serum and synovial fluid IL-6 levels and disease parameters has been identified (Madhok et al, 1993; Sack et al, 1993). Studies in mice give further support to the role of IL-6 in RA pathogenesis, suggesting that IL-6 is necessary for the induction of arthritis in the collagen-induced arthritis model and that IL-6 signalling inhibition with an antibody against IL-6R abrogates the inflammatory process. The blockade of IL-6 effects results in marked reduction acute phase reactants

produced by the liver and improvement of chronic inflammation anaemia due to hepcidin. It is not yet clear what happens to cell survival after binding of antibodies against IL-6R and further research is required.

The safety and efficacy of tocilizumab have been assessed in five phase III double-blind randomised controlled clinical trials that included more than 4000 patients with RA with moderate to high disease activity. In most of these studies the primary end point was the ACR 20 response at week 24 and it was found that intravenous administration every 4 weeks of 8 mg/kg tocilizumab was better than 4 mg/kg. *The AMBITION study demonstrated superiority of tocilizumab 8 mg/kg monotherapy versus MTX, in patients for whom MTX or biological agents had not failed previously (70% vs 53%) (Jones et al, 2010). Tocilizumab (8 mg/kg) in combination with MTX was also effective in MTX inadequate responders compared with placebo in the OPTION study (59% vs 26%) (Smolen et al, 2008). Similarly, when tocilizumab was added to DMARDs in monotherapy or in combination (76% receiving MTX), ACR 20 responses improved as compared with DMARDs alone (61% vs 25%), showing benefits in a more clinical representative population (TOWARD study) (Genovese et al, 2008b). The RADIATE trial demonstrated that 50% of the patients refractory to anti-TNF therapy achieved an ACR 20 response when treated with tocilizumab, as compared with 10% in the placebo arm (Emery et al, 2008b). Finally, protection from structural damage was evaluated in the LITHE trial at 52 weeks, which showed inhibition of radiographic progression as assessed by the modified Sharp score in the actively treated patients compared with placebo. Furthermore, this study highlighted an increase in the number of patients achieving DAS28 remission up to 2 years (Fleischmann et al, 2010). The results from the AMBITION study clearly showed that tocilizumab monotherapy is better than MTX at 24 weeks (Jones et al, 2010). Moreover, tocilizumab monotherapy also demonstrated non-inferiority to the tocilizumab combination with MTX in patients refractory to DMARDs (ACT-RAY) (Dougados et al, 2011) or in association with other DMARDs in DMARD or TNFi inadequate responders (ACT-SURE) (Bykerk et al, 2011). The absolute number for several end points in ACT-RAY—namely, rates of remission and radiographic progression, showed, however, slightly better results in favour of combination therapy. In the recent trial (ADACTA) comparing tocilizumab and adalimumab, both in monotherapy, tocilizumab demonstrated clinical superiority (Gabay et al, 2013). Despite the cautious interpretation of these data, as tocilizumab was not compared with an adequate comparator, i.e., ADA + MTX, it further supports the efficacy of tocilizumab as monotherapy. Together these data potentially position tocilizumab as a candidate for biological monotherapy when for whatever reason (e.g., other adverse effects and contraindications to other agents) this option is considered. From the analysis of data of patients receiving tocilizumab 4 mg/kg/month and 8 mg/kg/month there seems to be a clinical (even if non-significant) superiority of the higher doses. Use of the higher dose is further supported by an increased risk of anaphylactic reactions when lower doses are given.*

These data from clinical trials led to the approval of tocilizumab for the treatment of moderate to severe RA, in combination with MTX, in patients who have inadequate response to one or more anti-TNF agents (USA and

Europe) or DMARDs (Europe). Tocilizumab, 8 mg/kg (or 4 mg/kg in some areas at the start), is given intravenously every month in combination with MTX or other DMARDs. The maximum recommended dose is 800 mg for people weighing ≥ 100 kg. EMA has further considered the use of tocilizumab in monotherapy when MTX treatment is not tolerated or contra indicated. A recent consensus statement has been published (Smolen et al, 2013). Owing to the impressive reduction in CRP, it is important, while monitoring, to consider the different components of DAS28 and other scores besides CRP or to use the Clinical Disease Activity Index preferentially.

Safety concerns are in some respects similar to those of other biological DMARDs. So far, a slightly increased risk of infections and rare infusion-related reactions have been reported, which seem to be higher when low doses are used. Glucocorticoids should be tapered as soon as possible as they increase the risk of infection. Other reported adverse events might be more specific to the tocilizumab mechanism of action, including a decrease in neutrophils and platelet counts and an increase of liver enzymes (especially when combined with MTX) (**Table 10**). Recommendations are available on how to monitor the process according to laboratory levels and when treatment should not be started or should be interrupted. An increase in low-density lipoproteins (LDL) and high-density lipoproteins (HDL) has been seen but the risk of cardiovascular events in patients with RA treated with tocilizumab has not been quantified. The MEASURE study suggested that the changes in lipid particles mainly comprise creation of fewer atherogenic species—the clinical consequences of these observations, however, will probably require formal clinical endpoint follow-up. The rate of lower intestinal perforations (LIP) at 8 mg/kg was greater than in placebo recipients in randomised control studies, and a recent work on data from registries established that the incidence rates of LIP under TCZ found in the “real world” study are in line with those seen in randomised controlled trials of TCZ and higher than in all other DMARD treatments (Strangfeld, 2016). To ensure safe use of TCZ in daily practice, physicians and patients should be aware that, under TCZ, LIP may occur with mild symptoms only and without CRP elevation (because it is impeded by IL-6 blockade). Hence, caution must be used in patients with previous diverticulitis (Singh, 2011b; Strangfeld, 2016) (**Table 10**).

Recommendations concerning hepatitis B virus (HBV) or hepatitis C virus (HCV) infections and tuberculosis are similar to those for other biological agents. Finally, co-prescription of drugs metabolized by the CYP450 enzymes requires adjusting their dosage upon tocilizumab initiation or discontinuation. The most widely used medications metabolised by CYP450 are listed in **Table 9**. The full list is available online at <http://medicine.iupui.edu/clinpharm/ddis>

Table 9: Example of medications metabolised through CYP450 isoenzymes.

Principal interactions	Medications
CYP 1A2	Theophylline
CYP 2C9	Phenytoin
	Warfarin
CYP2C19	Benzodiazepines (alprazolam, diazepam, midazolam, prazépam, clorazepate...)
CYP 3A4	Cyclosporine
	Atorvastatin, simvastatin
	Calcium channel blockers (amlodipine, diltiazem, nifedipine, felodipine, isradipine, nifedipine, nitrendipine, bepridil, verapamil...)

Table 10: Precautions of use, prevention and management of neutropenia, thrombocytopenia, elevated liver enzymes and lower intestinal perforations in patients with rheumatoid arthritis treated by tocilizumab

Haematological abnormalities	
<ul style="list-style-type: none"> Neutrophils: 500-2,000/mm³ Platelets: 50-100,000/mm³ 	<ul style="list-style-type: none"> No contraindication; use TCZ with caution
<ul style="list-style-type: none"> Neutrophils: < 500/mm³ Or platelets: <50,000/mm³ 	<ul style="list-style-type: none"> The use of TCZ is not recommended
<ul style="list-style-type: none"> <u>Warning signs:</u> fever or signs of infection (suggest neutropenia) or purpura, gingival bleeding, or a hematoma developing in the absence of trauma (suggest thrombocytopenia) -> blood cell counts should be obtained Declines in all three cell lines should prompt investigations for infection-related macrophage activation syndrome 	
Liver abnormalities	
<ul style="list-style-type: none"> Liver disease with ALAT or ASAT levels >1.5 xULN but <5 x ULN 	<ul style="list-style-type: none"> TCZ therapy initiation can be considered but with special caution: <ul style="list-style-type: none"> Advice of an hepatologist Treatment of the cause of pre-existing liver disease (metabolic, alcohol-related, viral...) Non-invasive tests for fibrosis TCZ dosage should be adjusted Close monitoring of transaminases
<ul style="list-style-type: none"> Liver disease with ALAT or ASAT levels > 5 xULN 	<ul style="list-style-type: none"> TCZ therapy is not recommended
<ul style="list-style-type: none"> Patients with chronic viral hepatitis B or C 	<ul style="list-style-type: none"> TCZ can be considered but after obtaining the advice of a hepatologist to determine whether pre-emptive treatment with nucleoside analogues (lamivudine, entecavir) or nucleotide analogues (tenofovir) is in order to prevent viral reactivation
Lower intestinal perforations	
<ul style="list-style-type: none"> Patients with past history of diverticulitis 	<ul style="list-style-type: none"> Reappraise the risk/benefit ratio, and discussion with the gastroenterologist Correct any other risk factors for superinfection or perforation (poorly controlled diabetes, glucocorticoid or NSAID therapy) In patients who have had a prior episode of diverticular sigmoiditis, consider sigmoid colon resection surgery. Although surgery is generally indicated only in the event of a second episode, prophylactic surgery after the first episode

	should be considered in patients who are scheduled to receive treatment with TCZ
	<ul style="list-style-type: none"> Inform and educate the patient and primary-care physician (TCZ may mask classic signs of infection (fever and CRP elevation), and potentially devastating impact on patient outcomes of any delay in initiating appropriate treatment)
<ul style="list-style-type: none"> Before each TCZ infusion 	<ul style="list-style-type: none"> The absence of abdominal symptoms or signs should be checked
<ul style="list-style-type: none"> In case of abdominal symptoms 	<ul style="list-style-type: none"> Discontinue TCZ therapy and refer the patient to a gastroenterologist for diagnosis and treatment The evaluation by a gastroenterologist should be obtained very promptly in patients with a fever, bleeding, or abnormal abdominal physical findings
<ul style="list-style-type: none"> In patients who experience diverticulitis while on TCZ therapy 	<ul style="list-style-type: none"> The available data are inadequate to recommend re-starting the drug Prophylactic surgical resection should be considered.

TCZ, tocilizumab; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; ULN, upper limit of normal (ULN)

An antibody targeting IL-6R (sarilumab, Bridgewater, Nj, USA), and other agents targeting directly IL-6, are in development.

1.3.3.4 Anakinra (IL-1Ra)

Anakinra is a recombinant IL-1 antagonist which does not induce signalling upon binding to type I IL-1 receptor and therefore can act as a competitive antagonist to IL-1. Two randomised controlled double-blind trials provide the core evidence of benefit in RA. *Monotherapy leads to an ACR 20 response in 40% of patients at 8–12 weeks, with significantly fewer achieving significant improvement at ACR 50 and ACR 70 levels, and delays radiographic progression. In the pivotal phase III study, combination of anakinra (1 mg/kg/day) and MTX produced a higher ACR 20 response rate (42%) as compared with 23% in MTX only recipients (Bresnihan, 2001). From these studies a fixed dose of 100 mg/day in combination with MTX was selected and a post-approval third trial confirmed similar efficacy to that seen in previous trials. Adverse events were similar in nature and frequency to those with placebo. In the phase III study 13.6% discontinued because of an adverse event. Injection site reactions were common (>60% in trials) and, although mostly of mild to moderate severity, caused withdrawal in 7% of recipients. The severity of injection site reactions reduced with treatment cycles. Allergic reactions to anakinra were rare (<0.5%). Minor (about 30%, especially upper respiratory) and major infections (about 2%) were slightly more common than in placebo recipients in controlled trials. Neutropenia has occasionally been seen.*

These data supported the licensing of anakinra but in clinical practice it is not widely used, as it appears to be less effective than TNF blockers in RA (Thaler et al, 2009). Furthermore, the combination of anakinra and etanercept provided no additional benefit to etanercept alone and was associated with increased safety concerns (Genovese et al, 2004).

Other reagents targeting IL-1—including anti-IL-1 antibodies, anti-IL-1R and IL-1 ‘TRAP’ (consisting of IL-1 receptors and an Fc subunit)—have similarly failed to show clear-cut efficacy in RA.

1.3.4 Safety of biological agents (TNF blockers and non-TNF blockers)

The safety of TNFi has now been analysed for over 10 years, a little less for the non-TNF blockers. First, randomised controlled trials and their extension phases are now available (Ramiro et al. 2013, Singh et al. 2016 [Cochrane Network metaanalysis]). Then, important data from daily clinical practice has been established from the various national or international registries, such as the British BSR registry, the Swedish ARTIS or SSATG registry, the German RABBIT registries, the Spanish BIOBADASER registry, or the North-American RADIUS or CORRONA registries.

Although each molecule might have specificities (which are detailed above in each drug section), the majority of adverse events are similar for all bDMARDs (TNFi and non-TNFi), and so is their management (**Table 11**). Thus the pre-screening and monitoring is globally the same (**Table 7 and 8**). However, safety of TNFi was the better studied, and therefore stands as a reference for the description of global safety in this section.

➞ Localised skin reactions

They concern all the TNFi and non-TNFi administrated sub-cutaneously. They are frequent (10 to 50 %), and polymorphous: pain, pruritus, red patch or haematoma at the injection points. They are usually easily managed topically and don't require to stop the drug. Certolizumab pegol seems to be less prone to these localised skin reactions, probably because pegylation doesn't induce activation and degranulation of mast cells.

➞ General reactions

These general effects have mainly been described with infliximab, at the moment or during the two hours following the infusion. Several symptoms have been reported: headaches, fever, shiver, nausea, vagal reactions, pruritus, urticaria, pleuro-cardiac reactions. These manifestations usually occur during one of the 3 first infusions, and rarely require stopping the treatment. However, rare severe infusion reactions to infliximab have been reported, and appropriate resuscitation facilities should be available if needed.

➞ Infections

TNF α , and thus IL-1 and IL-6, play an important role in the human defence against infectious agents. So do T- and B-lymphocytes. The initial expectation that blocking a cytokine of such fundamental importance in the immune function would lead to profoundly immunosuppressed patients has not proved to be true. Infectious adverse events in randomised controlled trials are, in general, of a similar nature and frequency in patients treated with TNF blockers as in placebo-treated patients. However, registry datasets, post-marketing reports

and meta-analyses have highlighted a small, but real, increased risk of serious infections with the use of TNFs inhibitors in comparison with synthetic DMARDs (Ramiro et al. 2014; Yun et al. 2014; Zink et al. 2013). Furthermore, when an infection occurs, it can be particularly severe and life-threatening. The estimated risk of severe infection under TNFi is 3 to 5 for 100 patient-years. This risk is similar among infliximab, adalimumab and etanercept, and higher in the first 6 months of treatment, particularly in older people, glucocorticoid users and those who have other comorbidities and previous infections.

Table 11.A: potential adverse events of biological Disease-Modifying Antirheumatic Drugs (bDMARDs) and their management

Medical problem	Clinical expression	Medical response
Localised skin reactions	Pain, pruritus, red patch or haematoma at the injection points	<ul style="list-style-type: none"> Antihistamine treatment, local steroid therapy Get the biological treatment out of the fridge one hour before injection, and inject slowly (1 min) No need to stop the biologic in the vast majority of cases
General reactions	<ul style="list-style-type: none"> Headaches, fever, shiver Nausea, vagal reactions Pruritus, urticaria, Hypotension, pleuro-cardiac reactions Bronchospasm, anaphylactic shock (rare) 	<ul style="list-style-type: none"> Prevention: monitoring of the infusions (heart rate, blood pressure) Mild-to-moderate reactions: 50% decrease of the infusion rate; if needed, IV administration of an antipyretic agent (acetaminophen) or antihistamine; discontinuation if the symptoms persist despite the slower infusion rate Severe reactions: immediate permanent discontinuation of the infusion; appropriate resuscitation measures; adrenalin, antihistamines and glucocorticoids in patients with anaphylaxis; transfer to ICU if needed; definitive contraindication of the molecule
Bacterial or opportunistic infection	Not exhaustive: <ul style="list-style-type: none"> Fever, shiver, asthenia Cough, dyspnoea Skin rash Urinary burning or urgency Back pain (pyelonephritis, spondylodiscitis) Abdominal pain (diverticulitis) Hyperleucocytosis, acute phase response Fever absence is possible and must not reject the hypothesis of an infection 	<ul style="list-style-type: none"> Stop the treatment Look for severe clinical signs (high fever, hypotension, septic shock) that would impose a transfer to ICU Take samples for bacterial examination, according to the localisation of the infection (e.g. urinary). If respiratory signs, do an X-ray of the chest Antibiotics adapted to the infection type, and if possible to the antibiogram Once the infection treated, wait at least 1 week for mild infections (up to one month in case of severe infection) before reintroducing the drug under close monitoring; in case of infection reoccurrence, consider permanent interruption In case of severe infection, report to pharmacovigilance <ul style="list-style-type: none"> Prevention: Vaccination according to recommendations¶. Interruption before surgery†
Positive tuberculosis test before introduction	Tuberculin skin test or Interferon-Gamma Release Assays (IGRAs) positivity	<ul style="list-style-type: none"> Postpone the introduction of the biologic Appropriate prophylaxis according to local guidelines on duration, choice of antibiotic and threshold
Lymphoma or malignancies	Not exhaustive: <ul style="list-style-type: none"> Unexplained fever, decline in 	Preventively, before to introduction of the biologic, according to risk factors:

- | | |
|---|--|
| <p>general health</p> <ul style="list-style-type: none"> ▪ Weight loss, asthenia ▪ Suspicion of lymphoma: peripheral lymphadenopathy, hepatomegaly, splenomegaly, recurrent infections, diaphoresis, pruritus ▪ Suspicion of solid cancer: local signs depending on the organ involved | <ul style="list-style-type: none"> ▪ Full clinical examination, with breast and cervical (Papanicolaou smear) ▪ Mammography (systematic after the age of 50) ▪ X-Ray chest examination +/- chest tomography ▪ Blood in the stool detection +/- full colonoscopy ▪ Dermatological examination ▪ Ear-nose-throat examination in case of important smoking and/or alcohol abuse <p>In case of past medical history of lymphoma or malignancy:</p> <ul style="list-style-type: none"> ▪ Introduction of the biologic can be considered according to local guidelines (usually if the lymphoma or malignancy has been successfully and totally treated at least 5 years before) <p>In case of suspicion of apparition of lymphoma or malignancy during the treatment:</p> <ul style="list-style-type: none"> ▪ Discontinue the therapy (i.e. do not administer the next scheduled injection or infusion)‡ ▪ Perform investigations to confirm the diagnosis and assess the stage of the disease ▪ Adjust the RA maintenance treatment regimen and determine whether concomitant immunomodulators (MTX, LFL) should be stopped, at least during the treatment of the malignancy ▪ Report the case to the pharmacovigilance centre and start appropriate treatment if the diagnosis is confirmed ▪ The need for permanently discontinuing the biologic should be based on a case-by-case basis according to the nature of the malignancy, the multidisciplinary discussion (haematologist, oncologist, rheumatologist), and the local guidelines. |
|---|--|

ICU, intensive care unit; RA, rheumatoid arthritis; MTX, methotrexate; LFL, leflunomide; ¶ Detailed information and vaccination guidelines are given in **Appendix 3** †Perioperative management of bDMARDs is detailed in **In-Depth Discussion 3**. ‡ **Rituximab** aims at B Lymphocyte depletion and is thus the only bDMARD that **can be maintained in case of lymphoma**.

Table 11.B: potential adverse events of biological Disease-Modifying Antirheumatic Drugs (bDMARDs) and their management

Medical problem	Clinical expression	Medical response
Anti-drug antibodies (ADA)	<ul style="list-style-type: none"> Loss of efficacy of the treatment General reactions during infusions (rare, mostly reported with infliximab) 	<p>Prevention:</p> <ul style="list-style-type: none"> Prefer combination with MTX or another csDMARD if MTX not tolerated (avoid monotherapy) Respect treatment guidelines (doses, administration intervals) <p>In case of suspicion of appearance:</p> <ul style="list-style-type: none"> Confirm the diagnosis by dosing ADA (present) and the drug serum concentrations (decreased) Increase doses of biologic (with respect to guidelines) and/or associate MTX (or another csDMARD) if not previously prescribed and/or increase MTX dosage If not sufficient to recover a good clinical activity, consider discontinuing the biologic In case of general reaction, discontinue the biologic (please refer to table A)
ANA, anti-DNA Ab +/- drug-induced lupus*	<ul style="list-style-type: none"> Most of the time: no clinical signs Sometimes: lupus symptoms (not exhaustive: fever, skin rash, mouth ulcerations, chilblain, thromboses, myalgia, cytopenia...) 	<ul style="list-style-type: none"> ANA (and anti-DNA if present) screening <u>before</u> TNFi introduction In case of ANA and anti-DNA apparition during TNFi therapy <u>without</u> any clinical symptom: continue bDMARD In case of apparition of <u>clinical symptoms</u> suggestive of lupus: <ul style="list-style-type: none"> Immunological exploration: ANA, anti-DNA, complement, renal involvement +/- antiphospholipid syndrome research in case of thrombosis Most of the authors recommend to discontinue the TNFi, although it can be continued with close monitoring in case of minor manifestations (e.g. chilblains)
Demyelination manifestations	<ul style="list-style-type: none"> Paraesthesia Visual disturbances Cognitive disturbance, confusion Balance and walk disturbance Apraxia, facial paralysis 	<ul style="list-style-type: none"> Avoid prescribing TNFi in case of familial or personal demyelination past history In case of apparition during TNFi therapy: <ul style="list-style-type: none"> Immediately discontinue the TNFi Neurologic specialised examinations (cerebral and medullar MRI) Definitive contraindication of TNFi use
Cardiac failure	<ul style="list-style-type: none"> Dyspnoea at effort/permanent/orthopnoea Chest pain, tachycardia Crackling Lower limb oedema 	<ul style="list-style-type: none"> Contraindication of TNFi use in case of NYHA class III/IV cardiac failure In case of apparition during TNFi treatment: <ul style="list-style-type: none"> Discontinue the TNFi Refer the patient to a cardiologist
Paradoxal drug-induced psoriasis	<ul style="list-style-type: none"> Psoriatic skin eruption (polymorphic) 	<ul style="list-style-type: none"> Reconsider the diagnosis: real RA? Psoriatic arthritis? Look for personal and familial past history Confirmation of the diagnostic of paradoxal drug-induced psoriasis

		<ul style="list-style-type: none"> ▪ <u>In case of mild manifestations:</u> most of the cases can be managed locally without TNFi discontinuation ▪ <u>In case of more severe manifestations not controlled locally:</u> consider switching for another TNFi or bDMARD*
Dental care	▪ Variable	<ul style="list-style-type: none"> ▪ Regular oral hygiene and visits to the dentist are recommended. Patients with oral or dental health problems should receive appropriate treatment before starting therapy. ▪ <u>Routine dental care (cavities, scaling):</u> Prophylactic antibiotic therapy can be suggested. ▪ <u>Dental procedures associated with a risk of infection (extraction, apical granuloma, abscess...):</u> the infusion should be postponed and prophylactic antibiotic therapy given ▪ <u>Implants:</u> no contraindication to dental implants provided the alveolar ridge is adequate and the risk of infection is not unreasonably high

*RA, rheumatoid arthritis; ADA, anti-drug antibodies; MTX, methotrexate; csDMARD, conventional synthetic Disease-Modifying Antirheumatic Drug; bDMARD, biological Disease-Modifying Antirheumatic Drug; TNFi, Tumour Necrosis Factor inhibitors; ANA, antinuclear antibody; anti-DNA Ab, anti-deoxyribonucleic acid antibodies; MRI, Magnetic Resonance Imaging; NYHA, New York Heart Association. *In a patient, paradoxal drug-induced psoriasis can occur with only one TNFi molecule or there might be a “class effect”. The risk could be lower with soluble receptors when compared to monoclonal antibodies.*

The attitude to adopt in front of particular situations can vary from a country to another, and can be found in local guidelines for each country. As an example, clinical tool guides elaborated by the French “Club Rhumatismes et Inflammations” can be found in English version at <http://www.cri-net.com>

Different factors may contribute to this decrease in risk over time, including the drop out of susceptible individuals, upregulation of cytokines to compensate for the lack of TNF, reduction of glucocorticoids, etc. (Listing et al, 2005; Askling et al, 2007; Galloway et al, 2011*). The physician should particularly fear serious bacterial complications, in particular pulmonary, but also viral (especially Herpes group viruses), fungal or opportunistic (Singh et al. 2011).

Of particular importance, patients are more prone to intracellular bacterial infections (e.g., Mycobacterium tuberculosis), mainly owing to reactivation of latent infection (Nam et al, 2010). This increased risk has first been described for infliximab, but has been now reported for all the TNFi, even etanercept, although evidence suggests that this risk is higher with monoclonal antibodies. Indeed, the risk of tuberculosis reactivation is 2 to 4 times lower in patients treated with etanercept than with monoclonal antibodies (Tubach et al. 2009). One explanation could be linked to the different effects of the two drugs on the production of type 1 interferon and on the monocytes-macrophages: the monoclonal antibodies induce a lysis of these cells in a complement-dependent manner after binding the TNF, while the soluble receptor does not. The incidence of tuberculosis

may be significantly reduced (up to 80%) by screening and administration of appropriate prophylaxis (Carmona et al. 2005). Hence, a systematic search for a history or risk factors of tuberculosis, a clinical examination, a chest X-ray, and tuberculosis test (Tuberculin skin test or Interferon-Gamma Release Assays (IGRAs), according to local guidelines), should be done prior to starting a treatment with a bDMARD (**Table 7 and 8**). If necessary, an appropriate prophylaxis according to local guidelines on duration, choice of antibiotic and threshold for treatment should be carried out.

Because RA patients, especially when receiving a bDMARD, are at higher risk to develop an infection, they should be vaccinated according the guidelines that will be detailed in **Appendix 3**. Of importance, the use of live vaccines in patients receiving bDMARDs is contraindicated. Perioperative management depends on the half-life of the drug (**Table 7, 8 and In-Depth Discussion 3**).

➡ Malignancies and lymphoma

Immunosuppressive agents have been associated with an increased risk of specific types of cancers, such as lymphomas (often related to viral reactivation), skin cancer (due to sun exposure) and cervix cancer (related to HPV16). On the basis of such observations, there could be a theoretical risk of specific cancers with immunomodulating agents, such as bDMARDs (Bongartz JAMA 2006; Pham et al. 2011). Data from both British and Swedish registries suggest that the overall risk of malignancies is not increased in a short–medium follow-up period. There seem to be an exception for skin cancers (other than melanoma) for which a 2 fold increased risk has been identified (Mariette et al. 2011). Therefore, a monitoring with an annual dermatologic consultation should be proposed under these therapies.

Concerning the lymphoma, different studies have shown that the risk of lymphoma is higher in RA patients treated by TNFi than in patients who don't receive this therapy (Furst et al. 2012). However, the risk of lymphoma is increased in RA, especially when the disease is severe, and the relative risk for lymphoma does not seem to be further increased compared with the increased risk already seen in patients with RA (Askling et al, 2009a; Askling et al, 2009b; Dixon et al, 2010). Hence, the increased risk under TNFi could be due to a more severe disease (which justified the TNFi prescription) rather than to the drug itself. However, the French observatory RATIO showed an increased frequency of lymphoma in patients treated with monoclonal antibodies when compared to etanercept (Mariette et al. 2011).

Although the risk is not clearly increased, the physician should be very cautious while prescribing TNFi in patients with past history of malignancy of lymphoma. There is not clear cut-off, but the empiric period of 5 years has been proposed. However, this period might vary from to a centre to another, and should be modulated for each person medical history.

➡ Immunogenicity and autoimmunity

Antibodies directed against infliximab have been found in 24 to 37% of patients. These patients are more prone to develop general reactions during the perfusion. The systematic adjunction of methotrexate decreases the incidence of these antibodies. Other antibodies directed against adalimumab and the other monoclonal antibodies have also been reported, while the induction of antibodies directed against etanercept are still under debate. Such Anti-Drug Antibodies (ADA) can be neutralising: they can reduce the serum concentration of these drugs and hence reduce their efficacy at short and medium term. On the long term, they reduce the therapy maintenance of the TNFi (Bartelds et al. 2011). The immunogenicity of tocilizumab and abatacept has been poorly studied; the occurrence of ADAs to TCZ seems to be a rare event (Sigaux 2016).

Antinuclear and anti-DNA antibodies induced by TNFi have been reported. Most of the time, these antibodies don't have clinical repercussion, although rare drug-induced lupus is possible. However, these forms of lupus are usually mild, and often regress when the TNFi is stopped. Increased risk of demyelination conditions was also reported, and patients with a previous demyelinating disease should not usually receive TNF blocking agents. Although TNFi are effective for the treatment of psoriasis, a paradoxal drug-induced psoriasis has been observed in patients with RA treated with anti-TNF drugs, and can occur even if the patient has no personal or familiar medical history of psoriasis. When the skin eruption is reluctant to local therapy, it might sometimes require changing to another TNFi or bDMARD.

➡ Other adverse events

A study in patients with congestive cardiac failure indicated cardiac function deterioration in infliximab recipients (Daniel et al, 2002). Anti-TNF agents should not be given to patients with New York Heart Association (NYHA) class III/IV cardiac failure.

Transaminase elevation, leukopenia and thrombocytopenia have been reported. Some patients might experience a paradoxical fatigue or weight gain. Several cases of vasculitis or granulomatosis (sarcoidosis, Crohn disease...) have also been described.

1.3.5 Switching between bDMARDs

This concept will be detailed below, in the strategy section.

Summary points: bDMARDs

- ➔ When initial treatment with MTX (or with other csDMARDs if contraindication or adverse effect prevents the use of MTX) has failed, bDMARDs should be started if poor prognostic features are present (RF and/or ACPA, early erosions, high disease activity) (2016 EULAR recommendations update, please see the strategies section below).
- ➔ bDMARDs regroup molecules that inhibit either a cytokine (TNF inhibitors) or its receptor (tocilizumab, inhibiting IL-6receptor) or the T lymphocyte costimulation (abatacept). Rituximab induces B lymphocyte depletion (anti-CD20 monoclonal antibody).
- ➔ Anakinra is not commonly used in the treatment of RA, although it has proven clinical and structural efficacy.
- ➔ bDMARDs share common adverse events, mainly an increased risk of infection (Table 11). Hence, screening before treatment, vaccination according to guidelines and regular monitoring should be done (Tables 7 and 8).
- ➔ No current data enables to establish that a bDMARD is more efficacious than another and that it should be given first. However, owing to considerable experience in clinical practice, TNFi are, in many countries, often considered the first-choice biological agent.
- ➔ bDMARDs should be used in combination with a csDMARD, because this combination is more efficacious than bDMARD monotherapy. Furthermore, combination decreases the risk of immunogenicity.
- ➔ In patients who have a contraindication to csDMARDs and thus require bDMARD monotherapy with biological agents, tocilizumab may be the preferred choice (keeping in mind that tocilizumab combination with csDMARD is still more efficacious than tocilizumab monotherapy).
- ➔ Owing to their different half-lives, perioperative management is also variable for different bDMARDs (table 7, 8 and In-Depth Discussion 3).

1.4 Targeted synthetic DMARDs (tsDMARDs)

Target synthetic DMARDs are targeted molecules interfering with specific signal-transduction. The only tsDMARDs currently available in the treatment of RA are Janus-kinase (JAK) inhibitors.

1.4.1 Mechanism of action

JAKs are a family of non-receptor protein tyrosine kinase that affect intracellular signalling through their association with transcription factors known as signals transducer and activator of transcription (STATs), otherwise known as the JAK-STAT pathway. JAKs are constitutively bound to their associated receptors and are activated when the corresponding cytokine or growth factor binds to its receptor. Activated JAKs phosphorylate the tyrosine residues on the STAT proteins, allowing dimerization of the STATs, which then migrate into the cytoplasm and then translocate into the nucleus, allowing for transcription of their target genes (and mainly transcription of proinflammatory genes in RA pathophysiology) (Figure 9).

Within the family of JAKs, there are four members: JAK1, JAK2, JAK3 and tyrosine kinase 2 (Tyk2) (Kelly 2013). JAK1, JAK2 and Tyk2 are fairly ubiquitously expressed in mammalian cells, whereas JAK 3 has a more limited

repertoire, with expression primarily on haematopoietic cells (Kelly 2013). JAK pathways are normally involved in growth, survival, development and differentiation of a variety of cells, but are crucially important for immune and haematopoietic cells (Hodge 2015).

In RA, B cells, T cells, macrophages and other leukocytes infiltrate the synovium in response to pro-inflammatory cytokines and chemokines, leading to inflammation and tissue destruction. Cytokine signalling via JAK pathways leads to further induction of inflammatory gene expression, which continues the loop of inflammatory signalling. Inhibiting cytokine signalling by inhibiting the JAK pathways may, therefore, interrupt the cycle of leukocyte recruitment, activation and pro-inflammatory cytokines at site of inflammation (Hodge 2015) (Figure 9). Hence, JAK inhibitors act on innate and adaptive immunity, through interfering with signal transduction and thus cell activation elicited by interleukin (IL)-6, granulocyte-monocyte colony stimulating factor, interferons (type I and II), and common γ -chain cytokines (such as IL-2, 4, 7, 9, 15 and 21) (Schwartz et al, 2016).

1.4.2 Tofacitinib

Tofacitinib (Xeljanz®) is a pan-JAK inhibitor, which has been approved in the USA, Switzerland, Japan, Russia and many other countries for use in RA after failure of csDMARDs. It has not been yet (in 2016) been approved for use within the European Union.

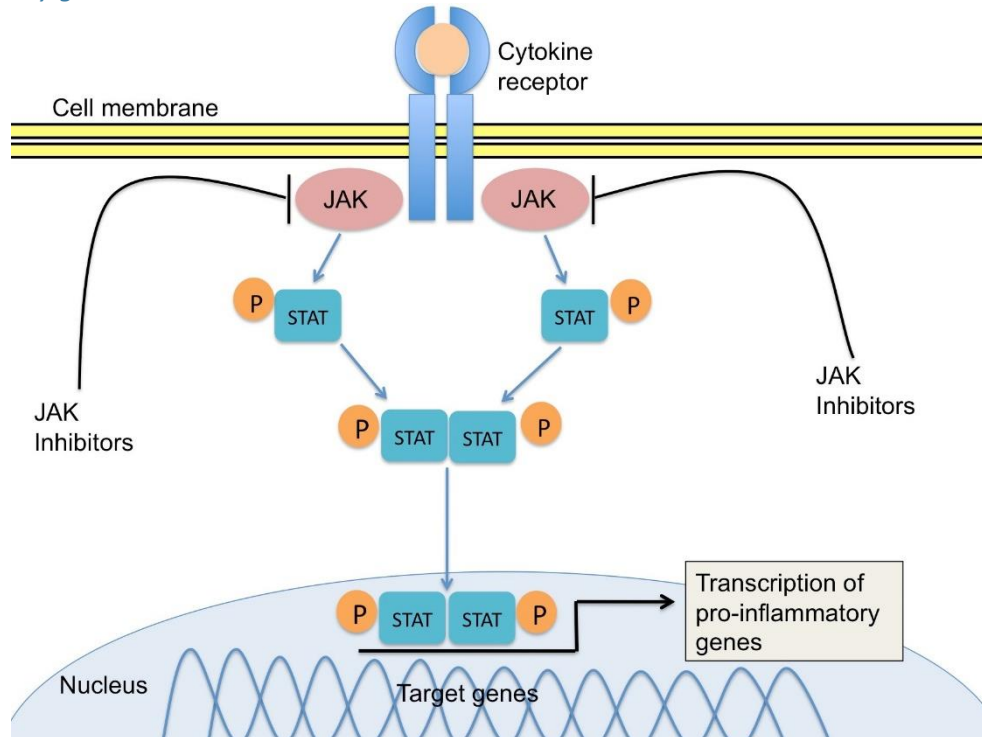
➡ Efficacy in RA

Tofacitinib is efficacious clinically and structurally in RA: the efficacy of tofacitinib plus methotrexate at the approved dose of 5 mg twice a day appears to be similar to that of biologics (Fleischmann 2010; van der Heijde et al, 2013; Lee et al, 2012; Smolen et al, 2016). Intriguingly, tofacitinib monotherapy is clinically superior to MTX (Lee et al, 2014; Fleischmann et al 2016).

➡ Tofacitinib prescription in practice

Tofacitinib, combined with a csDMARD or used in monotherapy, is indicated as second-line treatment for moderate-to-severe active RA in patients with an inadequate response or intolerance to MTX. It is given orally, 5mg twice a day. In case of insufficient clinical response, the dose can be increased to 10 mg twice a day. The intakes should be regular, if possible at the same hour every day. Screening investigations and monitoring are globally the same as for bDMARDs.

Figure 9. Simplified representation of the intracellular JAK-STAT signalling pathway, and mechanism of action of JAK inhibitors in the treatment of RA. JAKs are constitutively bound to their associated receptors and are activated when the corresponding cytokine or growth factor binds to its receptor. Activated JAKs phosphorylate the tyrosine residues on the STAT proteins, allowing dimerization of the STATs, which then migrate into the cytoplasm and then translocate into the nucleus, allowing for transcription of their target genes. JAK inhibitors hence block the synthesis of pro-inflammatory cytokines by blocking the transcription of pro-inflammatory genes.



JAK, Janus kinase; STAT, signals transducer and activator of transcription; P, phosphorylated.

➡ Safety

Currently available data is based on phase II and III trials, and little is known about its long-term safety. Herpes zoster infection in particular appear to be more common than seen with TNF inhibitors (van Vollenhoven et al, 2012; Fleischmann et al, 2016); several cases of tuberculosis (TB) and non-TB opportunistic infections have been reported; lymphocytopenia and anaemia also occur, and haemoglobin levels appear to increase less upon clinical improvement than seen with csDMARDs and bDMARDs. Of note, the serum creatinine increase, the elevation of transaminases and hypercholesterolemia (LDLc increase) is higher than in placebo (Riese et al, 2010; Fleischmann et al, 2016).

1.4.3 Other JAK inhibitors

➡ Baricitinib

Baricitinib is a selective JAK1-JAK2 inhibitor, which is currently in phase 3 trials, and has not yet been approved in any jurisdiction. It appears to convey a similar range of efficacy as the biological DMARDs and tofacitinib (ref). Interestingly, however, baricitinib plus MTX elicited a superior clinical and functional (although not

structural) outcome compared with adalimumab plus MTX (Taylor et al 2015). Moreover, the roughly 15% ACR70 response rate in patients whose disease had previously not responded to or not tolerated a TNF inhibitor was similar to the response rate in patients who had not responded to multiple biologics (Genovese et al, 2016).

➡ Filgotinib

Filgotinib is a selective JAK 1 inhibitor, which is currently under phase 3 trials.

2. Therapeutic strategies

2.1 General approach to the treatment of RA

The care and treatment of RA is complex, it involves pharmacological and non-pharmacological treatment, and should be multidisciplinary. This has been comprehensively summarized in the EULAR guidelines for early or established RA management (Combe 2010; Smolen et al, 2010; Smolen et al, 2014*). New guidelines 2016 will soon be published, and are available in a PDF form on the EULAR website (<http://www.eular.org>, Smolen et al, 2016*).

The 2016 updated EULAR recommendations have established four overarching principles:

- ➡ *Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.* Shared decision-making includes the need to inform the patient of the risks of RA and the benefits of reaching the targeted disease activity states as well as the pros and cons of respective therapies (Smolen et al, 2014*; Smolen et al, 2016*). Hence, the patient should be directly involved in the treatment decisions, which implies upstream the need for a good patient education.
- ➡ *When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues should be taken into account.* This overarching principle intends to raise awareness of several points:
 - Reaching the outcome of low disease activity or remission is not an absolute prerequisite, and it is equally important to account for comorbidities and other contraindications when targeting a good outcome.
 - Conversely, high disease activity is typically associated with comorbidities. A decrease of 5–9 years in life expectancy occurs in RA, mainly owing to increased cardiovascular morbidity, infection and lymphoma (Gonzalez et al, 2008; Baecklund et al, 2006). Evidence suggests that disease activity and severity have a significant effect on these outcomes and that effective

therapeutic intervention can modulate them (Choi, 2002; Westlake, 2010; Westlake, 2011). Hence, regular assessment of cardiovascular (measurement of blood pressure, lipid profile, body mass index, plasma glucose and recording of cardiovascular family history) and of risk factors for other medical complications (serious infection, cancer, fragility fractures and gastrointestinal haemorrhage) should be systematic, as well as their care. Smoking cessation should comprise part of the overall approach to a patient with RA (Goodson et al, 2008), because it has been recognised as a critical factor for the development of RF-positive RA, for the production of ACPA and is associated with more severe disease and reduced response to treatment.

- Finally, some patients with low disease activity may still develop seriously progressive radiographic joint damage, so after potential lag periods have been accounted for to recognise progression (Aletaha D, 2009), such patients may then need intensification therapy. Hence, early evaluation of erosive changes is essential (through plain hand and feet X-ray examinations complemented if needed by high-resolution US and/or joint MRI), and structural damage progression should be reassessed periodically (especially in the beginning of the disease, as the progression rate of erosion is the highest in the two first years).
- ➡ *Rheumatologists are the specialists who should primarily care for RA patients.* There is clear evidence that continuous care under the auspices of an experienced rheumatologist improves functional outcomes (Smolen et al, 2010; Smolen et al, 2014*). However, the care and treatment of RA should be multidisciplinary, and it involves a lot of other health professionals (primary care physician, nurse, physiotherapist, podiatrist, psychologist, occupational therapist, social worker...) whose role will be developed in **In-Depth Discussion 1** (www.eular-onlinecourse.org). These health professionals are also of great help for the achievement of non-pharmacological and local therapies, which are still useful in everyday management of RA (see in **In-depth Discussion 3** www.eular-onlinecourse.org).
- ➡ *RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist.*

2.2 EULAR recommendations for the management of RA with cs and bDMARDs

These recommendations are summarised in the algorithm presented in **figure 10**.

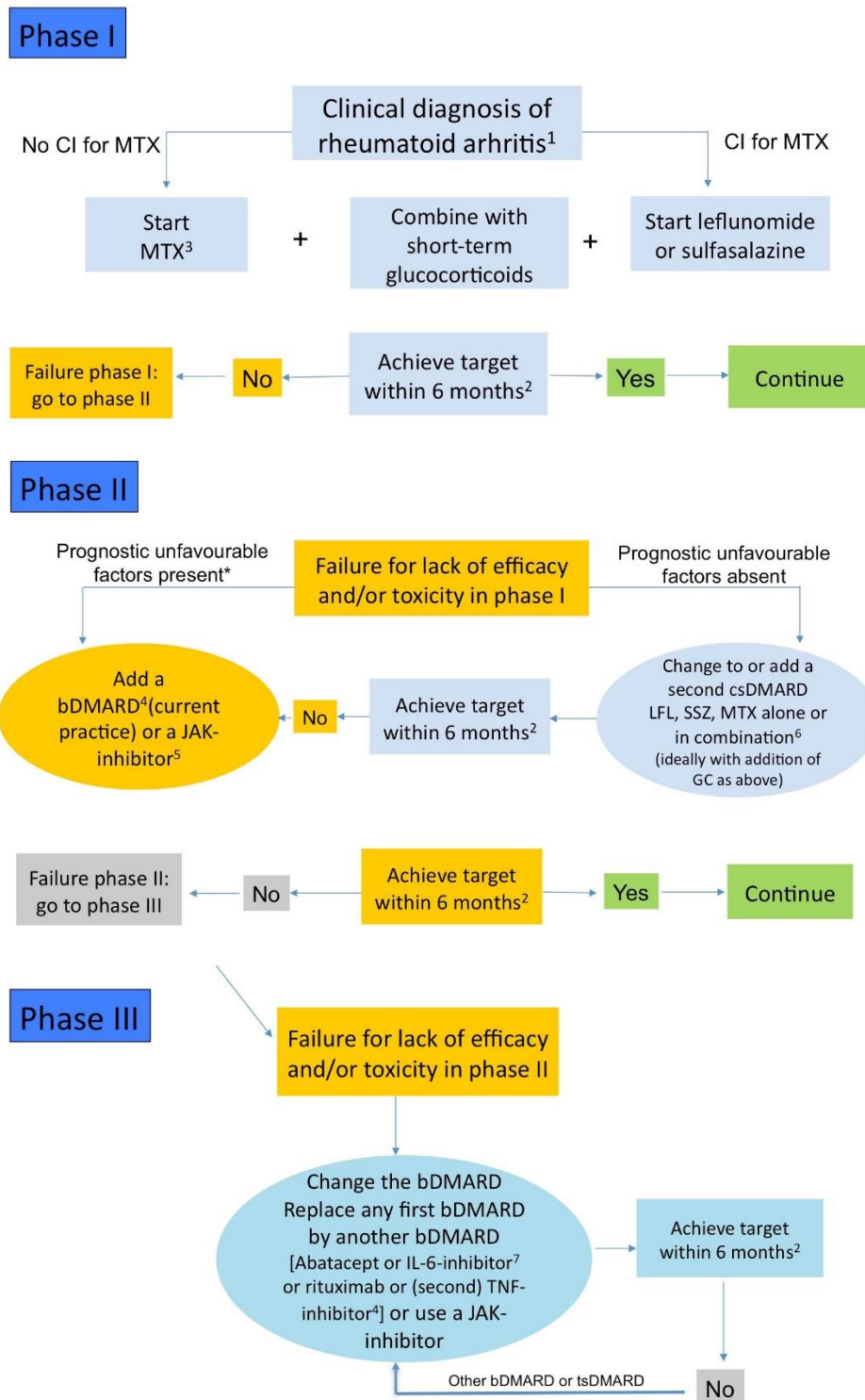
- ➡ *Therapy with DMARDs should be started as soon as the diagnosis of RA is made.* This implies the necessity to make an early diagnosis. To this end, the 2010 ACR-EULAR classification criteria should be used to support diagnosis and facilitate early introduction of effective therapy in RA (Radner et al, 2013). At time of diagnosis, the physician should be particularly cautious in identifying the patients at higher risk (Combe

et al, 2007), although there is as yet no clear paradigm to predict those patients with the poorest prognosis. Several features should, however, raise the clinical “index of suspicion”. Thus, rheumatoid factor (RF)-positive and/or anti-cyclic citrullinated peptide antibodies (ACPA)-positive patients, those possessing the shared epitope in the major histocompatibility complex class II region (not searched in regular practice) and those with high acute phase response, poor function, high swollen and tender joint counts, rheumatoid nodules, Felty syndrome, rheumatoid vasculitis, interstitial lung disease and erosion at presentation tend to do less well. Measurement of the autoantibody status (RF and ACPA) should be systematic at baseline and recheck later, if initially negative.

The era of personalised medicine is however not yet upon us, and at this stage an individual calculation of absolute risk is not possible in general practice. Matrix-based approaches have been developed and offer a rational approach to calculating the relative risk of progression based on baseline features (Figure 11a) (Vastesaeger et al. 2009). It has been hypothesized that the use of prediction matrices of risk of rapid radiographic progression (RRP) for early RA in clinical practice could help to better rationalise the first line of treatment. However a recent work on matrices to identify patients at risk of RRP tested in the ESPOIR cohort showed that these matrices seemed to perform moderately, and there was no matrix that showed clearly superior performance (Granger et al. 2016) (Figure 11b). Several research initiatives comprising transcriptomic (microarray), metabolomic and proteomic approaches are ongoing that may better help to identify those RRP patients in the future.

- *Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.* This implies treatment to target through tight-control, and the use of composite tools to achieve remission according to the ACR-EULAR remission criteria (Felson et al, 2011) (please see **Table 1** in the introduction of this course). When achieving remission is not possible, low disease activity defined by composite measures is a good alternative goal for many patients who cannot attain remission even today, especially those with long-standing disease who actually constitute the majority of patients in clinical care. Indeed, although somewhat worse than remission, low disease activity conveys much better functional and structural outcomes than moderate or high disease activity. Furthermore, a significant proportion of patients in clinical practice still do not attain a state of remission (ref), so once any patients has reached a low disease activity that is close to remission (Mireau et al 2007; Kiely et al, 2011), the individual disease activity variables have to be considered in detail before major therapeutic changes are made (Smolen et al, 2014*).

Figure 10. Algorithm based on the 2016 EULAR recommendations on RA management.



¹ACR-EULAR classification criteria can support early diagnosis. ²The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. ³MTX should be part of the first treatment strategy, while combination therapy of csDMARDs is not preferred by the Task Force, starting with MTX does not exclude its use in combination with other csDMARDs. ⁴TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, or respective well-studied and EMA/FDA approved biosimilars) abatacept, IL6-inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARD as comedication, IL6-inhibitors and tsDMARDs have some advantages. ⁵Current practice would be to start with a bDMARD (in combination

with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (JAK-inhibitors). ⁶The most frequently used combination comprises MTX, SSZ and hydroxychloroquine. ⁷ Efficacy and safety of bDMARDs after JAK-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. ⁸ Efficacy and safety of a JAK-inhibitor after insufficient response to a previous JAK-inhibitor is unknown.

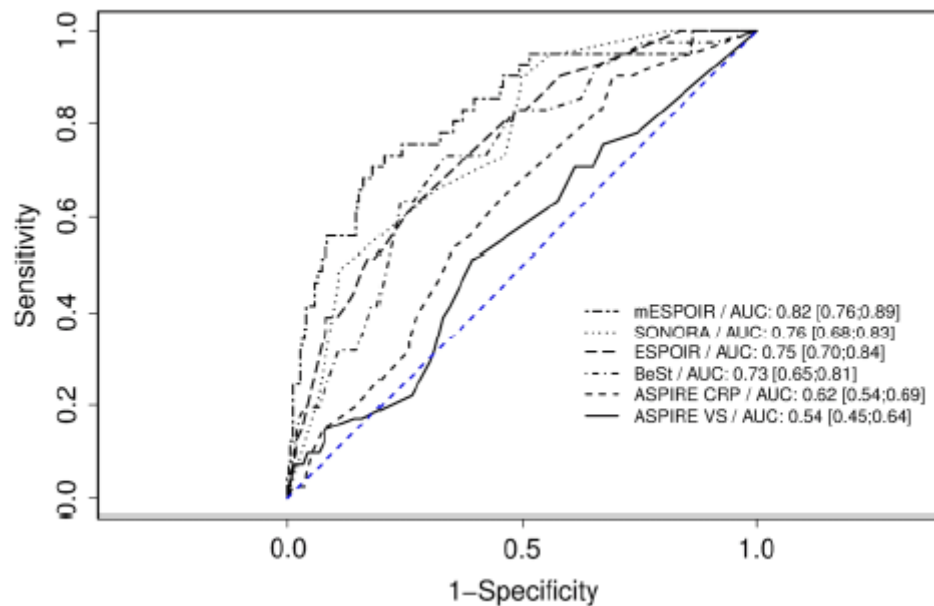
Prognostic unfavourable factors: RF/ACPA, especially at high levels; very high disease activity; early joint damage.

MTX, Methotrexate; SSZ, sulfasalazine; CI, contraindication; csDMARD, conventional synthetic Disease-Modifying Antirheumatic Drug; bDMARD, biological DMARD; tsDMARD, targeted synthetic DMARD; GC, glucocorticoids; TNF, Tumour Necrosis Factor; IL-6, interleukin 6; JAK, janus kinase.

Figure 11a. Prediction model of rapid radiographic progression (RPP) at one year generated from the ASPIRE early RA study (Adapted from Vastesaeger et al. 2009). The numbers in each cell represent the patients who had RRP as a percentage of all patients who had the same baseline characteristics and receive specific treatment. Blue (0-9%), green (10-19%), yellow (20-29%), orange (30-39%), red (40-100%)/ CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IFX, infliximab; MTX, methotrexate; RF, rheumatoid factor; SJC, swollen joint count).

		IFX+MTX			MTX				
28 SJC	>17	8 (5,14)	11 (7,16)	14 (9,20)	33 (22,47)	40 (30,51)	47 (36,59)	>3.0	CRP (mg/dl)
	10-17	8 (5,12)	10 (7,14)	13 (9,18)	31 (21,44)	38 (28,48)	45 (34,56)	0.6-3.0	
	<10	7 (4,12)	9 (6,15)	12 (7,19)	29 (18,44)	35 (24,49)	42 (29,57)	<0.6	
	>17	6 (4,10)	8 (6,11)	10 (7,15)	17 (11,26)	22 (16,30)	27 (19,37)	>3.0	
	10-17	6 (4,8)	7 (6,10)	10 (7,13)	16 (11,23)	20 (16,26)	25 (19,33)	0.6-3.0	
	<10	5 (3,8)	7 (4,10)	9 (6,13)	15 (9,23)	19 (13,27)	23 (16,33)	<0.6	
	>17	4 (2,8)	6 (3,10)	8 (4,13)	8 (4,15)	11 (6,19)	14 (7,24)	>3.0	
	10-17	4 (4,7)	5 (3,8)	7 (4,11)	7 (4,13)	10 (6,16)	12 (7,21)	0.6-3.0	
	<10	4 (2,7)	5 (3,8)	6 (4,11)	7 (4,13)	9 (5,15)	11 (6,20)	<0.6	
		<80	80-200	>200	<80	80-200	>200		
		RF (U/ml)			RF (U/ml)				
28 SJC	>17	11 (7,17)	14 (9,19)	17 (12,23)	30 (20,42)	35 (26,46)	41 (31,52)	<50	ESR mm/h
	10-17	9 (6,14)	12 (8,16)	15 (11,20)	26 (18,37)	32 (24,40)	37 (29,47)	21-50	
	<10	8 (4,14)	10 (6,16)	13 (8,19)	23 (14,36)	28 (19,40)	33 (23,46)	>50	
	>17	6 (4,9)	7 (5,11)	9 (6,14)	18 (12,27)	22 (16,30)	27 (19,36)		
	10-17	5 (3,8)	6 (5,8)	8 (6,11)	15 (11,22)	19 (15,25)	23 (17,31)		
	<10	4 (2,7)	5 (3,8)	7 (4,11)	13 (8,21)	17 (11,24)	20 (14,30)		
	>17	3 (2,6)	4 (2,7)	5 (3,9)	10 (6,17)	13 (8,20)	16 (9,26)		
	10-17	3 (1,5)	3 (2,5)	4 (3,7)	9 (5,14)	11 (7,17)	14 (8,21)		
	<10	2 (1,4)	3 (2,5)	4 (2,7)	7 (4,13)	9 (5,15)	12 (7,20)		
		<80	80-200	>200	<80	80-200	>200		

Figure 11b. Performance on the different matrices with the ESPOIR patients who initially received methotrexate or leflunomide by ROC curve analyses (Granger et al, 2016). Data are area under the ROC curve (95% CIs). AUC, area under the ROC curve; CRP, C reactive protein; ROC, receiver operating characteristic

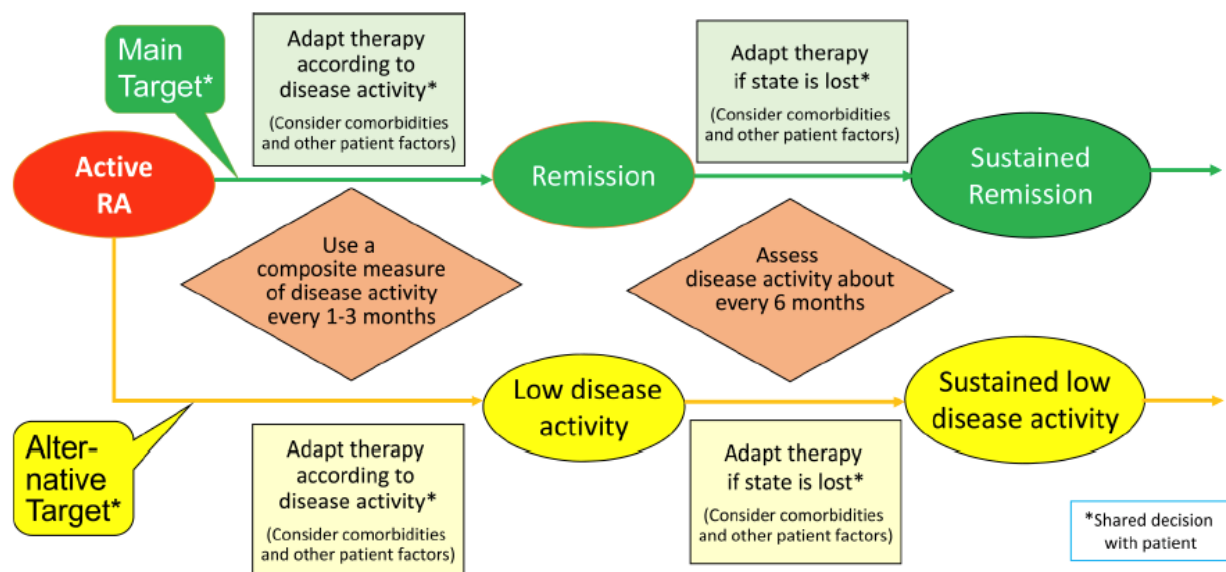


- *Monitoring should be frequent in active disease (every 1-3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.* This means that monitoring should be performed as frequently as disease activity necessitates, namely more frequently (such as 1-3 months) with active disease and less frequently (such as every 6-12 months) once the treatment target has been stabilised (**Figure 12**). EULAR advocates the use of composite measures of disease activity (**Table 1**), which include formal joint counts and the application of the ACR-EULAR criteria for remission (Felson et al, 2011). Further, this item clearly specifies that the treatment target (remission or at least low disease activity) should be attained within 6 months and not necessarily within 3 months; the 3-month time point relates solely to assessing improvement, meaning reduction of disease activity from a high to at least a moderate state by composite measures. If there is no improvement in disease activity (such as persistence of high disease activity) after 3 months, and provided that therapy has already been adjusted to maximise treatment effect, the ongoing therapy is usually unlikely to lead to the treatment goal in many additional patients even by 1 year and should be modified (Aletaha et al, 2007). Maximisation of treatment effects includes reaching an optimal MTX dose within a few weeks and maintaining the maximal dose (25-30 mg weekly) for at least 8 weeks. If improvement is achieved at 3 months, it must be borne in mind that maximal efficacy will not be seen before 6 months in many patients with most treatment strategies.

This is true for all types of therapies, including most biological agents. A similar approach should be made if the treatment target (remission or low disease activity) is not attained at 6 months.

Of note, individual patients may be well on their way to reaching the targets of low disease activity or remission at 6 months and might just take slightly more time to attain this desired state. Therefore the change in disease activity from treatment start to the 6-month time point will have to be taken into account when making final treatment decisions in the individual patients (Smolen et al, 2014*).

Figure 12. Algorithm of monitoring and treating RA to target according to the disease activity (Smolen et al, 2016). Adaptation of therapy should be usually done by performing control examinations with appropriate frequency and using composite disease activity measures that comprise joint counts, but should take comorbidities and other patient factors into account. Setting the target as well start and adaptation of therapy should be done as a shared decision with the patient.



MTX should be part of the first treatment strategy (Figure 10, phase I). Many systematic literature reviews reported that MTX is a highly effective agent both as monotherapy and in combination with glucocorticoids, other cs DMARDs and bDMARDs, and thus continues to serve as an anchor drug in RA (Pincus et al, 2003). As monotherapy with or without glucocorticoids, it is effective in DMARD-naïve patients and leads to low disease activity states or 70% improvement rates according to the criteria of the ACR (which corresponds to nearly a state of low disease activity (Aletaha et al, 2008)) in about 25-50% of patients with early RA within 6-12 months (Breedveld et al, 2006). The EULAR recommendations also insist on the importance of dose optimisation, optimal use of folic acid, and recognition that the maximum effect of MTX is attained only after 4-6 months. In this respect, the optimal dose (25-30 mg a week with folate substitution) should be maintained for at least 8 weeks as an important aspect on the way to ultimate treatment success.

- In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy (Figure 10, phase I). The term “early” has been added

to “intolerance” to indicate the Task Force’s view that early intolerance to MTX should be viewed as a contraindication and not as a failure of the 1st treatment strategy.

- ➡ *Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly clinically feasible.* Many glucocorticoid treatment strategies exist, such as application of oral low- or intermediate-dos, of a single intramuscular injection or a single intravenous application, the latter two approaches usually having lower cumulative doses. Although the efficacy of GCs is well recognized, and although most studies on their toxicity are of low quality and short duration, the EULAR taskforce felt glucocorticoids toxicity, particularly in the intermediate to long term, should not be disregarded and thus glucocorticoids should be used with caution and preferably for only short periods of time as “bridging therapy”, while waiting for a DMARD to reach full effect. The modalities of glucocorticoids management will be detailed in **In-Depth Discussion 2**.
- ➡ *If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered.* Of note, recommendations state that MTX should be part of the first treatment strategy; the term “strategy” inherently does not exclude combinations of csDMARDs. The most often used combination (which was thought for a long time to be more efficacious than MTX monotherapy) is MTX plus sulfasalazine plus hydroxychloroquine. However, the 2016 EULAR Task Force does not primarily recommend it. Indeed, several recent trials (tREACH, CareRA) revealed that MTX monotherapy in combination with glucocorticoids is not less efficacious than combination of csDMARDs plus glucocorticoids, but has less safety issues (Verschueren et al, 2015; de Jong et al, 2014). In patients with low risk of progressive disease, adding a csDMARD when MTX has not sufficiently improved disease activity is a possible therapeutic option, although switching the csDMARD is just as good an option (Goekoop-Ruiterman YP et al, 2005).

When the first treatment cycle fails, EULAR recommends stratification for predictors of severe disease (high disease activity despite the previous therapy, autoantibodies – ACPA or/and RF- especially at high titres, and early joint damage on radiography. Patients with these risk factors should receive a biological DMARD, whereas those without should receive another csDMARD again in combination with glucocorticoids (**Figure 10, phase II**).

- ➡ *In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs [TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab and EMA/FDA approved biosimilars), abatacept or tocilizumab, and under certain circumstances, rituximab] or a tsDMARD (JAK-inhibitor) should be commenced with MTX. However, current practice would be to start with a bDMARD because of the long-term experience compared with tsDMARDs.*

The Task Force reiterated that bDMARDs should primarily be started when patients did not achieve the therapeutic target after treatment with csDMARDs for 6 months (or had no improvement at 3 months). Concerning bDMARDs, solid data from registries, metaanalyses and head-to-head studies suggest that they seem to have similar clinical and structural efficacy (Nam et al, 2014; Schoels et al, 2012, Weinblatt et al, 2013), as well as a similar safety profile (Morel et al, 2013; Horak et al, 2013; Gottenberg et al, 2010; Godot et al, 2013; Weinblatt et al, 2013). Hence, the EULAR Task Force decided no preference of one over another bDMARD should be expressed. However, the 2013 Task Force recognized that there was still more experience with other bDMARDs, and that more safety data from registries would be desirable for the newer bDMARDs (Smolen et al, 2014*).

It is also important to note that the Task Force intentionally added “under certain circumstances rituximab”. While rituximab is approved for use after patients have responded insufficiently to TNF blockers, the Committee acknowledged that, in the presence of certain contraindications for other agents (such as a recent history of lymphoma, latent tuberculosis with contraindications to the use of chemoprophylaxis, living in a TB-endemic region, or a previous history of demyelinating disease) rituximab may be considered as first-line biological agent (Smolen et al, 2014*). Some rheumatologists also prioritise this drug in patients with a recent history of malignancy, because there are no indications that rituximab use is associated with the occurrence of cancers (Buch et al, 2011). Furthermore, rituximab is the least expensive agent at present.

Although the tofacitinib database has been enlarged by long-term extension studies which did not reveal new safety issues since 2013, and although baricitinib has completed phase 3 trials and revealed significant efficacy (also compared with a TNF-inhibitor) without new safety issues, the 2016 Task Force felt necessary to reiterate that current practice would be to start with a bDMARD because of the long-term experience compared with tsDMARDs.

- *bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared to other bDMARDs.*

There is compelling evidence that all bDMARDs, including tocilizumab, convey better clinical functional and structural outcomes in combination with csDMARDs, especially MTX. This may not be the case for JAK inhibitors, although baricitinib in combination with MTX had better structural, though not better clinical and functional outcomes than as monotherapy (Taylor et al, 2015).

- *If a bDMARD or tsDMARD has failed, treatment with another bDMARD should be considered; if one TNF inhibitor therapy has failed, patients may receive another TNF inhibitor or an agent with another mode of action.*

The second part of this recommendation expresses the conclusion of the Task Force that current evidence does not suggest any one agent to be better than another TNF inhibitor when active disease prevails despite initial treatment with a TNF blocker.

- ➡ *If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD.*

Achievement of low disease activity (LDA) or sustained remission raises the possibility of DMARD tapering, titration or/and discontinuation. Until quite recently, treatment was based on the paradigm of continuous treatment for a chronic and lifelong disease, with the underlying perception that drug-free remission is rare, and there is no rationale to change a winning “team” (Den Broeder et al, 2010). In addition, several publications have highlighted the risk of disease relapse in cases of DMARD cessation (O’Mahony R et al, 2010; Van Herwaarden et al, 2014), with the risk of subsequent secondary failure of the DMARD that was stopped. In the last decade, this point of view has changed. The first reason was that achievement of remission or LDA in increasing number of patients (Aga et al, 2015), raising the question of whether drug-free remission would be possible to achieve (Klarenbeek et al, 2010; Van Nies et al, 2015). In addition, with RA prognosis improving, it appeared that the risks or disadvantages of DMARD continuation, for example the risk of serious infections (Smolen et al, 2016, Singh et al, 2015) and costs, could exceed the risks of active RA. That is why the EULAR guidelines have included the tapering of RA therapies in the 2013 and 2016 recommendations (**Table 12**).

Practice points can be developed from these recommendations (Fautrel, 2015):

- bDMARD discontinuation/withdrawal in established RA patients who can achieve low disease activity (LDA)/remission is associated with a high risk of relapse, usually > 50% in the year following discontinuation (Fautrel, 2015). Relapses occur particularly in the first 6 months after treatment reduction and are associated with the presence of ACPA (Haschka et al, (RETRO study) 2016).
- bDMARD tapering – either dose reduction or injection spacing – can be proposed to any established RA patient in sustained remission or LDA, as no clear predictors of tapering success have been identified thus far (Fautrel et al, (STRASS trial), 2014).
- No difference among DMARDs has been demonstrated with regard to the risk of relapse after implementation of tapering or discontinuation strategy.
- DMARD tapering should be conducted in the following order: corticosteroids dose reduction when medium to high dose are used (up to complete discontinuation if feasible), bDMARD, and finally csDMARDs (see next EULAR recommendation below) and low-dose steroids.
- Careful patient monitoring needs to be maintained after implementation of a tapering strategy, according to tight-control and treat-to-target paradigms.

- For the maintenance of sustained remission or LDA in established RA patients, half-dose etanercept is reportedly similar to full dose (Van Vollenhoven et al, 2016).
- Progressive and disease-activity-driven tapering strategies should be preferred; in case of relapse, return to previous administration scheme usually enables the rapid control of increases in disease activity (Fautrel et al, (STRASS trial), 2014; Van Herwaarden et al, (DRESS trial), 2015).
- Risk of clinically relevant structural damage progression appears very low after the implementation of a disease-activity-driven DMARD tapering (Fautrel et al, (STRASS trial)).
- No relevant reduction in the risk of adverse events was observed with DMARD tapering, potentially due to the “dilution of the susceptible” phenomenon [or “survivor bias”; although the (dose-dependent) risk of serious infections seems to be maximal in the few months of the drug initiation (csDMARD or/and bDMARD), the more at-risk patients quit the treatment later] (Fautrel, 2015).
- bDMARD tapering strategies are associated with substantial reduction in costs ranging from 3000 to 6000 per patient per year, with no or limited loss in health benefits (QALY) (Fautrel et al, 2011; Fautrel, 2015).

Table 12: More evidence from literature supporting the possibilities of tapering in RA

- In established RA, the available data suggest that most patients flare upon withdrawal of a TNF inhibitor (Tanaka et al, 2010; Tanaka et al, 2013; Kavanaugh et al, 2013; Chatzidionysiou et al, 2012; Haschka et al, (RETRO study) 2016) and more profound and persistent responses increase the likelihood of maintenance of a good outcome with csDMARDs even after withdrawal of the bDMARD (Tanaka et al, 2010). In the PRESERVE trial, the time frame was at least 4 months (Smolen et al, 2013). However, for early RA, the data are somewhat contradictory. While the primary target in early RA clearly should be stringent remission (Smolen et al, 2010; Felson et al, 2011) most data on withdrawal of bDMARDs come from patients who are in sustained low disease activity.
- The OPTIMA trial showed that a 6-month induction regimen with adalimumab plus MTX soon after diagnosis may be sufficient to allow most patients to maintain low disease activity or remission after open label and even after double-blind withdrawal of the TNF inhibitor (Kavanaugh et al, 2012; Klarenbeek et al, 2011; Smolen et al, 2014); however, while similar findings on withdrawal of a TNF blocker were obtained in an open label fashion in the HIT HARD study (Detert et al, 2013), somewhat contradicting data were seen in the PRIZE trial, where dose reduction but not withdrawal of the biological agent was accompanied by maintenance of good outcome (Emery et al, 2013). Thus, only if further and more broadly confirmed can short-term inclusion of a biological agent in a first DMARD strategy become a true option. On the other hand, reduction of the TNF inhibitor dose after attainment of DAS28<2.6 in early RA allows excellent outcomes to be maintained (Emery et al, 2013), as also seen in established RA (Smolen et

al, 2013; Fautrel et al (STRASS trial), 2013).

- While most studies on dose reduction or withdrawal have been performed with TNF blockers, some data on other bDMARDs are emerging with similar overall results (Takeuchi et al (ORION study), 2013; Nampei et al, 2013; Batticciotto et al, 2013) but clearly more information is needed in this regard.
- Importantly, before bDMARDs are tapered, glucocorticoids should have been withdrawn in line with EULAR recommendations. Also of note, reinstitution of bDMARDs appears to allow the good outcome to be recaptured (Tanaka et al, 2010; Takeuchi et al, 2013; Brocq et al, 2009).

However, some points are still on the research agenda:

- The order and rapidity of DMARD reduction needs to be more fully investigated to identify optimal tapering strategies for all csDMARDs or bDMARDs.
- Soluble biomarkers and/or imaging markers are needed to identify patients most at risk of relapse after DMARD tapering.
- A reliable and consensual definition of flare is required to (1) disentangle loss of efficacy from transient and self-resolving flare, and to (2) organize the care of patients starting a tapering scheme, and be able to rapidly adapt a dose or an injection scheme in case of relapse.
- The potential impact of bDMARD tapering strategies on the development of antidrug antibodies deserves more attention.
- The cost-effectiveness ratio and the willingness to accept DMARD tapering strategies seem promising, but need additional investigation.

➞ *In case of sustained long-term remission, cautious reduction of csDMARD dose could be considered.*

This recommendation refers solely to those patients in whom glucocorticoids, if used, have already been stopped and/or who have attained and maintained the targeted therapeutic state on csDMARDs or those in whom bDMARDs have been successfully withdrawn (see above). It must be borne in mind that stopping csDMARDs in patients with established RA in remission is followed by flares in about 70% of patients, twice as frequently as maintaining therapy irrespective of regimen (ten Wolde et al, 1996; O'Mahony 2010). Therefore the focus of this item is on csDMARD reduction rather than cessation. On the other hand, drug-free remission may be an option in patients in whom therapy was initiated very early and who therefore also had achieved remission early in their disease course (van der Woude et al, 2011).

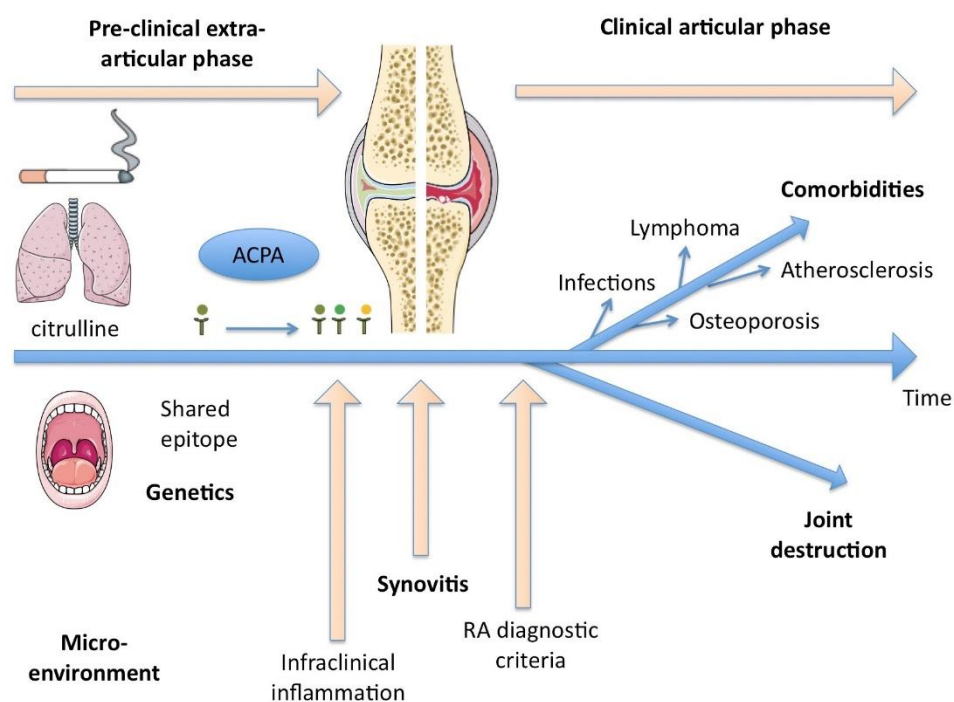
3. Future perspectives in the treatment of RA

Despite advances made over the past two decades, many open issues remain (*Smolen et al, 2016):

- It has been shown that RA is preceded by a pre-clinical phase, and that the immunologic conflict is anterior to the onset of the symptoms, with the presence in serum of ACPA many years before the first clinical sign (Klareskog et al, 2008; Schaeffer et al, 2012) (**Figure 13**). In this context, early treatment might be highly effective at preventing manifestation of rheumatoid arthritis if one could detect pre-rheumatoid arthritis or patients at increased risk. Future diagnostic approaches and therapeutics must address this issue (*Smolen et al, 2016).

Figure 13. The different stages of Rheumatoid Arthritis (adapted from Klareskog et al, 2008 and Schaeffer et al, 2012).

The current therapeutic approaches mainly focus on the clinical articular phase, with the goal of treatment-to-target and tight-control to prevent joint destruction, but also comorbidities such as atherosclerosis, lymphoma, osteoporosis or infections. The future approaches could focus on the pre-clinical articular phase, by preventing or treating the immunologic conflict or infraclinical inflammation, genetic modulation, modulation of the microenvironment and risk factors, etc.... This implies a better knowledge of RA's pathophysiology, and new diagnostic and therapeutic approaches in the future.



- It is not possible today to predict optimal responses or toxic risk for a given treatment. Molecular analyses have failed to answer this question (Ducreux et al, 2014; Ortea et al, 2012; Semerano et al, 2015) but works are ongoing to identify predictors to permit precision medicine approaches in rheumatology (*Smolen et al, 2016).

- Although stringent remission (or at least low disease activity) is today's therapeutic goal for RA, many patients do not reach this target or achieve it but remain dependent on medication, implying that new therapies are still needed (Smolen et al, 2016). New therapeutics are currently being developed on the basis of pathogenic insights and are being tested in early trials (**Table 13**).
- Many patients lose responsiveness over time. Immunogenicity and non-adherence are on explanation, but all the reasons are not totally clear and require better understanding (*Smolen et al, 2016).

Table 13. Potential future therapeutics for RA (adapted from *Smolen et al, 2016)

Biologics
▪ Cytokine inhibitors (human or humanised; e.g., targeting interleukin (IL)-6, IL-21, interferons, granulocyte-monocyte colony stimulating factors or its receptor)
▪ Cytokine-IgG fusion proteins (e.g., interleukin 4-IgG)
▪ Bi-specific antibodies
▪ miRNA targeting
Intracellular signal inhibitors
▪ Janus kinase inhibitors (e.g., baricitinib, filgotinib)
▪ Bruton's tyrosine kinase inhibitors
▪ PI3 kinase inhibitors
Cellular therapies
▪ Tolerogenic dendritic cell transfer
▪ Stem cell transfer
▪ T-regulatory-cell activation
Miscellaneous approaches
▪ Angiogenesis factors inhibition
▪ Osteoclast activation factors inhibition (anti-RANKL)
▪ Toll-Like receptors inhibitors
▪ PADI4 inhibitors
▪ Epigenetic modifiers (e.g., histone deacetylase inhibitors)

Appendix 1: Selection of the main clinical studies that have impacted RA care

Study name:

PROMPT study, adapted from Van Dongen H et coll. Arthritis Rheum 2007;56:1424-1432.

Objective

To demonstrate the ability of methotrexate to prevent the development of established RA in patients with early arthritis.

Population

110 patients with early undifferentiated arthritis, i.e., possible RA in ACR1958 criteria)

	MTX (n = 55)	Placebo (n = 55)
Age (yrs) / Female (%)	51 / 64	51 / 69
Disease duration (months)	10,2	8,6
SJC / DAS44	3 / 2.7	2 / 2.7
RF+ / ACPA+ (%)	37 / 22	36 / 27
VS / CRP (mg/L)	12 / 5	11 / 5
Erosive disease (%)	20	27

Design

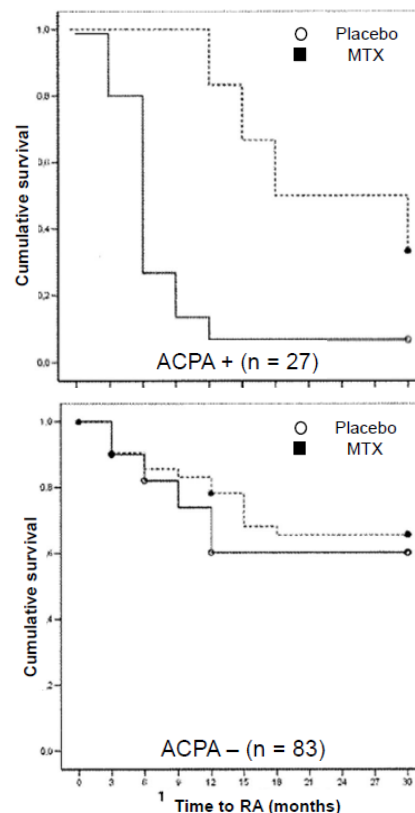
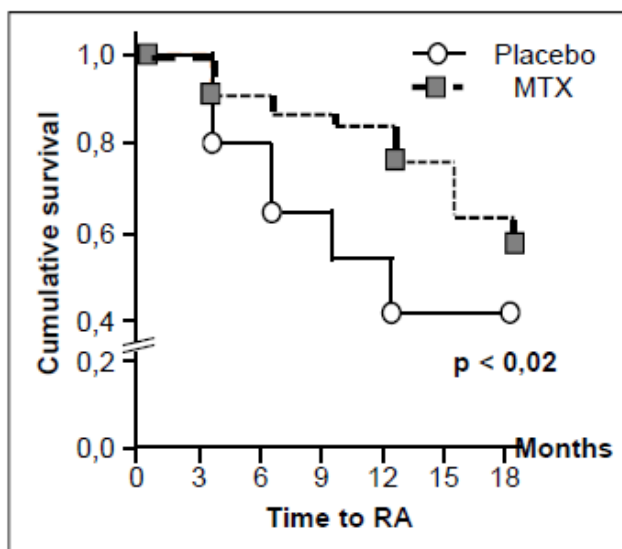
Randomized controlled trial vs placebo: Methotrexate 15 mg/week versus placebo

Endpoints: Satisfaction of ACR 1987 RA criteria, i.e., set up of a full RA presentation

Results:

MTX can prevent the development of established RA

The benefit is only obtained in ACPA+ patients



Study name:

GUEPARD trial, adapted from Rheumatology (Oxford). 2009 Nov;48(11):1429-34.

Objective

To assess the usefulness of a 3-month induction treatment with methotrexate + adalimumab in early RA patients.

Population

65 patients with early active RA: disease duration < 6 months AND DAS28 > 5.2

Mean DAS28 at baseline 6.2

RF+ 74% - ACPA+ 73% - erosive disease on X-rays 34%

Design

1-year randomized controlled trial with 2 arms:

MTX (0,3 mg/kg) monotherapy versus

MTX (0.3 mg/kg) + ADA (40 mg/wk) for 3 months, then MTX monotherapy if remission achieved.

Endpoints:

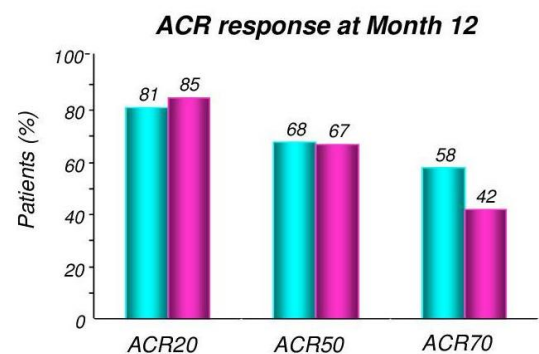
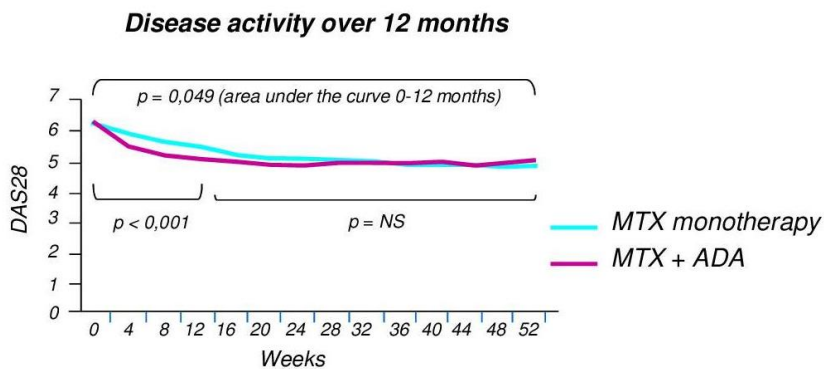
Disease activity at 12 months

Proportion of patients requiring TNF inhibitors at 12 months

Results:

No superiority of the MTX + ADA combination at 12 months in terms of disease activity and ACR responses.

The percentage of patients treated with TNF inhibitors at 12 months was similar between the 2 groups.



Study name:**BeSt trial**, adapted from:

- Goekoop-Ruiterman YP et al. Ann Intern Med 2007;146:406-15.
- Klarenbeek et al. 2011 ACR meeting and Ann Rheum Dis 2012;71:245-8.
- Markusse I et al. 2014 ACR meeting and Ann Intern Med. 2016 Apr 19;164(8):523-31.

Objective

To compare the efficacy in patients with early RA of 4 DAS-driven dynamic strategies based on “tight control” and “treat to target” paradigms.

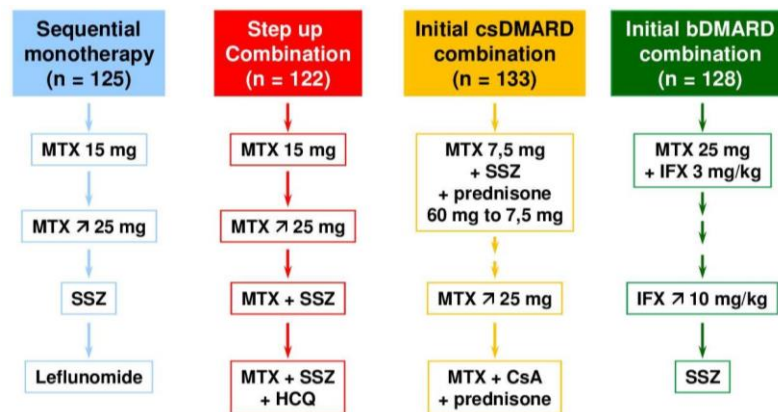
Population

508 people with active early RA (< 2 years), satisfying the 1987 ACR classification criteria, Active disease: swollen joint count ≥ 6 ; swollen joint count ≥ 6 ; ESR ≥ 28 or Patient global ≥ 20 , DAS28 assessment every 3 months and regular adjustment of DMARD according to the predefined strategy (see below) if DAS low disease activity (<2.4) was not achieved.

- DAS44 > 2,4 : next step regimen
- DAS44 $\leq 2,4$: same regimen
- DAS44 < 2,4 for more than 6 months: go back to previous step regimen

Design

Randomized controlled trial

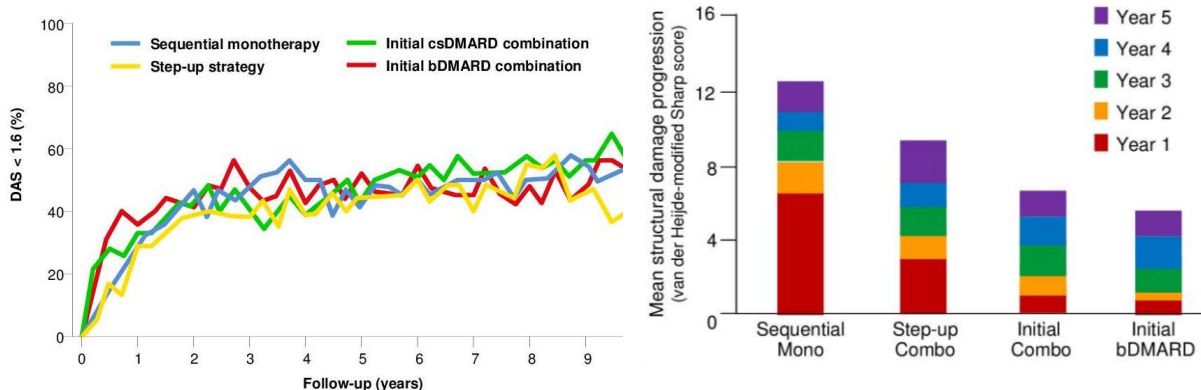


Endpoints: Disease activity on DAS (44 joints),
Structural damage on X-rays (van der Heijde-modified Sharp score)

Results:

There were no differences in terms of RA disease activity during the 10-year follow-up (except during the 1st year of the trial).

Structural damage progression was higher during the 2 first years in the 2 initial monotherapy arms, but the difference did not persist afterwards.



Finally, the 10-year mortality was similar in the 4 arms and not different from the general population mortality (disappearance of the RA-associated cardiovascular mortality).

Study name:**SWEFOT trial**, adapted from

Van Vollenhoven RF et al. 2008 ACR meeting and Lancet 2009;374(9688):459-66.

Van Vollenhoven RF et al. 2009 ACR meeting and Lancet 2012;379(9827):1712-20. .

Objective

To compare csDMARD combination therapy (MTX + SSZ + HCQ) to MTX + TNF inhibitor (IFX) in the treatment of early RA patients with inadequate response to MTX.

Population

258 patients with early RA with inadequate response to MTX defined as DAS28 > 3.2 despite treatment with MTX 20 mg/week for 4 months.

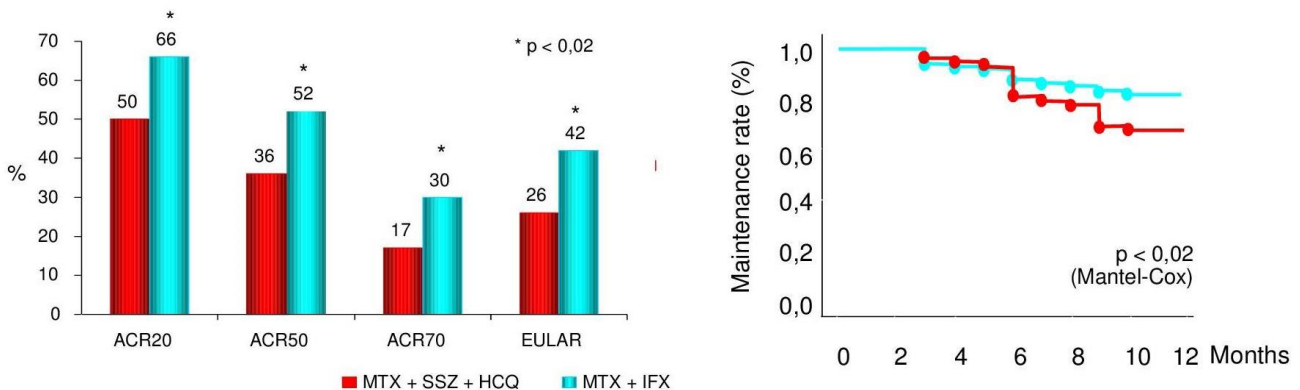
Design

Randomized controlled trial with 2 arms: triple combination of csDMARD versus MTX + IFX.

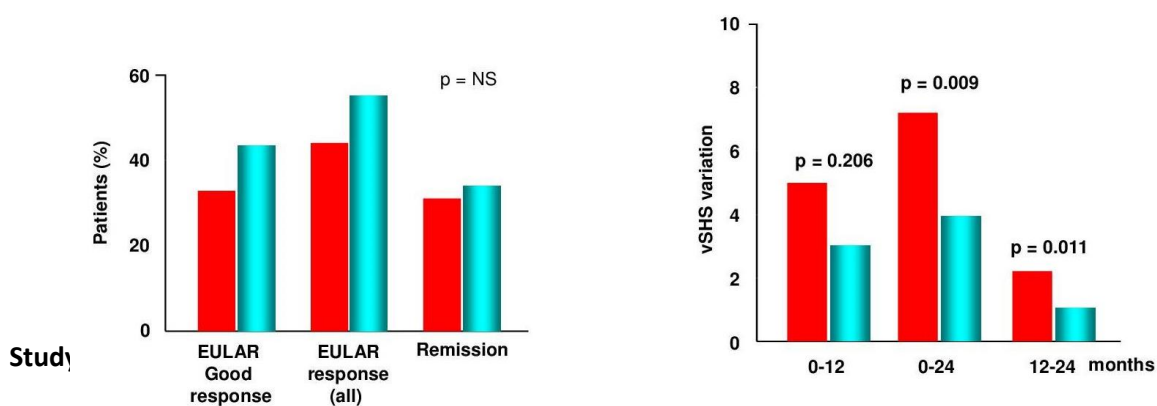
Endpoints: ACR and EULAR responses at 1 and 2 years,
Strategy maintenance at 1 year,
Structural damage progression at 2 years.

Results:

At 1 year, the association MTX + IFX was superior to triple csDMARD combination in terms of ACR and EULAR responses (left figure), as well as maintenance rate (right figure).



At 2 years, there was no more difference for disease activity (left figure). However the structural damage progression was higher in the group with MTX + SSZ + HCQ triple association (right figure).



Study name

RACAT trial, adapted from O'Dell J et al. N Engl J Med. 2013;369(4):307-18.

Objective

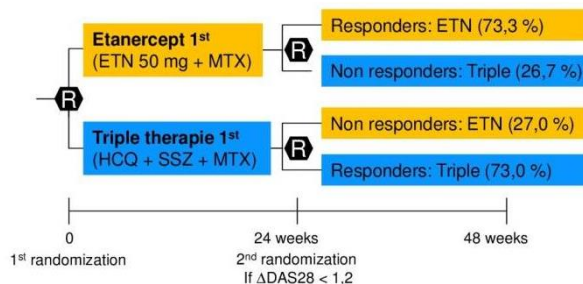
To assess the efficacy of Methotrexate + Etanercept compared to the triple association MTX + SSZ + HCQ in RA patients with inadequate response to MTX monotherapy.

Population

353 established RA patients with inadequate response to MTX, defined as DAS28 > 4.4 despite MTX 15-25 mg/wk for at least 12 months.

Design

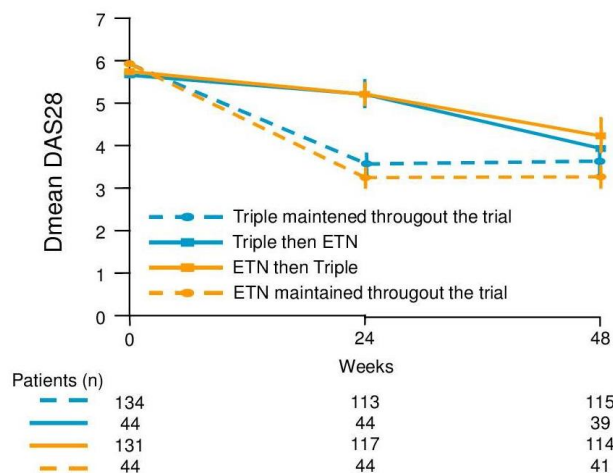
1-year equivalence randomized controlled trial with 2 arms



Endpoints: DAS28 at 1 year;
Structural damage progression

Results:

The percentage of patients who did not respond adequately at 24 weeks was equivalent in the 2 randomization arms. Triple csDMARD association was not inferior to MTX + ETN in terms of disease activity, with a mean DAS28 decrease of 2.1 vs. 2.3 in the MTX + ETN group.



Of note, the Triple therapy was associated with a cost minimization of approximately 15,000 € per patient over 1 year, for a minimal loss of quality of life (- 0.017 quality-adjusted life year).

Study name:

ROC trial, adapted from Gottenberg JE, et al. 2013 and 2015 ACR meetings.

Objective

To compare 2 strategies in RA patients with inadequate response to a first TNF inhibitor: a second TNF inhibitor versus a biologic agent with another mode of action.

Population

300 established RA patients with inadequate response (i.e., DAS28 > 3.2) to a first TNF inhibitor
 Concomitant DMARD (77%) and steroids (2%) at stable doses
 Mean DAS28 at randomization: 5.1

Design

Randomized controlled trial with 2 arms:

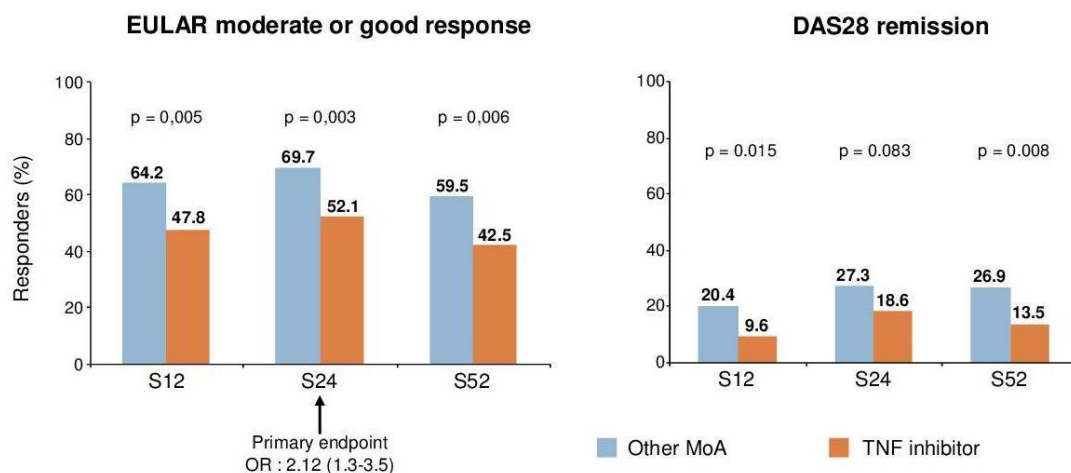
2nd TNF inhibitor: ADA 57 – CZP 23 – ETN 53 – IFX 8

Other mode of action: ABA 33 – RTX – TCZ 70

Endpoints: EULAR response at 6 months

Results:

The rate of EULAR responses was higher in the group treated with another mode of action.



In the group treated with a 2nd TNF inhibitor, the response rate was higher in the patients for whom anti-drug antibodies were found before the discontinuation of the 1st TNF inhibitor.

In the group treated with another mode of action, the difference with TNF inhibitor was higher with tocilizumab.

Finally, the 2nd bDMARD was discontinued more frequently in the group treated with a 2nd TNF inhibitor (48 versus 27), for a lack of efficacy in more than 75% of the patients.

Study name:

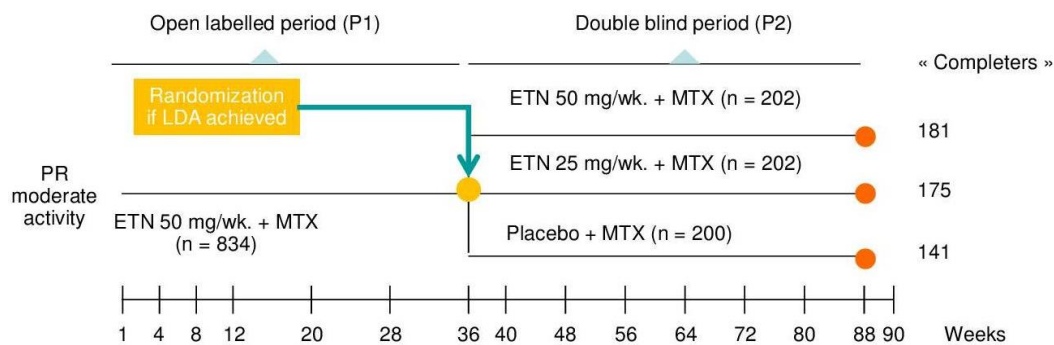
PRESERVE trial, adapted from Smolen et al. Lancet 2013; 381(9870):918-29.

Objective

To demonstrate the superiority of etanercept maintenance at full or half-dose over etanercept discontinuation in patients with established RA having achieved sustained low disease activity with Methotrexate + Etanercept.

Design

Randomized controlled trial with 3 arms.

**Population**

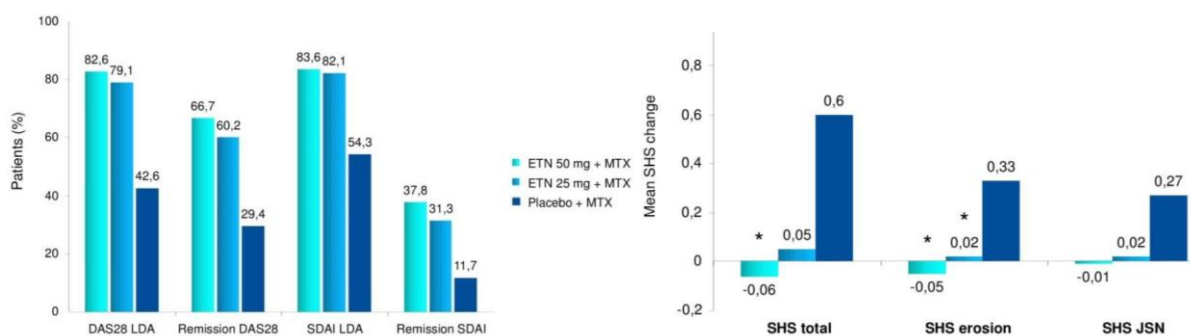
604 patients with established RA: mean age 47 yrs, female 79 %,
 RA duration 6.9 yrs,
 mean DAS28 4.8 at baseline of the open labelled run-in period

Endpoints: Percentage of patients with persisting LDA or remission according to DAS28 or SDAI
 Structural damage progression

Results:

Etanercept maintenance (full and half dose combined) was superior to etanercept discontinuation in terms of LDA persistence and structural damage progression.

There was no statistical difference between the full dose or the half dose etanercept arms.

**Study name:**

DRESS trial, adapted from van Herwaarden N et al. BMJ 2015;350:h1389.

Objective

To demonstrate that a DAS-driven progressive tapering of TNF inhibitor (injection spacing) was non inferior to full regimen in established RA patients in sustained low disease activity with TNF inhibitors.

Population

180 patients with established RA in DAS28 low disease activity for more than 6 months

Either treated with adalimumab or etanercept

Concomitant csDMARD 60 to 80% - Steroids 5% (both at stable dose)

Mean DAS28 at inclusion 2.5

Design

18-month non inferiority randomized controlled trial with 2 arms:

Full dose regimen, i.e., ADA 40 mg eow or ETN 50 mg/wk

Progressive injection spacing if low disease activity was maintained (3 monthly assessments), according to a predefined protocol: ADA 40 mg / 3 wk, then 4 wk, then stop

or ETA 50 mg/2 wk, then 3 wks, then stop

In case of flare, TNF inhibitor were set back to previous step

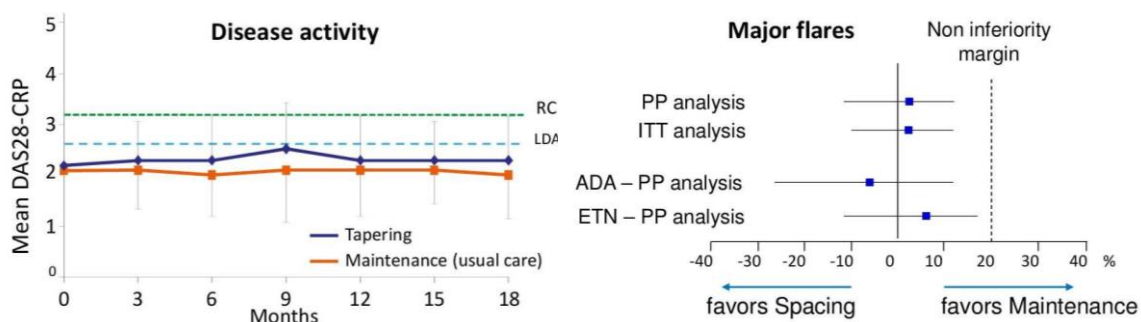
and intramuscular methylprednisolone injection was performed.

Endpoints: Flare, defined as DAS28 > 1.2 or Δ DAS28 > 0.6 AND DAS > 3.2
Major flare: flare persisting at 3 months despite dose escalation and IM prednisolone
Structural damage progression

Results:

At the end of the trial, 43% and 20% of the patients of the spacing arm were able to respectively space or discontinue their TNF inhibitor injections. The disease activity during the trial was not significantly different between the 2 groups (left figure).

Flares were more frequent in the spacing arm (88 of the 121 patients vs. 22 of 59 in the other arm). However, the frequency of major flare was equivalent in the 2 groups: 12 vs. 10, corresponding to a difference of 2 % (CI₉₅ : -12 ; 12), which was inside the equivalence margins (right figure)



Of importance, the equivalence with regards to major flares was counterbalanced by a significantly higher (but clinical meaningless) structural damage progression on X-rays (total Sharp score and joint space narrowing score).

Finally, the spacing strategy was associated with a cost minimization of approximately 9,000 € per patient over 18 months, for a minimal loss of quality of life (- 0.02 quality-adjusted life year).

Study name:

STRASS trial, adapted from Fautrel B et al. Ann Rheum Dis. 2016;75(1):59-67 and EULAR 2015 meeting.

Objective

To demonstrate that a DAS-driven progressive tapering of TNF inhibitor (injection spacing) was non inferior to full regimen in established RA patients in sustained remission with TNF inhibitors.

Population

138 patients with established RA in DAS28 remission for more than 6 months

Either treated with adalimumab or etanercept

Concomitant csDMARD 80% - Steroids 1% (both at stable dose)

Mean DAS28 at inclusion 1.8

Design

18-month non inferiority randomized controlled trial with 2 arms:

Full dose regimen, i.e., ADA 40 mg eow or ETN 50 mg/wk

Versus

Progressive injection spacing if remission was maintained (3 monthly assessments),

according to a predefined protocol: ADA 40 mg / 3 wk, then 4 wk, then 6 wk then stop
or ETA 50 mg/1.5 wk, then 2 wks, then 3 wk then stop

In case of flare, TNF inhibitor was set back to previous step (without steroid rescue).

Endpoints:

Weighted mean disease activity over the 18 months of follow-up

Relapse, defined as DAS28 > 2.6 AND Δ DAS28 > 0.6

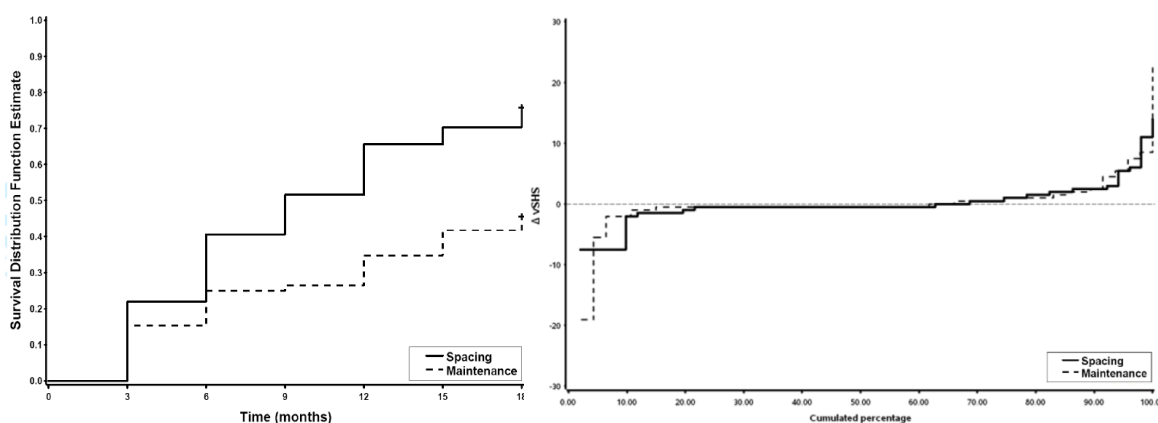
Structural damage progression

Results:

The equivalence between the 2 arms was not demonstrated with a DAS28 standardized mean difference of 19% [95% CI, -5% to 46%] (equivalence margin of 20%). The relapse frequency was significantly higher in the spacing arm (left figure). However, the structural damage progression was similar between the 2 groups (Right figure).

Etanercept maintenance (full and half dose combined) was superior to etanercept discontinuation in terms of LDA persistence and structural damage progression.

There was no statistical difference between the full dose or the half dose etanercept arms.



The spacing strategy was associated with a cost minimization of approximately 8,000 € per patient over 18 months, for a not negligible loss of quality of life (- 0.2 quality-adjusted life year).

Appendix 2: management of antirheumatic drugs before and during pregnancy and lactation

Drug treatment during pregnancy may be required in order to control maternal disease which itself can be a threat for foetal well-being and pregnancy outcome. The risk of leaving active inflammatory rheumatoid arthritis of the mother untreated for 9 months must be weighed against any potential harm through drug exposure of the foetus (Ostensen et al, 2009). Adjustment of therapy in a patient planning a pregnancy aims to use medications that support disease control in the mother and are considered safe for the foetus. However, only a limited number of antirheumatic/ immunosuppressive drugs fulfil these requirements. Several sources of information are available:

- European Network of Teratology Information Services (ENTIS): <https://www.entis-org.eu/about>
- Organization of Teratology Information Specialists (OTIS): <http://mothertobaby.org/>

With the rapidly increasing number of medications available for the treatment of rheumatic disorders, knowledge on safety in pregnancy lags behind. Therefore, a EULAR Task Force has recently published points to consider for use of antirheumatic drugs before pregnancy and during pregnancy and lactation (Götestam Skorpen et al. 2016). Based on a systematic literature review and pregnancy exposure data from several registries, this multidisciplinary Task Force has established 4 overarching principles and 11 points to consider (**Table 16**). Compatibility with pregnancy and lactation was found for antimalarials, sulfasalazine, azathioprine, cyclosporine, tacrolimus, colchicine, intravenous immunoglobulin and glucocorticoids. Methotrexate (MTX), mycophenolate mofetil (MMF) and cyclophosphamide require discontinuation before conception due to proven teratogenicity. Insufficient documentation in regard to foetal safety implies the discontinuation of leflunomide, tofacitinib as well as abatacept, rituximab, belimumab, tocilizumab, ustekinumab and anakinra before a planned pregnancy. Of note, adverse outcomes other than congenital malformations were not consistently reported; this also applies to miscarriages. Rates of miscarriages may be imprecise since they depend on the time point at which a pregnant patient is included in a study. Only MTX and MMF have been consistently shown to increase the rate of miscarriages. Combination therapies with MTX have sometimes also increased the rate of miscarriages (Götestam Skorpen et al. 2016). **Table 17** sums up the conclusions of the Task Force for the management of NSAIDs, glucocorticoids, csDMARDs and tofacitinib, and **table 18** for the management of bDMARDs (Götestam Skorpen et al. 2016).

The biologics with the most pregnancy experience are Tumour Necrosis Factor inhibitors (TNFi) which have been in use for 15 years, including for indications outside rheumatology. For biologics approved <5 years ago, data on pregnancy and lactation are either sparse or completely absent. Hence, among biologics TNFi are best studied and appear reasonably safe with first and second trimester use (**table 18**). As they have a transplacental passage, TNFi use should be avoided, if possible, during the third trimester, because they

increase the infectious risk of the newborn during the first weeks of life (depending on the half-life of the molecule). Thus vaccination of the newborn with live attenuated vaccines should be postponed (in accordance with the paediatrician) if the TNFi has not been stopped during the last months of pregnancy. The difference in placental transfer related to molecule structure and half-life needs to be taken into account when selecting a TNFi for women of fertile age. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage (**point 6, table 16**). Biologics are derivatives of IgG, and differ in structure, half-life and placental passage. The half-life ranges from 9 days to 23 days in complete IgG1 monoclonal antibodies and between 4 days and 13 days in Fc-fusion proteins (etanercept, abatacept) (Suzuki et al. 2010). Active transport of biologics containing the Fc part of IgG1 is mediated by the foetal Fc receptor expressed in the placenta (Suzuki et al. 2010). Transfer is thought to be very low during organogenesis, but to increase steadily after week 13 throughout pregnancy. Treatment of the mother with IgG antibodies expressing high affinity to the foetal Fc receptor after gestational week 30 can lead to foetal/cord serum levels equal to or higher than maternal levels (Mahadevan et al. 2013). IgG has a prolonged half-life, up to 48 days in the newborn (Sarvas et al. 1993); they typically disappear from the child's serum within the first 6 months of life. Pregnancy exposures in any trimester might have the potential to impair organ function, alter the immune response or influence neurocognitive development in children. One of the limits pointed out by the Task Force is that many studies have a short follow-up time and show large gaps in reported outcomes (Götestam Skorpen et al. 2016). Another striking data from this work was the observation of great heterogeneity in regard to clinical practice among experts, especially on breast-feeding management in patients receiving DMARDs. Since 30–50% of pregnancies are unplanned, a major question is how to manage pregnancies that occur in women receiving therapy with teratogenic drugs. Some patients opt for immediate termination whereas others contemplate continuation of the pregnancy. Confirmation of pregnancy by a gynaecologist and determination of exact exposure dates for individual risk assessment and counselling are mandatory. A detailed ultrasound examination of the foetus should be offered to all patients who have an unintended pregnancy while taking a teratogenic drug. Macroscopic anomalies can be assessed by experienced foetal medicine specialists at the end of the first trimester and scans should be repeated at later stages of the second trimester. Other prenatal tests like amniocentesis or chorionic villous biopsy are usually not indicated after maternal drug exposure, but might be considered in patients with high risk of chromosomal problems or anomalies at ultrasound examination.

Table 16: The EULAR points to consider for use of antirheumatic drugs before pregnancy and during pregnancy and lactation (adapted from Götestam Skorpen et al. 2016).

<i>Overarching principles</i>	
A Family planning should be addressed in each patient of reproductive age and adjustment of therapy considered before a planned pregnancy.	
B Treatment of patients with rheumatic disease before/during pregnancy and lactation should aim to prevent or suppress disease activity in the mother and expose the foetus/child to no harm.	
C The risk of drug therapy for the child should be weighed against the risk that untreated maternal disease represents for the patient and the foetus or child.	
D The decision on drug therapy during pregnancy and lactation should be based on agreement between the internist/rheumatologist, gynaecologist/obstetrician and the patient, and including other healthcare providers when appropriate.	
<i>Points to consider for use of antirheumatic drugs in pregnancy*</i>	<i>Grade of recommendation†</i>
1 csDMARDs‡ proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare.	B
2 csDMARDs‡ methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be withdrawn before pregnancy.	B
3 Non-selective COX inhibitors (non-steroidal anti-inflammatory drugs, NSAIDs) and prednisone should be considered for use in pregnancy if needed to control active disease symptoms. NSAIDs should be restricted to the first and second trimesters.	B
4 In severe, refractory maternal disease during pregnancy methylprednisolone pulses, intravenous immunoglobulin or even second or third trimester use of cyclophosphamide should be considered.	D
5 csDMARDs‡, tsDMARDs§ and anti-inflammatory drugs with insufficient documentation concerning use in pregnancy should be avoided until further evidence is available. This applies to leflunomide, mepacrine, tofacitinib and selective COX II inhibitors.	B–D
6 Among bDMARDs¶ continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.	B
7 bDMARDs¶ rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.	D
<i>Points to consider for use of antirheumatic drugs during lactation*</i>	<i>Grade of recommendation†</i>
1 csDMARDs‡ and anti-inflammatory drugs compatible with breast feeding should be considered for continuation during lactation provided the child does not have conditions that contraindicate it. This applies to hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus, colchicine, prednisone, immunoglobulin, non-selective COX inhibitors and celecoxib.	D
2 csDMARDs‡, tsDMARDs§ and anti-inflammatory drugs with no or limited data on breast feeding should be avoided in lactating women. This applies to methotrexate, mycophenolate mofetil, cyclophosphamide, leflunomide, tofacitinib and cyclooxygenase II inhibitors other than celecoxib.	D
3 Low transfer to breast milk has been shown for infliximab, adalimumab, etanercept and certolizumab. Continuation of TNF inhibitors should be considered compatible with breast feeding.	D
4 bDMARDs¶ with no data on breast feeding such as rituximab, anakinra, belimumab, ustekinumab, tocilizumab and abatacept should be avoided during lactation if other therapy is available to control the disease. Based on pharmacological properties of bDMARDs¶, lactation should not be discouraged when using these agents, if no other options are available.	D















*Level of evidence is given for each drug separately in the original article.; †A Category I evidence from meta-analysis of randomised controlled trials (1A) or from at least one randomised controlled trial (1B); B Category II evidence from at least one controlled study without randomisation (2A) or from at least one type of quasi-experimental study (2B), or extrapolated recommendations from category I evidence.; C Category III evidence from descriptive studies, such as comparative studies, correlation studies or case-control studies (3), or extrapolated recommendation from category I or II evidence.

D Category IV evidence from expert committee reports or opinions and/or clinical experience of respected authorities (4), or extrapolated recommendation from category II or III evidence.

‡Conventional synthetic DMARDs. §Targeted synthetic DMARDs. ¶Biologic DMARDs.

Table 17A: Consensus on statements and expert opinion on use of NSAIDs, csDMARDs and tofacitinib in clinical practice in pregnant and lactating patients (adapted from Götestam Skorpen et al, 2016)

Drug	Pregnancy			Breast feeding		
	Statement on compatibility of drug with pregnancy based on evidence	Percentage of agreement with statement	Expert opinion on use of drug in clinical practice*	Statement on compatibility of drug with breast feeding based on evidence	Percentage of agreement with statement	Expert opinion on use of drug during breast feeding†
Non-selective COX inhibitors (classical NSAIDs)	Current evidence indicates no increased rate of congenital malformations. Non-selective COX inhibitors can be continued during the first and second trimesters	92		Non-selective COX inhibitors are compatible with breast feeding	88	
Selective COX II inhibitors	Current evidence is insufficient. Selective COX II inhibitors should be avoided in pregnancy	100		Among COX II inhibitors only celecoxib has been sufficient studied; celecoxib is compatible with breast feeding, other COX II inhibitors should be avoided during lactation	94	
Prednisone	Current evidence indicates no increased rate of congenital malformations. Prednisolone/prednisone can be continued at the lowest effective dose throughout pregnancy (risk of gestational diabetes and infections)	100		Glucocorticoids are compatible with breast feeding	100	
Intra-articular/ Intramuscular glucocorticoids	Current evidence indicates no increased rate of congenital malformations. Can be given, when required, throughout pregnancy	100				
Intravenous glucocorticoids	Current evidence indicates no increased rate of congenital malformations. Can be given, when required, throughout pregnancy	100				
Fluorinated glucocorticoids	Current evidence indicates that fluorinated glucocorticoids should be used with caution because they are less metabolised by the placenta. They should only be used to treat foetal problems.	100				

Hydroxychloroquine	Current evidence indicates no increased rate of congenital malformations. Can be continued throughout pregnancy	100		Compatible with breast feeding	100	
Chloroquine	Current evidence indicates no increased rate of congenital malformations. Can be continued throughout pregnancy	100		Compatible with breast feeding	88	
Methotrexate	Current evidence indicates an increased rate of congenital malformations. In a planned pregnancy, MTX should be withdrawn 1-3 months before pregnancy‡. Need for contraception if patient under treatment	100		Only small amounts of MTX appear in breast milk, but data are limited, therefore MTX should be avoided in breast feeding	100	
Leflunomide	Current evidence is insufficient. In a planned pregnancy, a washout procedure should be completed before pregnancy¶. Leflunomide should be avoided in pregnancy (need for contraception if patient under treatment)	100		No data exist regarding leflunomide in breast milk, therefore it should be avoided in breast feeding	100	
Sulfasalazine	Current evidence indicates no increased rate of congenital malformations. Sulfasalazine can be continued at doses up to 2g/day with concomitant folate supplementation throughout pregnancy.	100		Compatible with breast feeding in the healthy, full-term infant	94	
Cyclosporine	Current evidence indicates no increased rate of congenital malformations. Cyclosporine can be continued throughout pregnancy at the lowest effective dose	100		Compatible with breast feeding	100	
Tofacitinib	Current evidence is insufficient. In a planned pregnancy, treatment with tofacitinib should be stopped 2 months before conception	100		No data exist regarding tofacitinib in breast milk, therefore tofacitinib should be avoided in breast feeding	100	

‡ In theory, MTX in women could be stopped one month before conception (one cycle). In men, MTX should be interrupted 3 months (duration of spermatogenesis cycle) before conception. It can also induce a reversible oligospermia. ¶ Cholestyramine 3x8g/day during 11 days.

*As an expert in the field.

I would recommend the drug in the same way as if the patient was not pregnant.

I would only recommend the drug if I feared at least moderate disease activity in its absence.

I would only recommend the drug if I feared at least severe disease activity in its absence.

I would never recommend the drug in pregnancy.

†As an expert in the field.

I would recommend the drug in the same way as if the patient did not breastfeed.









I would only recommend the drug if I feared at least moderate disease activity in its absence

I would only recommend the drug if I feared at least severe disease activity in its absence.

I would never recommend the drug while the woman was breast feeding.

Table 18A: Consensus on statements and expert opinion on use of biologic drugs in clinical practice in pregnant and lactating patients (adapted from Götestam Skorpen et al, 2016).

Drug	Pregnancy			Breast feeding		
	Statement on compatibility of drug with pregnancy based on evidence	Percentage of agreement with statement	Expert opinion on use of drug in clinical practice (%)*	Statement on compatibility of drug with breast feeding based on evidence	Percentage of agreement with statement	Expert opinion on breast feeding and medication (%)†
Infliximab	Current evidence indicates no increased rate of congenital malformations; infliximab can be continued up to gestational week 20; if indicated, it can be used throughout pregnancy‡	100		Infliximab is compatible with breast feeding	100	
Adalimumab	Current evidence indicates no increased rate of congenital malformations; infliximab can be continued up to gestational week 20; if indicated, it can be used throughout pregnancy‡	100		Adalimumab is compatible with breast feeding	100	
Golimumab	Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy‡	100		Golimumab is compatible with breast feeding	94	
Etanercept	Current evidence indicates no increased rate of congenital malformations; infliximab can be continued up to gestational week 30-32; if indicated, it can be used throughout pregnancy‡	100		Etanercept is compatible with breast feeding	100	
Certolizumab	Current evidence indicates no increased rate of congenital malformations; certolizumab can be	100		Certolizumab is compatible with breast feeding	94	

	used throughout pregnancy [‡]					
Rituximab	Current evidence indicates no increased rate of congenital malformations; in exceptional cases it can be used in early gestation; with use at later stages of pregnancy clinicians should be aware of the risk of B cell depletion and other cytopenia in the neonate	100		No data exist regarding rituximab in breast milk, therefore rituximab should be avoided in breast feeding	80	
Abatacept	No statement can be made in regard to safety during pregnancy due to scarce documentation; treatment with abatacept is therefore best avoided	94		No data exist regarding abatacept in breast milk, therefore abatacept should be avoided in breast feeding	75	
Tocilizumab	No statement can be made in regard to safety during pregnancy due to scarce documentation; treatment with tocilizumab is therefore best avoided	100		No data exist regarding tocilizumab in breast milk, therefore tocilizumab should be avoided in breast feeding	69	
Anakinra	Current evidence does not indicate an increased rate of congenital malformations; anakinra can be used before and during pregnancy when there are no other well studied options available for treatment	100		No data exist regarding anakinra in breast milk, therefore anakinra should be avoided in breast feeding	88	

*As an expert in the field.

I would recommend the drug in the same way as if the patient was not pregnant.
I would only recommend the drug if I feared at least moderate disease activity in its absence.

I would only recommend the drug if I feared at least severe disease activity in its absence.

I would never recommend the drug in pregnancy.

†As an expert in the field.

I would recommend the drug in the same way as if the patient did not breastfeed.

I would only recommend the drug if I feared at least moderate disease activity in its absence.

I would only recommend the drug if I feared at least severe disease activity in its absence.

I would never recommend the drug while the woman was breast feeding

[‡] Owing to their transplacental passage, TNFi use should be avoided, if possible, during the third trimester, as they increase the infectious risk of the newborn during the first weeks of life (depending on the half-life of the molecule). Thus vaccination of the newborn with live attenuated vaccines should be postponed (in accordance with the paediatrician) if the TNFi has not been stopped during the last months of pregnancy. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage

Appendix 3: Vaccination for patients with RA

Patients with RA are at higher risk of developing infections, owing to deregulation of the immune response against pathogens inherent to disease pathogenic mechanisms. The organ damage induced by disease activity additionally creates a “locus minor of resistance” that favours infections. DMARDs, particularly immunosuppressors and biological agents, might increase the risk of infections and at the same time impair vaccination response.

Data from individual analysis of different conventional synthetic and biological DMARDs indicate that the humoral response to vaccination can be decreased by DMARDs, mainly by biological agents, and the response depends on the type of antigen, the cell pathways that are required to mount the immune response and the mechanism of action of the specific drug. It is therefore advisable that patients are vaccinated before starting biological DMARDs. If this is not possible, vaccinations should probably be given in an ideal “window of opportunity”, difficult to define. There should be enough time from the previous drug administration, in order to minimise the effect of the drug on the immune system, and at the same time allow a minimum amount of time before the next administration to enable an adequate immune response to the vaccine. Considering rituximab as an example, vaccination should be performed at least 6 months after the previous course and 4 weeks before the next one.

The administration of live attenuated vaccines in immunosuppressed patients has a potential risk of severe infection by these pathogens (Table 14) and should be avoided (Van Assen et al. 2011).

Table 14. Live attenuated vaccines

• Measles
• Mumps
• Poliomyelitis (oral)
• Rubella
• VZV
• Typhoid fever (oral)
• Yellow fever
• Tuberculosis (BCG, bacilli Calmette-Guerin)
• Rotavirus

In spite of these concerns, small studies have reported vaccination with measles, mumps, rubella and varicella in immunosuppressed children without alarm signals (King et al, 1996; Levin et al, 2006). Clinical trials on herpes zoster vaccination in immunosuppressed populations are ongoing and interpretation of the results will shortly be of help.

In view of these arguments and the increased use of biological DMARDs in rheumatic diseases, recommendations for vaccination in autoimmune inflammatory rheumatic disease were developed by a EULAR Task Force and integrate the most recent update of ACR recommendations for the use of DMARDs in the treatment of RA (van Assen et al, 2011; Singh et al, 2012) (Table 15). Indeed, most of these recommendations can be directly applied to patients with RA. It is important to reiterate, however, that for many of these statements the level of evidence is low owing to the lack of appropriate studies.

Table 15: Grade of evidence according to EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

Recommended vaccines	Grade of evidence
Influenza	Ib–III
23-Valent pneumococcal polysaccharide	Ib–III
Tetanus toxoid	II
Human papilloma virus	III
Herpes zoster	III–IV
Hepatitis A and/or B	II–III

At first it is advisable to verify compliance with the national vaccination plan and if not, to recommend the missed vaccinations when the diagnosis of RA is established. Specifically, previous vaccination against tetanus toxoid, influenza, *Streptococcus pneumoniae*, hepatitis A and B, *Haemophilus influenzae* B, *Neisseria meningitides*, rubella (women in childbearing age) and human papillomavirus should be checked at the first visit (van Assen et al, 2011). Owing to a hypothetical risk of disease flare, vaccines should preferentially be administered during stable disease, according to expert opinion.

The rationale for prescribing vaccines in immunosuppressed patients is based on their potential ability to decrease infections. Influenza vaccination reduces admissions and mortality for influenza/pneumonia in elderly patients with rheumatic diseases. Influenza vaccine is efficacious in patients receiving conventional synthetic DMARDs, infliximab, adalimumab and etanercept, while the response after rituximab exposure is decreased. This response was not adequately assessed in patients treated with abatacept, tocilizumab, certolizumab and golimumab (Chalmers et al, 1994; Nichol et al, 1998; Hak et al, 2002; Del Porto et al, 2006; Fomin et al, 2006; van Assen et al, 2011). For this reason, seasonal and pandemic flu vaccinations are regularly recommended in patients with RA independently of which DMARD the patient is receiving (Saag et al, 2008; van Assen et al, 2011; Singh et al, 2012).

Pneumococcal vaccination immune response can be slightly reduced in patients with RA, particularly if receiving MTX, TNFi, rituximab and abatacept (Kapetanovic et al, 2006; Tay et al, 2007; Gelinck et al, 2008; Bingham et al, 2010). Pneumococcal vaccine is therefore recommended before the initiation of synthetic DMARDs and before starting any biological agent (Saag et al, 2008; van Assen et al, 2011; Singh et al, 2012).

Tetanus toxoid vaccination is included in the global plan of vaccination for the general population and it is, consequently, also given to patients with RA. Although after 24 weeks of rituximab therapy the response to tetanus toxoid stimulus is adequate, the effective protection offered before this period of time is unknown, making it advisable to treat patients with RA with tetanus immunoglobulins whenever a wound occurs in an environment with a high risk of tetanus infection. This is also probably true for patients receiving abatacept treatment (van Assen et al, 2011).

Herpes virus vaccination is controversial. Patients with RA have an increased risk of herpes zoster infection and this risk is further increased by glucocorticoids, csDMARDs and TNFi. No studies are available but there are concerns related to primary varicella infection caused by the vaccine strain in immunosuppressed patients. Given the high risk of herpes zoster infection, EULAR suggests that this vaccine could be administered in selected patients, who are not severely immunosuppressed and are seropositive for varicella zoster antibodies (to protect them from primary varicella infection), but emphasises that these recommendations are not validated but are based on expert opinion and require further investigation (van Assen et al, 2011). In line with this ACR experts consider that herpes zoster vaccine can be given before starting conventional synthetic DMARDs but it is not recommended for patients receiving biological DMARDs (Singh et al, 2012).

Human papilloma virus vaccination is generally recommended in many countries for women under 25 years old but there are no data on the prevalence of the infection or the efficacy of the vaccination in patients with RA. Recently, the administration of bivalent HPV16/18 vaccine to patients with juvenile idiopathic arthritis induced immunisation in all patients, even if the titre of antibodies was lower than in healthy controls. Although a slight increase in the risk of cervix dysplasia or cancer has been described in women with systemic lupus erythematosus or with organ transplantation – for whom powerful immunosuppressive agents are used – , there were no significant differences in patients receiving MTX or TNFi and vaccination was well tolerated without an increase in disease activity (Heijstek et al, 2014). Therefore the ACR panel recommends recombinant human papilloma virus vaccination to all patients before starting synthetic/biological DMARDs or during this treatment (Singh et al, 2012).

Vaccination for A and/or B hepatitis is advised by EULAR for patients who are at increased risk of infection, whereas the ACR states that this should be given to all patients with RA starting or currently receiving synthetic or biological DMARDs (Saag et al, 2008; van Assen et al, 2011; Singh et al, 2012).

Bacillus Calmette-Guérin (BCG) vaccination has not been clearly proved to prevent tuberculosis in adults and as it contains attenuated mycobacteria there is an increased risk of inducing infection in immunosuppressed patients. Additionally, most cases of tuberculosis in patients with RA are due to reactivation of previous infections, which cannot be prevented by vaccination. Therefore, BCG is not recommended for adult patients with RA (van Assen et al, 2011).

Concerns about disease flare after vaccination, owing to a broad stimulation of the immune response mediated by adjuvants, has led experts to advocate that vaccination should be performed when the disease is inactive. On the other hand, there is no formal evidence suggesting that the safety or efficacy of a vaccine is decreased during active disease (van Assen et al, 2011). This hypothetical risk has been based on various case reports of onset or exacerbation of various rheumatic diseases—for example, RA after vaccination. Some authors have suggested that genetic predisposition (major histocompatibility complex class II HLA-DR4 and/or HLA-DR1) might be an important risk factor. The phenotype of HBV vaccination-induced RA is similar to the idiopathic form. Many of these cases started 1 day after vaccination up to 20 days after immunisation and while some had a self-limiting course, in others the disease evolved into established RA that required chronic DMARD therapy (Vautier and Carty, 1994; Gross et al, 1995; Treves et al, 1997; Pope et al, 1998). However, more recently, in a large population case–control study the vaccinations for influenza, tetanus, diphtheria, tick-borne encephalitis, hepatitis, polio and pneumococcus were not associated with an increased risk of developing RA, including in smokers or patients expressing HLA-DRB1 shared epitope alleles (Bengtsson et al, 2010). Similarly, a retrospective case–control analysis of patients receiving vaccination against B hepatitis, tetanus and influenza did not show a significant association between these vaccinations and RA onset (Ray et al, 2011).

Awareness of the importance of performing vaccination, especially in patients receiving biological therapies, is now high, at least in some countries, but this is in contrast with the effective degree of immunisation of these populations (Feuchtenberger et al, 2012). This highlights the importance of applying in clinical practice guidelines for vaccination, aiming at decreasing the risk of severe infections. Finally, it is clear that evidence from appropriate studies is still lacking for most of the proposed vaccines and further research is needed.

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Summary points

- Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
- RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist.
- When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues should be taken into account.
- Therapy with DMARDs should be started as soon as the diagnosis of RA is made. This implies to make an early diagnosis, and ACR-EULAR diagnostic criteria might be of help.
- Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient (through “treatment-to-target” and “tight-control”).
- Assessment of a patient with RA should include at least the 28-joint count, patient’s assessment of global health, HAQ, acute phase markers, RF, ACPA, X-ray pictures of the affected joints and in selected patients (e.g., early disease and in established disease for clarifying the existence of active inflammation) ultrasonography with power Doppler and/or magnetic resonance.
- Monitoring should be frequent in active disease (every 1-3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.
- Assessment of risk factors for several medical complications, including cardiovascular diseases, serious infection, cancer, fragility fractures and gastrointestinal haemorrhage, should comprise part of the assessment and approach to the patient.
- MTX should be part of the first treatment strategy. In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.
- Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly clinically feasible (“bridging therapy” concept).
- If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered.
- In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs [TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab and EMA/FDA approved biosimilars), abatacept or tocilizumab, and under certain circumstances, rituximab] or a tsDMARD (JAK-inhibitor) should be commenced with MTX. However, current practice would be to start with a bDMARD because of the long-term experience compared with tsDMARDs.
- bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared to other bDMARDs.

Summary points

- If a bDMARD or tsDMARD has failed, treatment with another bDMARD should be considered; if one TNF inhibitor therapy has failed, patients may receive another TNF inhibitor or an agent with another mode of action.
- If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD.
- In case of sustained long-term remission, cautious reduction of csDMARD dose could be considered.
- Patients with RA are at higher risk of infections, and vaccination should be performed according to guidelines.
- The management of antirheumatic drugs before and during pregnancy and breast feeding should be perfectly known by rheumatologists because many are contraindicated owing to their potential dramatic effects on the foetus.
- Rheumatologists are the specialists who should primarily care for RA patients, but allied health professionals have an important role in the treatment of patients with RA and should be involved throughout as required (In-Depth Discussion 1).
- Symptomatic treatments (analgesics, NSAIDs) might be of help punctually, and local non-pharmacological should not be disregarded (In-Depth Discussions 2 and 3).
- Education and inclusion of patients (together with their family) in decision-making are critical to optimal care of this chronic condition.

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EULAR on-line course on Rheumatic Diseases

Treatment of rheumatoid arthritis

Bruno Fautrel, Stéphane Mitrovic, Peter Taylor

A previous version was co-authored by Peter Taylor, Elsa Vieira-Sousa, João Eurico Fonseca The rheumatology

IN-DEPTH DISCUSSION I

The Role of Health Professionals in the Treatment of Rheumatoid Arthritis

In RA, besides the rheumatologist and general practitioner, multidisciplinary team care is provided by specialist health professionals including the rheumatology nurse specialist, physiotherapist, podiatrist, and occupational therapist (Figure 1). The role of each health professional will vary according to the model of care, setting, level of specialist training and expertise. It will also vary according to the disease phase (Table 1). In some areas, roles may overlap and be complementary and in all professions, extended scope practice is rapidly developing.

Figure 1 – Multidisciplinary approach of health professional in the care of rheumatoid arthritis patients.



The rheumatology nurse specialist/practitioner

The role of the RNP is to enable patients to maintain their physical, psychological and social functioning thanks to patient-centred care. RNP-led programs underpin this and have been shown effective:

- at the time of diagnosis to:

- facilitate *will work along with the other health professionals, and EULAR has recently established recommendations for education people with inflammatory arthritis (Zangi et al, 2015)]*,
- help them facing fatigue, anxiety or any difficulties in social participation, either in domestic or occupational lives,
- develop preventive medicine actions such as immunization check or screening for osteoporosis, hypertension or other cardiovascular disorders like demonstrated in the COMEDRA trial (Dougados et al, 2015) and like established in the “2016 EULAR points to consider for reporting, screening for

and preventing selected comorbidities in chronic inflammatory rheumatic diseases” (Baillet et al, 2016),

- coordinate patient care within the hospital or between hospital and community care when several health providers are needed.
- disease announcement
- and alleviate anxiety and fear associated with such an important news;

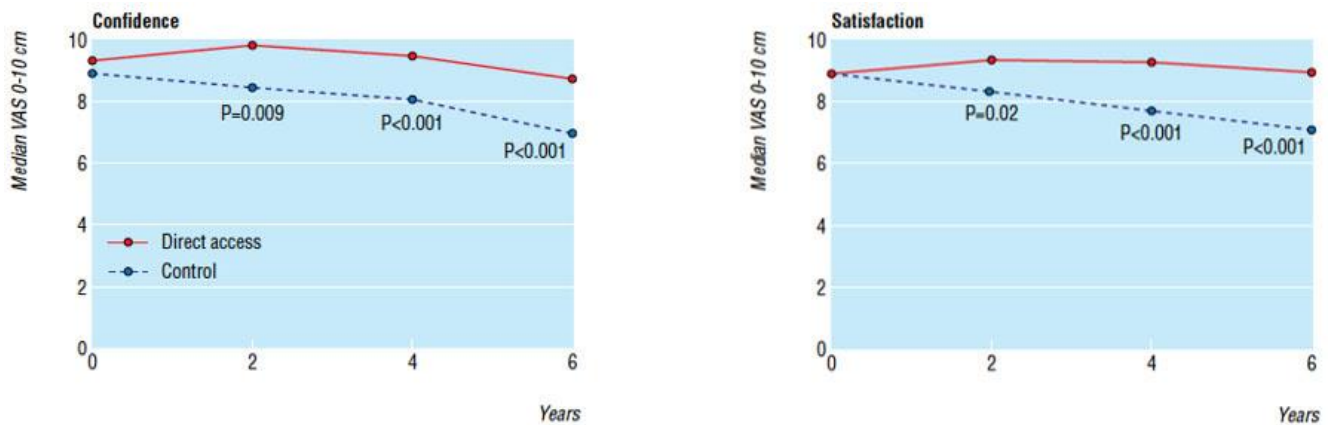
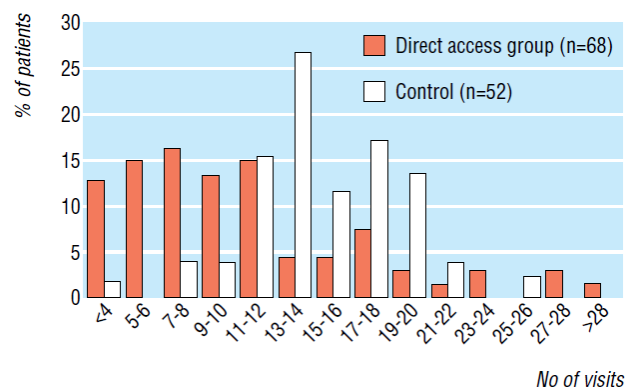
- during the course of the disease, as frequently as needed, to:

- improve disease and treatment understanding and acceptance by the patients,
- reinforce patient adherence to RA care and coping skills through dedicated educational programs *[on this topic which will be further developed in **In-Depth Discussion 3** (www.eular-onlinecourse.org), the RNP care can be implemented by face-to-face meetings (individual or group), by phone or other connected devices, or through community-based user-led self-management programs. The RNP will also direct patients to written information, internet resources and books as well as local and national arthritis organisations.*

An important study was conducted more than 10 years ago in United Kingdom: the implementation of a nurse helpline, easily reachable by RA patients whenever needed, led to higher patient satisfaction and fewer consultation to the rheumatologist compared to usual care (Hewlett et al, 2005) (**Figure 2 A and B**).

Recently, a cost comparison study in a randomised control trial showed that patients with chronic inflammatory arthritis and low disease activity or in remission undergoing biological therapy can be monitored with a reduced resource use and at a lower annual cost by a nurse-led rheumatology clinic, based on person-centred care, with no difference in clinical outcomes, when compared to a rheumatologist-led clinic (Laarson I et al, 2015). This could free resources for more intensive monitoring of patients early in the disease or patients with high disease activity.

EULAR recommendations regarding the contribution of nurses to the care of inflammatory arthritis patients have been developed in 2012 (van Eijk-Hustings et al. 2012). A more recent work two years later showed that these recommendations had been disseminated among nurses, rheumatologists and patients across Europe and the USA, and that agreement with these recommendations were high (van Eijk-Hustings et al, 2014). However, application was lower and differed across regions, and the most common barriers for application of the recommendations were time constraints and unavailability of the service. This underlines the need for developing the means in the future in some regions (van Eijk-Hustings et al, 2014).

Figure 2-A. Patient's confidence and satisfaction in the system (adapted from Hewlett et al, 2005)**Figure 2-B. Hospital rheumatologist appointments over six years (adapted Hewlett et al, 2005)**

The physiotherapist

In the management of RA the physiotherapist will work closely with patients to set goal-orientated treatment plans aimed at optimising function and independence. In early disease, information and advice is provided on joint protection, management of flare, pacing and activity cycling, fatigue and pain relief (see In-Depth Discussion 3 (www.eular-onlinecourse.org), Interventions for pain management include ice, heat, hydrotherapy, electrotherapy and muscle strengthening exercise may be used to improve function, posture and mobility. Some physiotherapists will assess gait and prescribe insoles, walking aids and gait adaptations to improve function and mobility. In addition, relaxation/mind-body approaches such as Tai Chi, relaxation and stress management can be implemented by such health professional.

The occupational therapist

The role of the occupational therapist in the management of RA is to improve/maintain the patient's ability to perform activities of daily living. Comprehensive occupational therapy programmes include activities of daily living assessment and training, joint protection, splinting, pain and fatigue management, assistive devices and environmental modification, patient education, counselling and work and leisure rehabilitation and these are beneficial in the short term for improving functional ability in patients with moderate to severe RA (see In-

Depth Discussion 3 (www.eular-onlinecourse.org). Hand and wrist splints and hand exercises are commonly prescribed and relaxation/mind-body approaches such as Tai Chi, relaxation and stress management may be beneficial for some RA patients. The occupational therapist may also provide counselling, psychological support and use cognitive behavioural therapy approaches and group programmes to help support change so this may involve family and carers.

The podiatrist

Foot problems are common in patients with RA and the role of the podiatrist is to reduce pain, maintain/improve function and mobility, and to protect the skin and soft-tissues of the foot. Correct footwear and specialised insoles (orthoses) are prescribed to protect joints and alleviate symptoms (see In-Depth Discussion 3 (www.eular-onlinecourse.org)). Advice is provided on basic foot hygiene and self-management, joint protection and muscle strengthening exercises and palliative care is provided for painful nail and skin lesions. The podiatrist will provide specialist wound care management for patients with foot ulceration. In an extended role the podiatrists may administer intra-articular or soft-tissue injections and in the UK there are a growing number of surgically trained podiatrists able to undertake forefoot reconstruction procedures.

Other health professionals

Other health professionals within the multidisciplinary team include the dietician who can advise RA patients on aspects of weight management, dietary interventions and dietary supplements (see In-Depth Discussion 3 (www.eular-onlinecourse.org)). The pharmacist has a role educating patients about drug therapy and monitoring for drug interactions and side effects. Newer roles include pharmacist-led DMARD clinics in primary care and expert input in outpatient clinics in support of supplementary prescribes. With a greater understanding of the burden of pain and fatigue in RA, enhancing self-efficacy and achieving behavioural change are the key treatment challenges. These concepts are central to cognitive behavioural therapy and more recently the clinical psychologist has become an increasingly valuable member of the team.

In conclusion

Optimal RA care needs to associate both physician and health professional care in a comprehensive and holistic care. For some authors, a patient annual (or every-other-year) review could be the best way to achieve this goal.

Table 1: Health care circuit for patients with rheumatoid arthritis (RA)

Health professional	Installation stage “pre-RA” or EUA*	Early stage Early RA	Established stage Established RA	Advanced stage Advanced RA
General Practitioner (GP)	Role: evocation of the diagnosis in front of: - ≥ 2 swollen joints - Morning stiffness > 30 min - Positive squeeze-test Action: - Prescription of paraclinical examinations (biology, X-rays) - Orientation to the rheumatologist - Symptomatic treatment: analgesics, NSAIDS	Role: following of the prescription of the rheumatologist, initiation of the collaboration with the rheumatologist (shared follow-up) Action: according to the severity of RA and the country's health system organisation, initiation of the social full medical care	Role: continuation of the collaboration with the rheumatologist (shared follow-up) Action: - Treatment tolerance monitoring - If necessary, renewal of medical prescription between two consultations with the rheumatologist - Prevention and shared management of comorbidities (vaccinations, cardiovascular evaluation)	
Rheumatologist	Role: confirmation of the diagnosis Action: - Diagnosis established on clinical features, biology, X-rays +/- echography - Symptomatic treatment : analgesics, NSAIDS, even oral steroids according to the inflammatory activity	Role: Initiation of therapy, sustained follow-up to evaluate efficacy and tolerance of the treatments Action: - Diagnosis announcement - Explication of RA issues - Establishing the objectives: low disease activity at 3 months, remission at 6 months - Initiation of csDMARD (MTX or other, according to tolerance and CI) - Treatment tolerance monitoring In practice: - Appointment every 3 months (+/- appointment 1 month after treatment initiation) - X-rays at 6 months, then every year	Role: Disease and treatment evaluation Action: - Disease activity evaluation through a composite index and biology - Articular deterioration evaluation through conventional X-rays - Evaluation and prevention of handicap - Treatment adaptation (step up or down) according to disease activity - If necessary, prescription of a bDMARD (private practice-hospital link) - Treatment tolerance monitoring In practice: - Appointments every 6 months (closer if RA not controlled) - X-rays every 1 to 2 years - Comorbidities management (in collaboration with the GP)	Role: Disease evaluation, of its consequences and treatments Action : - Disease activity evaluation, through a composite index and biology - Articular deterioration evaluation through conventional X-rays - Handicap evaluation and adaptation - Treatment adaptation (step up or down) according to disease activity - Treatment tolerance monitoring In practice: - Appointments every 6 to 12 months (according to disease activity) - X-rays every (1 to) 2 years - Establishment of social help for disability (according to the country's health system)

	- Proposition to participate to a therapeutic educational program	- If necessary, discussion of surgical procedures (correction or others)
Rheumatology nurse specialist/practitioner (RNP)	Role: Educational diagnosis Action: Therapeutic educational program (disease; treatments; biotherapies)	
Physiotherapist	Role: Advice on physical activity management Action: to define with each patient	Role: Handicap prevention, maintenance of physical activity Action : Maintenance of joint mobility and muscular trophicity
Occupational therapist	Role: Evaluation within the framework of a therapeutic educational program Action: to define with each patient, orthoses if necessary	Role: Evaluation of technical needs Action: technical assistance, aides techniques, orthoses making
Psychologist	Role: support and coaching Action : to define with each patient	
Pharmacist	Role: Reinforcement of medical drug information Action: Explication of daily drug medicine, information about alert signals, reinsurance	
Social worker	Role: Response to possible social questions Action: to define with each patient	Role: Evaluation of handicap and social help needs Action: according to each country's health system organisation
Occupational Medical Doctor	Role: Job maintenance help Action: Assessment of functional abilities according to the job position constraints, adaptation of the working conditions if necessary	
Patient associations	Role: Information and orientation of the patient Action: Organisation of meetings/ information sessions, development of information support, integration to therapeutic educational programs	

RA, Rheumatoid Arthritis; NSAIDS, non-steroidal anti-inflammatory drugs; DMARD, Disease-Modifying Anti-Rheumatologic Drug; csDMARD, conventional synthetic DMARD; bDMARD, biological DMARD; MTX, methotrexate; CI, contraindication; GP, General Practitioner;

*EUA, early undifferentiated arthritis

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EULAR on-line course on Rheumatic Diseases

Treatment of rheumatoid arthritis

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IN-DEPTH DISCUSSION II

Analgesics, NSAIDs, Coxibs and glucocorticoids in the treatment of RA

Introduction

Pain in patients with rheumatoid arthritis (RA) can have several pathophysiological mechanisms, for example inflammation and secondary osteoarthritis (nociceptive pain), secondary fibromyalgia (non-nociceptive pain due to sensitisation), and compression neuropathy (neuropathic pain, as in carpal tunnel syndrome). In addition, the experience of pain is influenced by socio-psychological factors. The approach of rheumatic pain involves evaluation of mechanisms for the optimal choice of (combinations of) pharmacological and non-pharmacological treatments (Fitzcharles, Almahrezi et al. 2005). This in-depth discussion will first focus on the use of analgesics and non-steroidal anti-inflammatory drugs (NSAID) including cyclooxygenase-2 (COX-2) inhibitors (Coxibs) as adjuvant in the treatment of nociceptive pain in RA. Then, a section will be dedicated to the (often controversial) glucocorticoids use in RA, specially emphasizing the now consensual concept of “bridging therapy”.

1. Analgesics

From the perspective of safety and cost, the American College of Rheumatology recommends that acetaminophen (also known as paracetamol) be tried first as adjuvant treatment for pain in RA, although most patients rate the effectiveness of NSAIDs higher (Lee et al. 1975; Wolfe et al. 2000; Wienecke and Gotzsche 2004). In the EULAR recommendations for the management of early arthritis, it is stated that symptomatic patients presenting with early arthritis should be treated with NSAIDs after careful evaluation of gastrointestinal, renal, and cardiovascular status (Combe et al. 2007). If the effect of either acetaminophen or NSAIDs alone is insufficient, these drugs can be combined (see below). Alternatively, the weak opioid tramadol (Lee et al. 2006) can be added to acetaminophen. Absorption and the analgesic effect of acetaminophen are enhanced if acetaminophen is combined with caffeine, e.g. as combination drug (Renner et al. 2007). Opioid analgesics have additive effects to acetaminophen, since their mode of action is different. Adverse effects, such as nausea and drowsiness, can limit their use; progressive dose increase may facilitate their tolerance.

Chronic use of acetaminophen is not perfectly safe; it could be associated with a significantly increased risk for major cardiovascular events, gastro-intestinal events such as dyspepsia and chronic renal failure (Forel et al. 2001; Garcia Rodriguez and Hernandez-Diaz 2001; Abramson 2002; Rahme et al. 2002; Chan et al. 2006). These adverse effects resemble those of NSAIDs. Acetaminophen indeed seems to have weak COX inhibiting properties in specific pathophysiological conditions (Abramson 2002). However, there might also be confounding bias because patients with more severe disease (who are more prone to cardiovascular and renal complications because of the uncontrolled disease) usually take more analgesics. Furthermore, acetaminophen might not be as safe during pregnancy as previously thought, because it has been reported that foetal exposure might increase the risk of cryptorchidism (Mazaud-Guittot S et al. 2013) or autism (Liew et al. 2015).

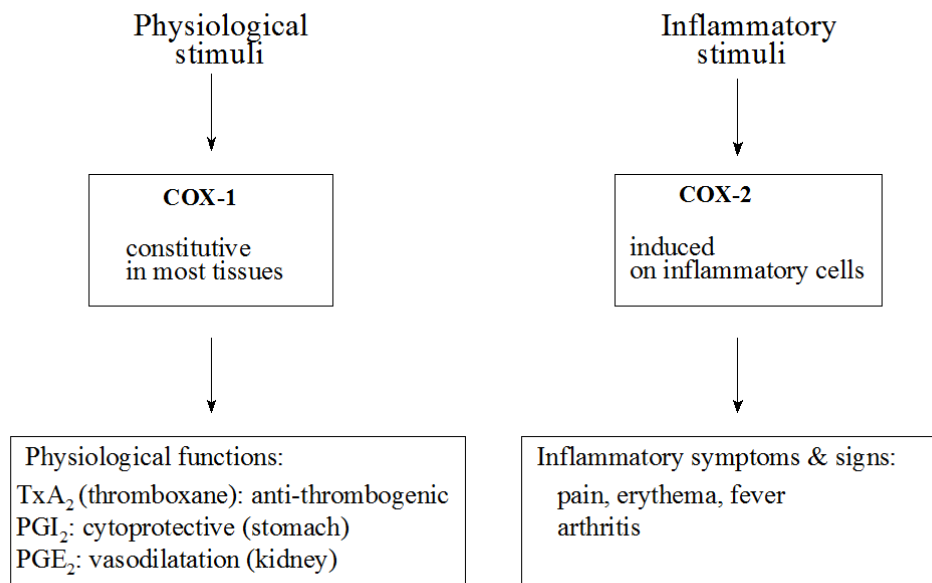
2. Non-steroidal anti-inflammatory drugs (NSAIDs) and Coxibs

2.1-NSAIDs mode of action

NSAIDs inhibit prostaglandin synthesis by inhibiting the enzyme COX which converts the precursor molecule arachidonic acid into various prostaglandins. Prostaglandins (PG) are ubiquitous locally synthesized mediators of inflammation. However, this effect is not as straightforward as it seems. Certain prostaglandins, such as PGE₂ and PGI₂ have not only pro-inflammatory but also anti-inflammatory properties (and numerous physiological functions). Non-acetylated salicylates, such as sodium salicylate, are about 100 times less effective than the acetylated salicylate aspirin in inhibiting COX, yet they are about as effective clinically in suppressing joint inflammation (Furst 1994). Aspirin, at doses sufficient to inhibit COX, inhibits platelet aggregation as expected but does not suppress inflammation: the doses needed to achieve anti-inflammatory effects are substantially higher ($\geq 1\text{g}$). Furthermore, NSAID also have other modes of action (Table 1), (Furst 1994). For most NSAID, both inhibition of COX and inhibition of neutrophil functions seem to play an important role in their anti-inflammatory properties. There are at least two isoenzymes: COX-1 and COX-2. COX-1 is a constitutive enzyme and it is present in most tissues. It has a role predominantly in physiological functions (Figure 1). Whatever the molecule, the delay of action is short, between 15 and 30 minutes, which makes oral administration as quickly efficacious as parenteral administration. The tolerance, especially the risk of digestive ulcer, is not influenced by the route of administration.

Table 1: Modes of action of NSAIDs

• Inhibition of prostaglandin synthesis (COX-mediated)
• Inhibition of leukotriene synthesis (lipoxygenase mediated)
• Inhibition of formation of toxic oxygen radicals from stimulated neutrophils
• Inhibition of lysosomal enzyme release
• Inhibition of neutrophil aggregation / adhesion / chemotaxis
• Altered T-lymphocyte function by inhibiting rheumatoid factor production (in vitro)
• Inhibited cartilage metabolism: impaired proteoglycan synthesis (in vitro)
• Cell membrane functions and signal transduction:
• Inhibited enzyme activity: NADPH oxidase, phospholipase C
• Inhibited transmembrane anion transport (erythrocytes, renal tubules)
• Uncoupling of oxidative phosphorylation
• Inhibited uptake of arachidonate
• Central analgesia

Figure 1: Outline of the COX-1 / COX-2-concept

According to this concept, inhibition of COX-1 causes predominantly side-effects and inhibition of COX-2 anti-inflammatory effects. For critical points that can be raised on this concept, see text and Table 3

COX-2 is present especially in inflammatory cells if induced by pathological, inflammatory stimuli, such as the cytokine interleukin 1. It has been hypothesized that inhibition of COX-1 results predominantly in gastro-intestinal side effects and that inhibition of COX-2 leads to inhibition of inflammation. On the basis of this hypothesis, COX-2 selective NSAIDs have been developed: the Coxibs. However, some critical points regarding the COX-2/COX-1 concept can be raised (Table 3).

Table 3: Items of discussion on the COX-1 / COX-2 concept

- The COX-1/COX-2 ratio for each individual NSAIDs depends on the laboratory model used
- Inhibition of COX is only one mode of action of NSAIDs, so the COX-1/COX-2 ratio is only one (albeit important) aspect of NSAIDs
- Clinical efficacy and superiority regarding side-effects over “old” NSAIDs has to be proven for each individual COX-2 selective NSAID
- There is probably no strict separation between the effects of the COX-1 and COX-2 isoenzymes
- There are probably more COX-isoenzymes than just two

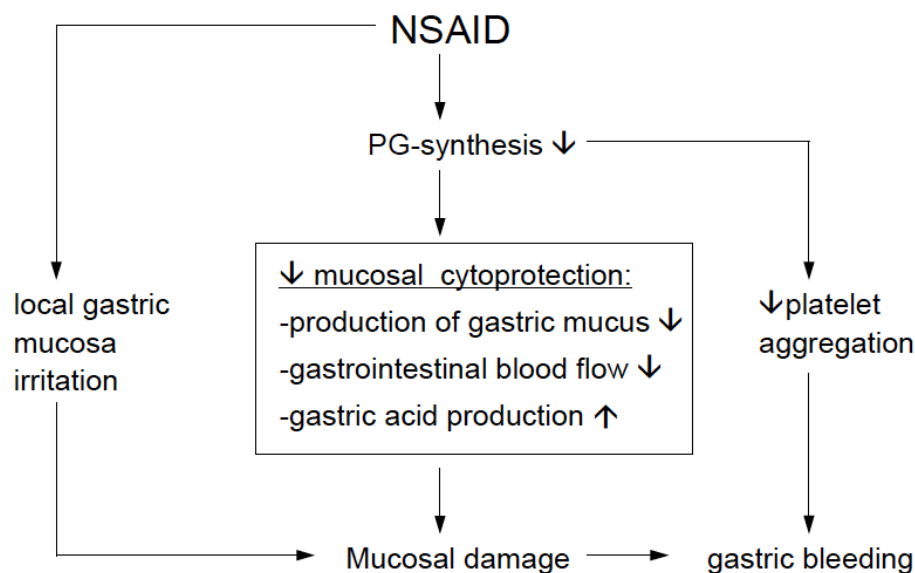
Furthermore, Coxibs may increase the risk of cardiovascular events for long term exposition (see below).

Coxibs do not inhibit platelet aggregation and do not lengthen bleeding time; this, combined with the decreased risk of peptic complications reduces the risk of gastro-intestinal bleeds (Figure 2). Of course, gastro-intestinal risk not only depends on the drug but also on the dose used daily, patient characteristics (e.g. age),

concomitant medication, the disease treated (e.g. osteoarthritis versus rheumatoid arthritis) and disease activity (Figure 3).

Beneficial effects that can be expected of NSAIDs are improvement of patient's global evaluation of disease activity, pain, and morning stiffness; these drugs have no effect on erythrocyte sedimentation rate (ESR) joint swelling or radiological progression (Gotzsche 1990). NSAIDs do not change the course of RA like disease modifying drugs (DMARDs); this means that they are no substitute for DMARDs in active RA, because joint damage will continue, possibly even at a higher rate due to the elevated pain threshold, leading to easier overuse of inflamed joints.

Figure 2: Effects of NSAID locally on gastric mucosa and systematically on gastrointestinal and platelet physiology, leading to gastric complications, especially bleeding.



↓ = decrease; ↑ = increase

2.2-NSAIDs tolerance

Several adverse-effects are clearly related to the specific COX iso-enzyme, in contrast to other adverse-effects, e.g. on the kidney (Gooch et al. 2007), (Table 4).

2.2.1-Digestive toxicity

The inhibition of COX-1 by NSAIDs increases the risk of gastric or duodenal ulcer (Figure 2). Several risk factors have been identified (Figure 3). This potential toxicity is not influenced by the route of administration (oral or parenteral) and is similar whether the drug is taken during the meals or not (the gastric toxicity is not due to the presence of the NSAID in the upper digestive tract but to its action once absorbed and circulating in the serum).

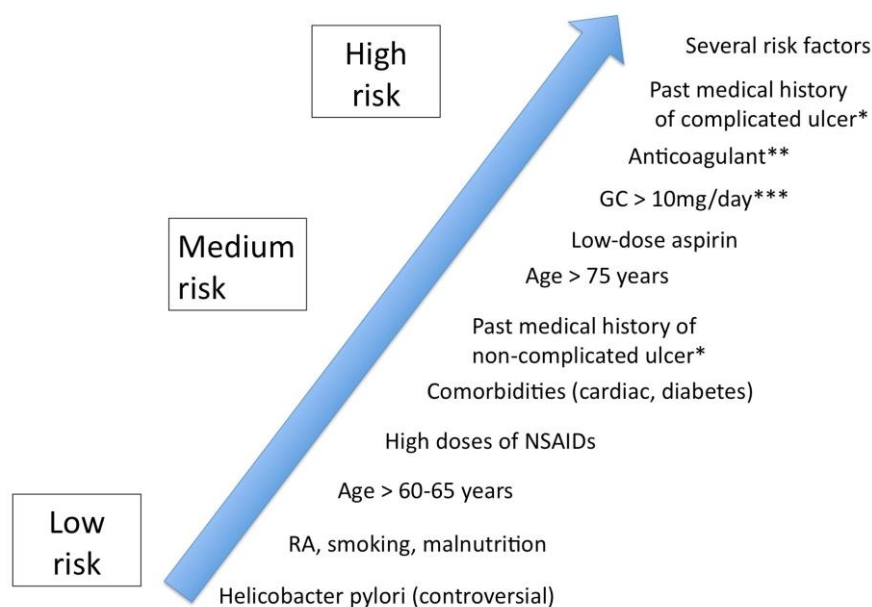
The toxicity of NSAID on gut can also occur in the lower digestive tract (small intestine, colon and rectum), with a higher risk associated with NSAID suppository.

Table 4: Adverse effects of NSAID; between brackets examples of drugs known to cause this adverse effect

Related to inhibition of COX	
◇	Bleeding due to inhibition of platelet aggregation (aspirin)*
◇	Fluid and sodium retention, with clinical manifestations: Hypertension, oedema, congestive cardiac failure
◇	Renal insufficiency
◇	Gastric and duodenal ulcers (piroxicam)
◇	Bronchospasm (aspirin)
◇	Central nervous system dysfunction, headache (indomethacin)
Not related to inhibition of COX	
◇	Rise in transaminases, hepatitis (diclofenac, phenylbutazone, sulindac)
◇	Rash (piroxicam, sulindac, tolfenamic acid)
◇	Pseudoporphyria (naproxen)
◇	Neutropenia, thrombocytopenia, red cell aplasia (phenylbutazone)
◇	Pulmonary infiltrates (naproxen)
◇	Cystitis (tiaprofenic acid)
◇	Interstitial nephritis (fenoprofen)

* Inhibition of platelet aggregation is used as therapeutic effect of aspirin

Figure 3: risk factors for digestive toxicity of NSAIDs



The more risk factors present, the higher the risk is.

* Gastric and/or duodenal ulcer; **anticoagulant or/and antiplatelet therapy; ***GC, glucocorticoids > 10 mg equivalent prednisone per day.

Proton pump inhibitors (PPIs) are able to inhibit gastric acid secretion and are efficacious in healing NSAID-associated ulcers. PPIs also demonstrated efficacy in reducing the risk of ulcerations associated to NSAID use in comparison with NSAIDs alone in randomized controlled trials (RCTs) (Scheiman 2013). The actual risk of NSAID-induced upper gastrointestinal complications could be less however, if patient compliance to the protective medication and physician compliance to therapeutic guidelines was improved (Dincer et al. 2006; van Soest et al. 2007; Vonkeman et al. 2007). Eradication of *Helicobacter pylori* infection does not prevent occurrence or recurrence of NSAID-induced peptic ulcers (Chan et al. 1997; de Leest et al. 2007).

2.2.2-Renal toxicity

All NSAIDs are associated with renal adverse events. NSAIDs can increase sodium retention, increasing the risk of hypertension and exacerbations of congestive heart failure (Table 5). Acute renal failure due to NSAIDs use is uncommon but can be caused by its vasoconstrictive effects and acute interstitial nephritis (Crofford 2013). Based on a cohort study of 4101 RA patients, the use of NSAIDs was an independent factor for accelerated decline of renal function in patients with an estimated glomerular filtration rate (eGFR)<30ml/min but this negative effect not observed in patients with higher eGFR (Moller, Pruijm et al. 2013).

Table 5: Renal side-effects of NSAID*

Side-effect	Mechanism**	Risk factor***
Sodium retention	↓ prostaglandin synthesis: intrinsic effect of NSAID	<ul style="list-style-type: none"> • dehydration, diuretics • heart failure
Hyperkalaemia	↓ prostaglandin synthesis → hyporeninaemic hypoaldosteronism: intrinsic effects of NSAID	<ul style="list-style-type: none"> • renal diseases • heart failure • diabetes mellitus • multiple myeloma • K⁺-sparing diuretics
Acute deterioration of renal function	↓ prostaglandin synthesis: intrinsic effect of NSAID	<ul style="list-style-type: none"> • renal diseases • heart failure • diabetes mellitus • dehydration, diuretics • old age
Nephrotic syndrome with interstitial nephritis	↑ interstitial lymphocyte recruitment and activation: idiosyncrasy / allergy	<ul style="list-style-type: none"> • fenoprofen
Papillary necrosis	cumulative toxicity	<ul style="list-style-type: none"> • Phenacetin • diabetes mellitus? • sickle cell disease?

* In all cases, therapy is stopping of the NSAID therapy; in some cases dosage can be reduced

**Intrinsic effect: related to mode of action; idiosyncrasy: reaction of an individual patient to a specific drug; direct toxicity: related to (cumulative) dose; ↓ = decrease; ↑ = increase

***Heart failure, dehydration, diuretics: increased angiotensin II or adrenergic states.

2.2.3-Cardiovascular toxicity

All NSAIDs have a potential deleterious effect on cardiac function due to their effect of blood pressure (with an intensity which is different depending on molecule). The risk is maximal in patients with a previous history of heart failure and it has been shown that the NSAID use in this population is associated with a risk of congestive heart failure (McGettingan et al, 2006; Bhala et al, 2013; Ungprasert P et al, 2016).

The risk of cardiac ischemic disease such as angina pectoris or myocardial infarction is more complex to establish. Naproxen seems to have a low risk on cardiovascular events (Scheiman 2008). Recent findings from a very large meta-analysis of clinical trials of NSAIDs may now allow physicians to quantify the cardiovascular and gastrointestinal risks associated with these drugs. The results of the Coxib and traditional NSAID Trialists' (CNT) Collaboration, employing data from more than 350,000 randomized patients, show that the risk of major vascular events— mostly major coronary events— was increased by one-third in people taking coxibs or high-dose diclofenac. Ibuprofen significantly increased the risk of major coronary events but not major vascular events. Compared with other traditional NSAIDs (not coxibs), high-dose naproxen was not associated with an increased risk of major vascular or coronary events.

Some authors have hypothesized a class effect of coxibs with regards to the risk of cardiovascular events, notably myocardial infarction. Actually, such a risk has been identified for rofecoxib when used daily for more than 1 year (which has led to the withdrawal of the drug off the market) (Bombardier, et al 2000; Chan et al, 2006; Psaty and Weiss 2007). More recent studies indicate that it was probably a drug effect, not observed with celecoxib, another coxib still on the market (McGettingan et al, 2006).

2.3-Choice of an NSAID

For an individual patient, the choice of an NSAID depends on characteristics of that patient (Table 6). Coxibs or non COX-specific NSAID should be used at the lower end of the recommended dose ranges, since the risk adverse effects increases with the dose (Gotzsche 1989; Psaty and Furberg 2005). If the effect is insufficient, the dose can be increased or the drug can be combined with analgesics to avoid adverse effects (Seideman and Melander 1988; Seideman 1993). The association with glucocorticoids should be avoided, due to increase risk of cardiovascular and gastrointestinal toxicity. In patients with chronic kidney disease chronic NSAID or coxib therapy should be avoided (Gooch et al. 2007). Other advice for prescription is given in table 7.

NSAIDs with long acting effect are particularly useful to control nocturnal awakening and morning stiffness. They can be for instance taken in the evening, before going to sleep, and the sustained release drug formulation will be active during the second part of the night.

Table 7: Advice for prescription of analgesics, NSAIDs and Coxibs for RA

- Pain in active RA is effectively and preferentially treated by DMARD
- Be aware of contra-indications, e.g. allergic asthma, renal insufficiency
- It is sensible to start with acetaminophen and to add a NSAID and Coxib, if needed
- Choice of a specific NSAID
 - ◊ use a frequently used NSAID with known (low frequency of) side-effects
 - ◊ if increased risk of peptic ulceration and low risk of cardiovascular disease: prescribe a COX-2 selective NSAID
 - ◊ if presence or increased risk of cardiovascular disease: avoid NSAID, especially COX-2 selective NSAID
- Prescribe one NSAID at a time; there is no evidence for synergism for 2 or more
- Prescribe the lowest clinically effective dose for a fixed period of time (e.g. 2 weeks), before deciding on therapeutic effect
- In case of insufficient effect:
 - ◊ the dose can be increased, but the increase in effect obtained with the highest doses of NSAID is small and the highest doses cause more adverse-effects
 - ◊ the addition of an analgesic to a medium-dose NSAID results in a better effect and less risk of adverse-effects compared to the highest dose of the NSAID
- Do not use a NSAID or prescribe a COX-2 selective NSAID or add co-medication to the NSAID for gastric protection if there is a history of peptic ulceration or if 2 or more of the risk factors for (complications of) peptic ulceration are present:
 - ◊ concomitant use of anticoagulants
 - ◊ age over 60 years
 - ◊ concomitant use of glucocorticoids
 - ◊ active RA, especially when leading to immobility
- Be aware of drug interactions with NSAID:
 - ◊ *cyclosporin, ACE-inhibitors*: (increase of) renal failure
 - ◊ *diuretics and antihypertensives*: reduced effect due to sodium retention
 - ◊ *cyclosporine*: increased risk of hypertension
 - ◊ *ACE-inhibitors, potassium-sparing diuretics*: risk of hyperkalaemia
 - ◊ *anticonvulsants*: increased effect due to competitive protein binding
 - ◊ *lithium, methotrexate and digoxin*: increased effect of these drugs due to reduced renal clearance induced by NSAID
 - ◊ *methotrexate*: increased risk of liver enzyme elevations (diclofenac)
 - ◊ *aspirin (acetylsalicylic acid)*: decrease of therapeutic platelet aggregation by ibuprofen
 - ◊ *anticoagulants*: increased effect due to inhibition of platelet aggregation
- Check blood pressure, haemoglobin, serum liver enzymes and creatinine regularly

Table 6: Example of a simple scheme for prescription of NSAID, coxibs and gastro protection (PPI, proton pump inhibitor) for patients with RA, according to cardiovascular (CV) and upper gastrointestinal (GI) risk

	GI-risk low	GI-risk moderate	GI-risk high
CV-risk low	Any NSAID	NSAID & PPI or coxib	Coxib & PPI
CV-risk moderate	NSAID, preferentially naproxen	NSAID, preferentially naproxen & PPI	Naproxen & PPI or Coxib & PPI
CV-risk high	Naproxen	Naproxen & PPI	No NSAID nor coxib

3. Glucocorticoids

Glucocorticoids (predniso(lo)ne, dexamethasone) are a unique class of drugs with well-defined effects (table 8 and 9). They are invaluable in the treatment of a range of chronic inflammatory conditions, including RA, because of their rapid and effective mode of action, their pleiotropic well-characterized anti-inflammatory and immunosuppressive effects and long history of use in medicine.

Of the oral glucocorticoids, predniso(lo)ne is most frequently used. Prednisone itself is inactive and hepatically converts to prednisolone, which is the active compound. However, prednisolone is less well absorbed and has a less good bioavailability than prednisone. That is why this latter is often preferred in the treatment of RA.

With normal renal function it is quickly eliminated. It can be used in pregnancy and during lactation at the lowest effective dose, since high doses may lead to fetal immunosuppression or gestational diabetes (Göstetam Skorpen et al. 2016).

Table 8: Main corticosteroids derivatives.

The anti-inflammatory and mineralocorticoid effects of each molecule are estimated in comparison with hydrocortisone, which stands for reference. The inhibitory effect is related to the slowing down effect on the adrenal axis.

Effect	Anti-inflammatory	Mineralocorticoid	Effect duration (hours)
Hydrocortisone*	1	1	8-12
Prednisone	4	0.8	12-24
Prednisolone	4	0.8	12-24
Methylprednisolone	5	0.5	12-24
Triamcinolone (F)	5	0	24-36
Betamethasone (F)	25	0	> 36
Dexamethasone (F)	30	0	> 36

*Cortisol and hydrocortisone the same molecule, cortisol being endogenous, hydrocortisone being the name given to the medication. F = fluor derivative

Table 9: Glucocorticoid equivalence table

Prednisone	5 mg
Hydrocortisone	20 mg
Prednisolone	5 mg
Methylprednisolone	4 mg
Triamcinolone	4 mg
Bethamethasone	0.75 mg
Dexamethasone	0.75 mg

3.1- Glucocorticoids as DMARDs

Glucocorticoids provide actual clinical and radiological benefits in RA: various COCHRANE meta-analyses showed that short-term or moderate-term low-dose corticosteroids were clinically superior to placebo or NSAIDs (Criswell et al. 2000; Gotzsche et al. 2004), but also structurally, as they reduce the rate of radiological progression in RA. Indeed, low-dose glucocorticoids (≤ 10 mg prednisone daily equivalent, or 0.1 mg/kg/day) slow the rate of joint damage and this rate may increase when glucocorticoids are stopped (Kirwan et al, 2007). A meta-analysis even suggested that glucocorticoids would have a structural effect (in absolute value) similar to Disease Modifying Anti-Rheumatic Drugs (DMARDs) and close to biotherapies (Graudal et al. 2010). However, glucocorticoid monotherapy is not specifically recommended by the EULAR Task Force and should only be used in exceptional cases when all other DMARDs have contraindications (Smolen et al., 2014; Smolen et al, 2016).

When combined with csDMARDs, glucocorticoids increase clinical, functional and structural efficacy (Bakker et al., 2012; Svensson et al. 2005; Landewe et al. 2002; Wassenberg et al. 2005), and this combination has similar efficacy when compared with TNF inhibitors plus methotrexate (Heimans et al. 2013; Goekoop-Ruiterman et al. 2005). The beneficial effects on joint damage have been convincingly shown in several clinical trials in patients with early RA (disease duration up to 2 years, possibly up to 4 years), in whom prednisone at a mean daily dose of 6.3 mg (range 0.7–15.9 mg) was added to other DMARDs, resulting in a reduction of about 50% in the rate of progression of radiographic erosion. In studies lasting 2 years, the benefit was slightly lower in the second year but was still significant. Glucocorticoids have therefore been progressively accepted as DMARDs in early RA (Kirwan et al. 1995; Bijlsma et al. 2006) and, by many, as part of the initial treatment plan. These structural effects seem to be maintained even after glucocorticoids are stopped (Mouterde et al, 2010; Bijlsma, 2012).

3.2- Glucocorticoids side effects: less interesting profiles than csDMARDs or bDMARDs

Studies on harm are often of low quality: observational designs with high risk of bias (especially confounding by indication), poor documentation of glucocorticoid exposure and differing models of risk attribution.

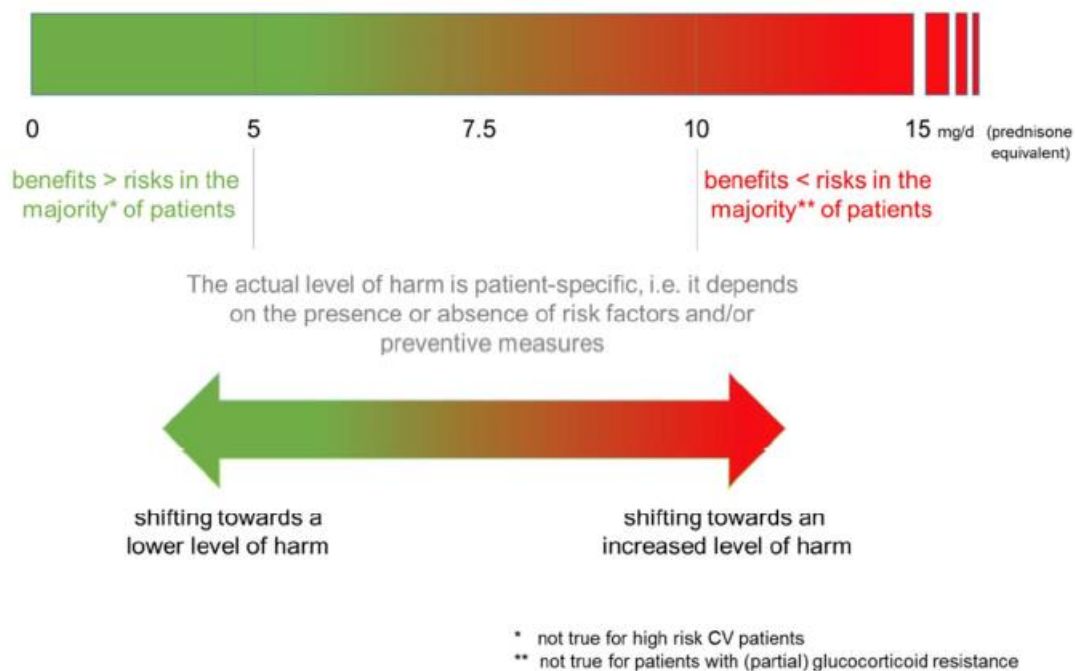
Moreover, clinical trials of glucocorticoids have often been small, short and with limited assessment of adverse events (Strehl et al. 2016). Nevertheless, glucocorticoid treatment, notably with high doses, is associated with serious side effects, such as osteoporosis, hyperglycaemia, hypertension, skin fragility, peptic ulcer disease, premature atherosclerosis, cataracts, myopathy, osteonecrosis, infection (eg, reactivation of latent tuberculosis), mood changes, sleep disturbances and weight gain (Table 10). In addition, the data from the German RABBIT registry clearly showed that steroids are associated with an increased mortality in RA, contrarily to csDMARDs or bDMARD (Listing et al, 2015) (Table 10).

Table 10: Excess mortality risk associated with corticosteroids (adapted from Listing 2015).

	Unadjusted HR		Adjusted HR: 6 (rituximab 12) months risk window approach			Adjusted HR: Ever exposed approach			Deaths	PYRS
	HR	95% CI	HR	95% CI	p Value	HR	95% CI	p Value		
Prednisone most recent 12 months: 0 mg/d	Ref.		Ref.			Ref.			88	9036
1–5 mg/d	1.33	1.00 to 1.76	1.05	0.80 to 1.38	0.71	1.04	0.79 to 1.37	0.77	177	13 615
>5–10 mg/d	2.22	1.65 to 2.98	1.46	1.09 to 1.95	0.013	1.41	1.06 to 1.89	0.021	140	7086
>10–15 mg/d	3.95	2.61 to 5.98	2.00	1.29 to 3.11	0.0033	2.01	1.30 to 3.11	0.0030	37	1170
>15 mg/d	6.68	4.06 to 11.0	3.59	2.11 to 6.13	<0.0001	3.43	2.01 to 5.86	<0.0001	21	448
FFbH* in % of full function per 10% improvement	0.76	0.73 to 0.79	0.88	0.84 to 0.93	<0.0001	0.89	0.85 to 0.93	<0.0001		31 378
Methotrexate	Ref.		Ref.			Ref.			96†/78†	7012†/6469†
Other synth. DMARDs	2.53	1.95 to 3.28	1.14	0.86 to 1.51	0.36	0.98	0.60 to 1.59	0.92	126†/31†	3513†/1581†
TNF α inhibitors	0.77	0.61 to 0.98	0.64	0.50 to 0.81	0.0007	NA			182†	16 843†
Rituximab	1.01	0.70 to 1.46	0.57	0.39 to 0.84	0.0062	NA			36†	2599†
TNF α inhibitors or rituximab	NA		NA			0.77	0.60 to 0.97	0.0312	330†	22 370†
Other biologics	1.02	0.68 to 1.52	0.64	0.42 to 0.99	0.043	0.91	0.66 to 1.25	0.54	25†/51†	1654†/2806†

Evidence for the risks of low-dose glucocorticoid treatment is scarce, and several controlled randomized clinical trials have shown that the frequency and severity of adverse reactions is often not statistically different from that of placebo. Nevertheless, data from registries suggest that concern remains about potential long-term adverse reactions to glucocorticoid therapy, such as increased cardiovascular risk. Recently, a multidisciplinary EULAR Task Force aimed at defining conditions under which long-term glucocorticoids may have an acceptably low-level of harm (Strehl et al. 2016). The group agreed that the risk of harm is low for the majority of patients at long-terms dosages of ≤ 5 mg prednisone equivalent per day (with the exception of patients at high risk for cardiovascular diseases), whereas at dosages of > 10 mg/day the risk of harm is elevated. At dosages between > 5 and ≤ 10 mg/day, patient-specific characteristics (protective and risk factors) determine the risk of harm (Figure 3). Hence, the level of harm of glucocorticoids depends on both dose and patient-specific parameters, and general and glucocorticoid-associated risk factors and protective factors such as healthy lifestyle should be taken into account when evaluating the actual and future risk (Figure 3, Strehl et al. 2016). Screening and monitoring for adverse events as part of standard care in clinical practice should therefore be performed (van der Goes et al, 2010) (Table 10).

Figure 3. The level of harm of long-term glucocorticoid therapy in rheumatic diseases (Strehl et al, 2016).



Bearing in mind the beneficial effects of glucocorticoids, the Task Force members agreed that at dosages of ≤ 5 mg/day prednisone equivalent, there is an acceptably low level of harm that is elevated at dosages of >10 mg/day. At dosages between >5 and ≤ 10 mg/day, there still exists uncertainty and therefore patient-specific characteristics (ie, disease activity, the presence of additional risk factors) need consideration when estimating the risk of harm. These patient-specific factors can shift the level of harm towards the better or worse.

Table 11: Main adverse effects of glucocorticoids and their management

Side effects	Prescreening, prevention and monitoring
Cardiovascular: <ul style="list-style-type: none"> ➤ Hypertension ➤ Perturbation of serum lipoproteins ➤ Premature atherosclerotic disease ➤ Arrhythmias with pulse infusions 	<ul style="list-style-type: none"> ➤ Blood pressure measure ➤ Weight measures, and lower limb oedema detection ➤ Electrocardiogram, especially before pulse infusions ➤ Serum lipid profile
Endocrine and metabolism: <ul style="list-style-type: none"> ➤ Weight gain ➤ Diabete mellitus ➤ Hypothalamic-pituitary-adrenal insufficiency 	<ul style="list-style-type: none"> ➤ Regular weight measures ➤ Dietician consultation, low sugar and salt diet ➤ Regular fasting glycaemia measures ➤ Patient education: never stop medication without medical agreement
Renal: <ul style="list-style-type: none"> ➤ Hypokalemia ➤ Fluid volume shifts 	<ul style="list-style-type: none"> ➤ Regular ionogram check, and potassium supplementation if needed ➤ Weight measures, and lower limb oedema detection
Gastrointestinal: <ul style="list-style-type: none"> ➤ Gastritis, peptic ulcer disease (PUD) ➤ Visceral perforation, diverticulitis ➤ Steatohepatitis ➤ Pancreatitis 	<ul style="list-style-type: none"> ➤ Respect digestive contraindications: avoid prescribing glucocorticoids if medical history of gastritis, PUD, perforation ➤ If prescription cannot be avoided: find the minimally efficacious dose, add PPI* and avoid other gastrotoxic co-medication (especially NSAIDs)
Bone: <ul style="list-style-type: none"> ➤ Osteoporosis ➤ Avascular necrosis 	<ul style="list-style-type: none"> ➤ Detect, prevent and treat (if necessary) osteoporosis: <ul style="list-style-type: none"> ○ modify if possible other risk factors (smoking) ○ dietician consultation to increase calcium intakes +/- D-vitamin and calcium supplementation (except if sarcoidosis) ○ osteodensitometry ➤ Find the minimal efficacious dose, and especially avoid too frequent pulse infusions (↑ avascular necrosis)
Infectious disease: <ul style="list-style-type: none"> ➤ Heightened risk of bacterial, viral (herpes zoster) and opportunistic infections ➤ Malignant anguillulosis (if the patient comes from or went to endemic zones) 	<ul style="list-style-type: none"> ➤ Detect and treat potential chronic infectious sources (dental, ear-nose-throat...) ➤ Avoid prescription if chronic uncontrolled infection (AIDS, recurrent urinary infection...) ➤ If pulse infusions: hemogram, cytobacteriological urinary analysis +/- chest X-rays ➤ If at risk: tuberculosis test ➤ If patient at risk for anguillulosis: stool sample and prevention with ivermectin prior to glucocorticoid prescription
Muscle: <ul style="list-style-type: none"> ➤ Myopathy 	<ul style="list-style-type: none"> ➤ Avoid chronic use, or found the minimal efficacious dose ➤ Patient education: sportive activity, rehabilitation
Dermatological and soft tissues: <ul style="list-style-type: none"> ➤ Skin thinning and purpura ➤ Cushingoid appearance ➤ Alopecia ➤ Acne, hirsutism, hypertichosis ➤ Striae 	<ul style="list-style-type: none"> ➤ Avoid chronic use, or found the minimal efficacious dose
Eye: <ul style="list-style-type: none"> ➤ Posterior subscapular cataract ➤ Elevated intraocular pressure, glaucoma 	<ul style="list-style-type: none"> ➤ Detect by regular ophthalmologic assessments, especially in patients at risk and in the elderly
Neuropsychiatric: <ul style="list-style-type: none"> ➤ Euphoria, dysphoria/depression ➤ Insomnia/akathisia ➤ Psychosis ➤ Dizziness 	<ul style="list-style-type: none"> ➤ Respect the psychiatric contra-indications: bipolarity, psychosis
Genitourinary and reproductive: <ul style="list-style-type: none"> ➤ Amenorrhea, infertility ➤ Gestational diabetes ➤ Intrauterine growth retardation 	<ul style="list-style-type: none"> ➤ Avoid if possible during pregnancy. If not possible, find the lowest effective dose ➤ Tight maternal and foetal monitoring during pregnancy: intrauterine growth, gestational diabetes detection and prevention...

*PPI: proton pump inhibitor; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; ↑, increase; AIDS, Acquired Immune Deficient Syndrome; CBC, complete blood count.

3.3- Glucocorticoids as “bridging therapy”

Although the efficacy of GCs is well recognized, and although most studies on their toxicity are of low quality and short duration, the EULAR taskforce felt glucocorticoids toxicity, particularly in the intermediate to long term, should not be disregarded and thus glucocorticoids should be used with caution and preferably for only short periods of time. Thus GCs were proposed for a limited period, as “bridging therapy” while waiting for a DMARD to reach full effect, with the goal of tapering the GC dosage or stopping the GC as soon as allowed by the clinical situation, due to its cumulative toxicity. Hence, the 2013 and 2016 update EULAR recommendations stipulate that “low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible” (Smolen et al, 2014; Smolen et al, 2016). Different strategies have been proposed for “bridging therapy” for example, prednisone at moderate doses (10–30 mg/day), at high doses (30–60 mg/day) to induce remission in conjunction with another DMARD (usually MTX), followed by rapid tapering to the lowest effective dose, as used in the COBRA trial, or at low doses (5–10 mg/day), in combination with another DMARD, to maintain a state of low disease activity (Gaujoux-Viala et al. 2014). Some teams prefer 1 to 3 intramuscular injections or intravenous infusions of methylprednisolone, which might have the advantage to limit the risk of chronic use (Gaujoux-Viala et al. 2014). Glucocorticoids should not be considered as a long-term treatment of RA.

When stopping or tapering glucocorticoids after the initial 6 months of “bridging therapy” is not possible, the minimal efficient dose should be the goal, ideally below 0.1 mg/kg/day, which is considered by many as acceptable (Strehl et al. 2016). In case of important polyarticular flairs and/or of visceral impairment (mainly vasculitis), intravenous or intramuscular boluses of methylprednisolone might be used. Detailed recommendations by the EULAR Task Force for the management of medium- to high-dose glucocorticoids have been published (Duru et al, 2013). Another Task Force established recent recommendations for long-term glucocorticoid treatment (Strehl et al. 2016).

3.4- Local intra-articular injections of glucocorticoids

This point will be developed in **In-Depth Discussion 3** (www.eular-onlinecourse.org)

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EULAR on-line course on Rheumatic Diseases

Treatment of rheumatoid arthritis

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IN-DEPTH DISCUSSION III

**Local and non-pharmacological therapeutics in the
treatment of rheumatoid arthritis**

Introduction

Rheumatoid arthritis care is not limited to the prescription of Disease-Modifying Antirheumatic Drugs (DMARDs) or symptomatic drugs. It should also include:

- Patient education and counselling performed by the rheumatologist, a rheumatology nurse or physiotherapists (see In-Depth Discussion 1, www.eular-onlinecourse.org) in order to improve patient knowledge and skills to face the disease. It could include learning of self-administered techniques to better cope with pain and anxiety related to the disease.
- Local therapies when needed, mainly intra articular injections in case of active synovitis or surgery (Fontaine 2014) when a joint is severely and irreversibly damaged.
- Non-drug therapies which includes physiotherapy, rehabilitation occupational therapy.
- Diets (Combe et al. 2016).

1. Patient education

Patient education aims to improve patient skills to accept the RA diagnosis and face RA consequences in the activities of daily living. Patient education and counseling (PEC) should be conducted by a multidisciplinary team including the rheumatologist and the other rheumatology health professionals, i.e., rheumatology nurses, physiotherapist, ergotherapist, etc... (Zangi et al, 2015) (see In-Depth Discussion 1, www.eular-onlinecourse.org). The PEC programs need to be structured and 4 main steps have been identified (Table1):

Table 1: main steps and aims of patient education and counselling:

Steps	Aims
- Educational diagnosis:	To identify the patient educational / learning needs To identify the key motivation points that could be used
- Learning objectives	To define the objectives shared by the patient and the health professionals to be addressed during the program
- Hierarchized action plan	To define the number, the order and content of the educational sessions
- Evaluation	To assess the skills, knowledge and competences that the patient should have achieved during the educational sessions To identify the potential remaining educational needs that could be targeted by future sessions.

In addition, the learning and training of specific self-administered techniques such as relaxation, hypnosis, sophrology or mindfulness could facilitate the patient ability to cope with fatigue, pain and anxiety, which are often associated with RA.

Recently, a EULAR Task Force has established overarching principles and recommendations for education for people with inflammatory arthritis (Zangi et al, 2015) (table 2):

Table 2: EULAR recommendations for patient education for people with inflammatory arthritis (Zangi 2015)

<i>Overarching principles</i>		
1. Patient education is a planned interactive learning process designed to support and enable people to manage their life with inflammatory arthritis and optimise their health and well-being		
2. Communication and shared decision making between people with inflammatory arthritis and their healthcare professionals are essential for effective patient education		
Recommendations	Category of evidence	Strength of recommendation
1. Patient education should be provided for people with inflammatory arthritis as an integral part of standard care in order to increase patient involvement in disease management and health promotion	1A-2B	A-C
2. All people with inflammatory arthritis should have access to and be offered patient education throughout the course of their disease including as a minimum; at diagnosis, at pharmacological treatment change and when required by the patient's physical or psychological condition	3-4	C-D
3. The content and delivery of patient education should be individually tailored and needs-based for people with inflammatory arthritis	1B	A
4. Patient education in inflammatory arthritis should include individual and/or group sessions, which can be provided through face-to-face or online interactions, and supplement by phone calls, written or multimedia material	1A-B	A
5. Patient education programmes in inflammatory arthritis should have a theoretical framework and be evidence-based, such as self-management, cognitive behavioural therapy or stress management	1A-B	A
6. The effectiveness of patient education in inflammatory arthritis should be evaluated and outcomes used must reflect the objectives of the patient education programme	4	D
7. Patient education in inflammatory arthritis should be delivered by competent health professionals and/or by trained patients, if appropriate, in a multidisciplinary team	3	C
8. Providers of patient education in inflammatory arthritis should have access to and undertake specific training in order to obtain and maintain knowledge and skills	3-4	C-D

2. Local treatments

Local therapies include intra articular injection, as well as orthopaedic procedures. Intra articular therapies are used in complement of systemic DMARDs when persistent synovial inflammation remains in one or a limited number of joints. Two drug categories can be injected:

- Steroids in the majority of the cases;
- Isotopic compounds less frequently, after the failure of steroid injections.

For small joints or for injections with the most powerful compounds, a fluoroscopic or ultrasound guidance is highly recommended to warrant a strictly intra-articular injection and avoid peri-articular soft tissue damage (risk of irreversible cutaneous and subcutaneous atrophy or tendon rupture if injected inside the tendon, which is strictly forbidden).

2.1 Intra-articular steroid injections

Synovial fluid aspiration, also called arthrocentesis, should be done each time when necessary, for diagnostic purposes (synovial fluid analysis) but also for therapeutic reasons. Glucocorticoids, in contrast to the other DMARDs, are also effective as an intra-articular treatment (Hetland et al. 2012). They have an anti-inflammatory effect on synovitis through induction of synovial atrophy, especially fluoride compounds (Table 1). Several preparations for parenteral use are used in clinical practice (Table 3). Although they share common physical and chemical characteristics, these molecules are not identical, and the physician should know the properties of each preparation, and respect the contraindications (Table 4) in order to reduce the risk of side effects (Table 5). Habit is another parameter that might guide the choice of the compound.

Oral information should be given to the patient, and strict measures of asepsis should be taken according to local guidelines. Some teams associate an anaesthetic such as lidocaine, but this attitude is controversial, as it might decrease the steroid efficacy (Dernis et al. 2010). The triamcinolone preparations are less soluble and therefore longer acting but have a slightly higher risk of local skin atrophy. Hence, triamcinolone hexacetonide should be used strictly intra-articularly (which makes fluoroscopic or ultrasound guidance recommended), while other steroids can be used para-articularly (with caution not to inject inside the tendon because this might induce rupture). In some cases, especially for smaller joints, image guided procedures (through X-rays or echography) might be of help to be sure the needle is inside the joint before injection (Mandl et al. 2012). Most of the authors recommend resting the joint for at least 24 hours after the injection, in order to obtain maximal effect (Dernis et al. 2010). Intra articular steroid injections can be renewed up to 3 injections per joint and per year. The failure of 3 injections make quite unlikely that a fourth one will be efficacious quite.

Table 3: main steroids used locally in rheumatoid arthritis

Generic name	Volume	Prednisone equivalence (mg)	Mean effect duration	Solubility	Crystal
Betamethasone phosphate and acetate (combination)	1 mL	40	9 days	+	+
Betamethasone phosphate and dipropionate (combination)	1 mL	46	45 days	+	+(F)
Cortivazol	1.5 mL	62.5	40 days	-	+
Hydrocortisone acetate Prednisolone acetate	5 mL	125	~ 7 days	+	-
Methylprednisolone acetate	1mL 2 mL	50 100	7 days 7 days	+	+/-
Triamcinolone acetonide	1mL (40mg) 1mL (80mg)	50 100	15-20 days	-	++ (F)
Triamcinolone hexacetonide*	2mL	50	~ 60 days	-	+++ (F)

* Strictly intra-articular use; F, fluorinated

Table 4: Absolute and relative contraindications to intra-articular steroid injections

Absolute	Relative
<ul style="list-style-type: none"> ▪ Active infection: <ul style="list-style-type: none"> ➤ Systemic ➤ Septic arthritis ➤ Local skin infection or dermatosis ▪ Surgical osteosynthesis material or prosthesis ▪ Allergy to an excipient ▪ Osteonecrosis ▪ Severe coagulation disorders* ▪ Severe immunosuppression† 	<ul style="list-style-type: none"> ▪ Diabetes‡ ▪ Hypertension‡ ▪ Patient on haemodialysis¶ ▪ Psychosis or bipolarityϕ ▪ Mild coagulation disorders**

*Especially for deep joints – **especially for deep joints. The procedures depend on local guidelines. A hemostasis specialised advice should be taken if necessary – †The risk/benefit ratio and the degree of immunosuppression should be considered for each patient – ‡Ok if equilibrated, please see table 3 – ¶ Higher risk of infection – ϕRisk of psychiatric decompensation due to the systemic effect. A specialised authorisation should be sought.

Table 5. Main adverse effects of intra-articular steroid injections.

Adverse events	Preventive measures and monitoring
Systemic: <ul style="list-style-type: none"> ➤ ↑ blood pressure ➤ ↑ serum glucose level 	<ul style="list-style-type: none"> ➤ Avoid injection if uncontrolled diabetes and/or blood pressure ➤ Monitor blood pressure and capillary glucose levels, and adapt therapy for the steroid effect period (table 1)
Infection	<ul style="list-style-type: none"> ➤ Follow strict aseptic measures according to local guidelines ➤ Do not proceed to the injection if local skin problem ➤ Do not proceed to the injection if surgical material in the joint
Microcrystalline arthritis	➤ Proceed to synovial fluid aspiration to rule out septic arthritis
Local skin atrophy or periarticular calcifications	<ul style="list-style-type: none"> ➤ Favoured by less soluble steroids and fluorinated preparations ➤ Proceed to a strictly intra-articular injection with triamcinolone hexacetonide, through image-guided injection if necessary
Tendon rupture	➤ Never inject inside a tendon
Allergic reactions	➤ Rare, usually related by excipients and not steroid itself
Minor reactions: vasovagal response, flush	<ul style="list-style-type: none"> ➤ Patient reassurance ➤ Prefer a lying flat position for the injection

2.2 Radioisotopic synoviortheses

Radioisotopic synoviortheses are rarely used nowadays, but they can be of great help, in case of persisting synovitis despite 3 steroid injections. They are contraindicated in women of childbearing age.

They consist in colloids containing radioisotopes, injected directly inside the joint, with the purpose of inducing an atrophy of the synovitis. The choice of the radionuclides depends on their physical properties and the joint to treat (table 6). Yttrium penetrates further, and should be reserved for the knee. Although radionuclides can in theory be used in the youth, because the gonadic irradiation is low, radioisotopic synoviortheses of the hip should be avoided before the age of forty. The treatment is generally well tolerated, but can lead to severe skin necrosis if not strictly intra-articularly injected. Hence, the injection should be image-guided to be sure that the needle is inside the joint, and measures of radioprotection taken to prevent complications (Brillouet et al. 2005). A corticosteroid is often added in order to prevent rare painful reactions, and the joint should be rested for at least 48 to 72 hours.

Table 6. Pharmacological characteristics of radioisotopic medications.

Radionuclide	Physical period (days)	Therapeutic indications in RA	Doses
169 Erbium	9.5	Small joints of the hand or feet	Distal or proximal interphalangeal joint: 10 to 20MBq Metacarpophalangeal joint: 20 to 40 MBq Trapezometacarpal joint: 20 to 80 MBq
186 Rhenium	3.7	<ul style="list-style-type: none"> Shoulder Elbow Wrist Hip Ankle 	Shoulder, elbow, wrist and ankle: 70 MBq Hip: 110 MBq
90 Yttrium	2.7	Knee	112 to 222 MBq per joint

MBq, Megabecquerel.

Synoviorthesis with osmic acid are nowadays very rarely used and even contraindicated in some countries, because less tolerated and more difficult and dangerous to prepare (Brillouet et al. 2005).

2.3 Surgery

2.3.1 - Generalities

The development of new treatments of RA over the two past decades have drastically reduced surgical indications and considerably modified the clinical presentation of the patients. Whatever the surgical procedure, there is a significant trend for a reduction of the need of these procedures in RA patients, which highlights the progressing efficacy of cs and bDMARD (Momohara et al, 2010) (Figure 1).

2.3.2 - Overview of the surgical procedures

The main goals of surgery are: to remove (or at least relief) pain, and to maintain or restore function which doesn't always correspond to restoration of a "close-to-normal" anatomy (*Fontaine 2014). The different surgical techniques are:

- Synovectomy, ideally performed under arthroscopy (shaving and joint lavage), after the failure of steroid injections; tenosynovectomy can also be performed in case of persistent tenosynovitis which exposes the patient to a significant risk of tendon break;
- Tendon rupture repair
- Stabilization surgery to prevent further joint dislocation or tendon break (e.g., Sauve-Kapandji procedure in the wrist) (Figure XYZ) (Figure 2).
- Finally, total joint replacement when cartilage and subchondral bone loss is too important.
- Surgery of nervous complications

Figure 1: Biannual number of surgeries for Japanese outpatients with rheumatoid arthritis (RA) participating in a single institute-based large observational cohort (IORRA) (Momohara et al, 2010). Data on the number of outpatients and operations were collected from April to May and October to November each year from 2001 to 2007. The number of outpatients is limited for valid response. The joints for arthroplasties mainly included wrist, metacarpophalangeal, elbow and metatarsophalangeal joints. The joints for arthrodeses were interphalangeal, trapeziometacarpal, wrist and ankle joints.

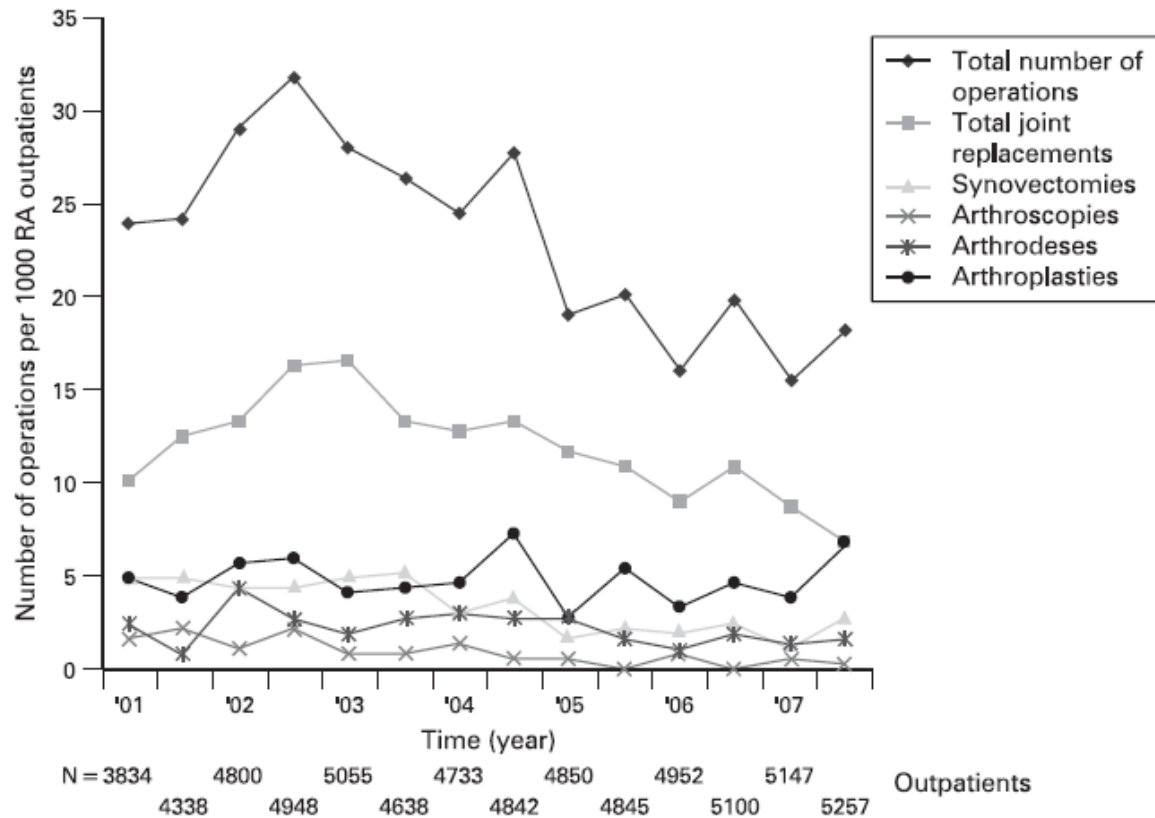
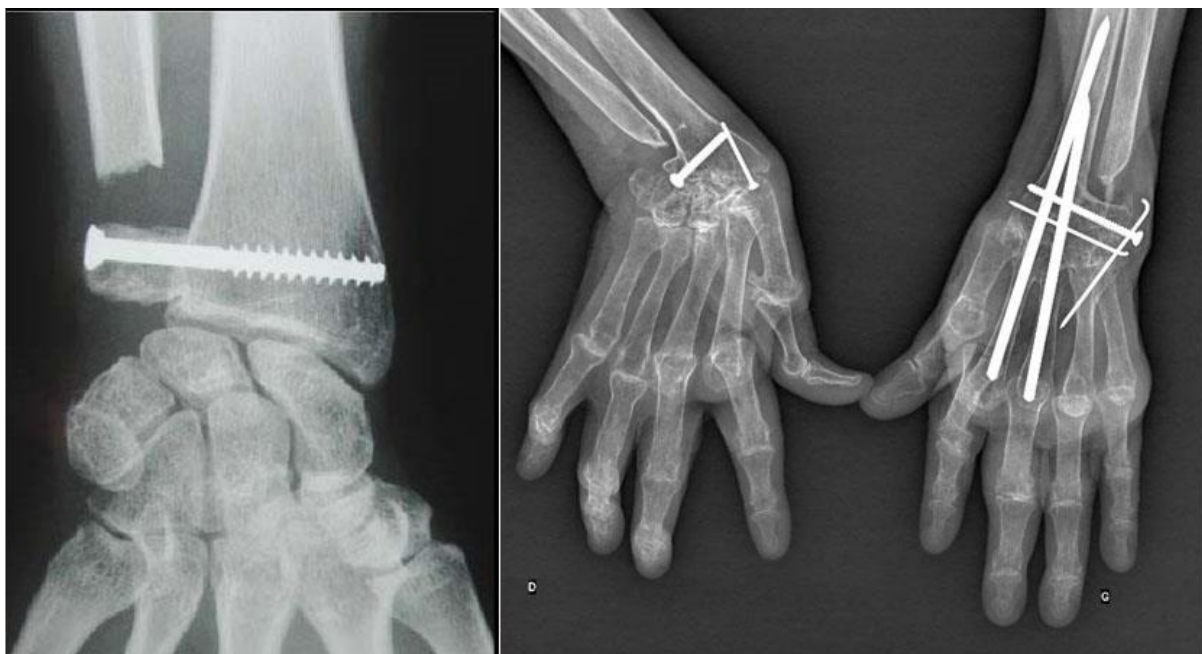


Figure 2. Arthrodesis of the left wrist, and distal radioulnar surgery with Sauvé-Kapandji technique of both wrists.



2.3.3 - Cervical spine management

Involvement of the cervical spine is important, because of the possible fatal complications, and often begins during early stages of the disease, especially during the two first years (Bouchaud-Chabot A, Lioté F. 2002; Zikou et al. 2005). Cervical spine involvement occurs in over half of patients with rheumatoid arthritis (RA). The most common abnormality is atlanto-axial dislocation, followed by atlanto-occipital arthritis with cranial settling and by lesions of the lower cervical spine. Cervical spine involvement usually occurs in patients with severe RA (Bouchaud-Chabot A and Lioté F. 2002). Pain and neurological evidence of spinal cord injury are the main symptoms. The presence of symptoms is not correlated with the severity of radiological abnormalities. Computed tomography and magnetic resonance imaging provide detailed images of the bone and spinal cord lesions. Because the course is unpredictable, conservatively treated patients usually require regular follow-up (Bouchaud-Chabot A and Lioté F. 2002).

Surgical indications are nowadays rare. Surgery is in order in patients with pain unresponsive to major narcotics or with progressive neurological impairment (Table 7 and 8) (Bouchaud-Chabot A and Lioté F. 2002). The choice between the anterior and the posterior route depends on the experience of the surgical team. It is reasonable to stabilize the spine before the development of cranial settling or major neurological loss (Ranawat's stage III). The good functional results of spinal surgery are frequently overshadowed by major impairments related to severe peripheral joint disease. Safety is acceptable when somatosensory evoked responses are monitored intraoperatively. Surgery can provide substantial improvements in symptoms, particularly pain.

Table 7. Ranawat's scale from pain (adapted from Bouchaud-Chabot A and Lioté F. 2002)

Stage 0	No pain
Stage I	Intermittent pain responsive to standard analgesics
Stage II	Intermittent pain partially responsive to standard analgesics – need for immobilization by a cervical collar
Stage III	Incapacitating continuous pain unresponsive to analgesics

Table 8. Ranawat's scale for neurological involvement (adapted from Bouchaud-Chabot A and Lioté F. 2002)

Class I	No neurological abnormalities
Class II	Subjective impression of muscle weakness with brisk deep tendon reflexes and dysesthesia
Class IIIA	Moderate objective motor loss leaving some degree of self-sufficiency and/or posterior cord syndrome
Class IIIB	Severe neurological impairment with complete loss of self-sufficiency

2.3.4 - Planification of an orthopaedic surgery

Patients with RA are considered “more fragile” for several reasons: psychological difficulties, higher risk of infection (due to RA per se, but also to treatments, in particular biological DMARDs), more fragile skin (mainly owing to steroids) with a higher risk of post-operative necrosis and complications, more fragile bones (osteoporosis and endosteal resorption) (*Fontaine 2014). Local guidelines for the peri-operative management of pharmacological treatment can be found in each country (see Module 4, www.eular-onlinecourse.org). The majority of them recommend maintaining methotrexate in case of scheduled surgery, because the risk of infection is low. The interruption of other DMARDs, especially biologics, depends on their half-life (Table 9).

Table 9: Half-lives and required interruption of the drug treatments before surgery.

Peri-operative septic risk			Low	Medium	High	Very high
<i>Half-life</i>			<i>2 half-lives</i>	<i>3 half-lives</i>	<i>4 half-lives</i>	<i>5 half-lives</i>
csDMARD						
	Methotrexate	10 hours	Can be continue without discontinuation around surgery			
	Leflunomide	15-18 days*				
	Salazopyrine	6-10 hours				
	Antimalarial	40 days				
bDMARDs						
TNFi	Etanercept	70 hours	10 d ~ 2 w	15 d ~ 2 w	20 d ~ 3 w	25 d ~ 4 w
	Infliximab	~10 days	20 d ~ 3 w	30 d ~ 4 w	40 d ~ 6 w	50 d ~ 8 w
	Adalimumab	~15 days	30 d ~ 4 w	45 d ~ 6 w	60 d ~ 8 w	75 d ~ 10 w
	Certolizumab	10-15 days	30 d ~ 4 w	45 d ~ 6 w	60 d ~ 8 w	75 d ~ 10 w
	Golimumab	10-15 days	30 d ~ 4 w	45 d ~ 6 w	60 d ~ 8 w	75 d ~ 10 w
Anti-IL6R	Tocilizumab	12-15 days	~ 30 days	~ 45 days	~ 60 days	~ 75 days
CTLA4-Ig	Abatacept	15 days	~ 30 days	~ 45 days	~ 60 days	~ 75 days
Anti-CD20	Rituximab	20-22 days	~ 40 days	~ 60 days	~ 80 days	~ 100 days

csDMARDs, conventional synthetic Disease Modifying Antirheumatic Drug; bDMARD, biological DMARDs; TNFi, TNF inhibitors; anti-IL6R, anti-Interleukine 6 receptor; CTLA4-Ig, recombinant fully human protein CTLA-Immunoglobulin; anti-CD20, monoclonal chimeric antibody against Cluster Differentiation 20 (B lymphocytes); d, days; w, week.

*Leflunomide has long persistence because of entero-hepatic circulation. Hence, its interruption is not adequate, but some author proceed to a wash out with cholestyramine in case of high septic risk surgery.

The physician should aim at the lowest glucocorticoids dosage, as they can slow down skin cicatrisation. The therapeutic decisions should ideally be taken in multidisciplinary staffs, between the surgeon, the rheumatologist, the radiologist and if possible the rehabilitation specialist.

3. Rehabilitation and other non-drug therapies

Although rehabilitation's place in the therapeutic strategy has considerably changed over the past 15 years because of the development of very efficacious drug therapies, it is still integral part of the therapeutic arsenal. It is very useful and indicated at all stages of the disease (Combe et al. 2016). There is no real contraindication, although intensity should be modulated according to the evolution of the disease. The objectives are to prevent or limit the deformations, to maintain and improve muscular trophicity, joint mobility and to prevent ankylosis (Combe et al. 2016), with the ultimate goals to improve the personal and social quality of life, to cope with pain disability and to allow maintenance of work ability. Rehabilitation should be lead by a multidisciplinary team of different health professionals: the physiotherapist, the occupational therapist, the podiatrist, and the rheumatology nurse specialist/practitioner (see In-Depth Discussion 1, www.eular-onlinecourse.org).

3.1 Orthoses and splints

Orthoses and splints, although less used nowadays, can play a very important role for pain relief and prevention of joint deformation (Combe et al. 2016) (Figure 3).

Different devices can be prescribed:

- standard devices, often semi-rigid, made of highly resistant fabric;
- or rigid tailor-made devices, made of heat-formable material in order to be perfectly adapted to joints (whatever their deformities) and comfortable to wear for the patients.

Some of these devices are to be worn when the person is inactive (rest orthosis) to facilitate joint rest and tendon/muscle relaxation during RA flare, notably at night. Others are made to be worn during physical activities (function orthosis) in order to make the joint stable during these activities and limit pain and risk of further dislocation. The sooner they are made, the better it is, in order to prevent deformations.

Figure 3. Rest orthosis of the wrist and hand.



3.2 Plantar orthoses

Foot problems are common in patients with RA and the role of the podiatrist is to reduce pain, maintain/improve function and mobility, and to protect the skin and soft-tissues of the foot (see In-Depth Discussion 1, www.eular-onlinecourse.org). Three options are possible:

- Adequate footwear: shoes should be large enough around the MTP joints and flexible enough to take into account toe deformities. In case of joint instability or subluxation, the insole should be more rigid to reduce the mechanical demand on the damaged joint(s).
- Specific custom insole, made in heat-formable material, could be prescribed to homogenize and improve the ground support of the feet. In addition, they could reduce the pressure and mechanical demand on the most damaged foot joints.
- Finally, tailor-made orthopaedic shoes can constitute the only option when the feet are severely damaged and dislocated due to RA.

The podiatrist will provide specialist wound care management for patients with foot ulceration

3.3 Physiotherapy

The physiotherapy should be undertaken as soon as possible in order to prevent deformity or ankylosis, which are difficult to correct once established (Combe et al. 2007). It should be global and adapted to each patient (“personalised”), and the patient should be clearly involved (Zangi et al. 2015). It should be undertaken by specialised physiotherapists and occupational therapists who will teach the patient daily exercises, and *participate to patient education*.

3.3.1 - Physical treatment

Physical treatment such as fangotherapy, cryotherapy, paraffin therapy or balneotherapy can be of help to relieve pain and symptoms, although the level of proof of the efficacy on the disease course is insufficient (Verhagen et al. 2015). In addition, massages of painful anatomic regions could enable the reduction of muscle and tendon contractures and careful passive mobilization of the joints could improve their range of motion.

3.3.2 – Self-exercise learning and training

Physiotherapists actively participate to patient education and can teach them specific self-exercise to:

- reduce stiffness in the morning (Figure 4),
- improve range of motion of the joints,

- strengthen muscles by isometric exercises (muscle contractions with no movement of the joints or limbs) in order to maximize joint stability.

3.4 Occupational therapy

Occupational therapy could be part of rehabilitation or a complementary offer on top of physiotherapy and rehabilitation. Its aim is to help patients performing their usual physical activity, either domestic, leisure or professional.

Occupational therapists have to take into account the nature of patient usual activities of daily living. On this basis, they propose to RA patients specific exercises and training to improve their skills to use their body and joints – especially hands – optimally with regards to their damaged joints, and thus to facilitate their social participation either at home or on the workplace.

Finally, occupational therapists can propose multiple technical aids, among which:

- orthoses (see above);
- specific hand grips for kitchen utensils, kitchenware, pens or keys;
- adaption of the home for doorknob, tap or access to the bath tub;
- adaptation of the work place such as chair and desk adaptations, or more ergonomic keyboard;
- walking sticks, rarely walkers or wheel chair.

Figure 4. Daily exercises against morning stiffness. (Courtesy C Larnicol, A Lambert and P Louvrier)

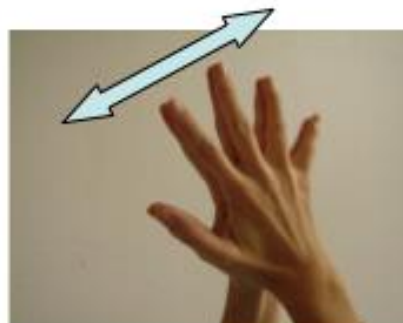
A. Shoulders. Elbow to the body and bent at 90°, move your forearms to the outside during inspiration. Hands joined, elbows in extension, elevate your arms.



B. Elbows. Hands joined, arms parallel to the body: bring your hands to your breast by bending your elbows. Hands joined on the thigh, arms and forearms in extension: lift your arms while putting your elbows in extension as far as possible.



C. Hands and wrists. Hands joined, fingers not crossed: move your fingers from right to left. Same position: separate your fingers then retighten them.



D. Hands and wrists. With the help of the other hand, gently roll up your fingers, and then your wrists. Do little circles with the too thumbs. When the hands and fingers are too tender or stiffened, these exercises can be done under warm water.



E. Hips and knees. Lying down, feet slightly apart, do “wipers” movements with your feet. Bring a knee to the chest with the help of your two hands. Extend your knee as far as you can while bringing the tip of the foot in your direction.



F. Feet. Do little circles with the top of your feet. Bend and extend your ankles and your toes.



4. Diet

Diet in the treatment of RA is a controversial but important issue that implies at first several remarks:

- studies have so far failed to give clear evidence that a particular diet (or dietary supplements) could have a direct effect on disease activity and symptoms (pain, joint swelling, natural history), although several pathophysiologic hypothesis have been advanced;
- cardiovascular risk is increased in RA (in link with increased risk of diabetes, hypertension and hypercholesterolemia), and muscular loss and osteoporosis are frequent in RA, owing to several factors (inflammation and increased catabolism, glucocorticoids). An adapted alimentation, especially in case of chronic glucocorticoids intake, could help to prevent or/and restore muscular and bone trophicity and decrease cardiovascular risk. The appropriate assessment and advice of a dietetician might be of help (see In-Depth Discussion 1, www.eular-onlinecourse.org);
- although no direct link between RA and obesity exist (on the contrary, increased catabolism induces rather weight loss), RA can occur in obese patients. In this case, heavy weight can worsen weightbearing joint destruction, and once again the help of a dietician is important.

4.1 Can a particular diet directly influence disease activity (pain, joint swelling, natural history) in RA?

Many theories (sometimes seducing) have been generated, but clear scientific evidence is lacking to support them.

4.1.1- Fasting

Several authors have suggested that fasting could decrease inflammation, and thus improve osteoarticular symptoms (Kjeldsen-Kragh et al, 1991). However, no significant benefit on the long term has been demonstrated, and fasting on a long period can be very dangerous and induce nutritional deficiencies.

4.1.2-The exclusion of one or several nutrients

Besides fasting, several authors have suggested that the exclusion of one or several nutrients mainly dairy products, gluten and/or red meats, could also improve disease activity and symptoms (Seignalet, 1992). These hypotheses are based on individual observations in some patients who describe an improvement on symptomatology when suppressing the identified nutrient, and a degradation of pain and symptoms when it is reintroduced. However, studies trying to evaluate the effect of different diets in cohorts of patients with RA did not show consistent results, and their interpretation is not easy (Hagen et al, 2009). Mediterranean diet seems however to have the more reproducible results on disease activity (Smedslund et al, 2010), with a now clearly establish benefit on cardiovascular complications - especially myocardial infarction- (Serra-Majem et al, 2006), which are precisely the first cause of mortality in RA.

4.1.3 - The supplementation in polyunsaturated fatty acid

Supplementation in omega-3 and -6 polyunsaturated fatty acid (through dietary complements often extracted from fish oil) has been proposed, because these unsaturated fatty acids have an anti-inflammatory effect. However, results from randomised controlled are disappointing, because they often require high doses for a too-moderate clinical effect (Goldberg, 2007). Nevertheless, they seem to be harmless, and they can be prescribed to patients who are willing, although their price is sometimes high.

4.1.4 – Other supplementation

Probiotics have been proposed, as there seem to be a dysregulation of gut microbiota in RA (like in other rheumatic disease), but to our knowledge only preliminary results exist in animal models (Abhari et al, 2016), and no concluant randomised controlled trials has been led. It has been suggested that Vitamine D could have immunomodulatory effects in autoimmune diseases (Ishikawa et al, 2016), but the impact of its supplementation on RA activity has not been proven. However, it is essential to optimise vitamine D serum levels, to prevent secondary osteoporosis. Oligo-elements supplementation (zinc, copper, vitamine C, selenium...) has not shown efficacy on disease activity in randomised controlled trials.

Diet and Rheumatoid arthritis, summary points:

- ➔ Patients should have a balanced diet
- ➔ Patients should not fast.
- ➔ Clear scientific evidence is lacking for the recommendation of the exclusion of specific nutrients, such as gluten (except concomitant medically confirmed Coeliac Disease), dairy products or red meats.
- ➔ Mediterranean diet has not proven its efficiency in the control of RA activity; however, it has shown clear benefit in prevention of the cardiovascular risks, which is the main cause of mortality in RA.
- ➔ Scientific evidence is lacking for the systematic prescription of polyunsaturated fatty acids; however, they do not seem to have side-effects, and can be safely prescribed if the patient is willing, having in mind their high price.
- ➔ No “immunomodulatory” (probiotics, vitamin D, oligo-elements) molecule has been identified so far; however vitamin D deficiency can have an impact on secondary osteoporosis, and should be hence corrected.

4.2 The role of the dietitian in the management of RA

The dietitian is an essential health professional for the management of RA, especially required in several situations:

- when glucocorticoids are prescribed, especially if medium to high doses, in order to prevent metabolic complications (hypertension, diabetes, hypercholesterolemia, osteoporosis, etc see In-Depth Discussion 2, www.eular-onlinecourse.org). The dietitian will play an important role in patient education, and prescribe an adapted diet low in quick-release carbohydrates, fat and salt;
- for the prevention and treatment of secondary osteoporosis, through the calcium intakes evaluation, and eventually advice and supplementation;
- in very active and catabolic flares. The dietitian will optimise the patient renutrition, through nutritional complements if needed.

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5

module

EULAR on-line course on Rheumatic Diseases

Immunology and the rheumatic diseases

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LEARNING OUTCOMES

- To describe and explain a basic understanding of immunology that is of direct relevance to the pathogenic pathways that underpin autoimmune rheumatic disease
- To describe and explain the cellular and molecular components of the innate and adaptive immune systems, with emphasis on the role and functions of antigen-presenting cells, and cellular and humoral immunity
- To describe and explain how these systems interact to provide robust host defence mechanisms
- To list and characterise the cell subsets and inflammatory mediators contributing to immunity
- To evaluate how aberrations of immunity may predispose to chronic inflammatory immune-mediated pathology

1 Introduction

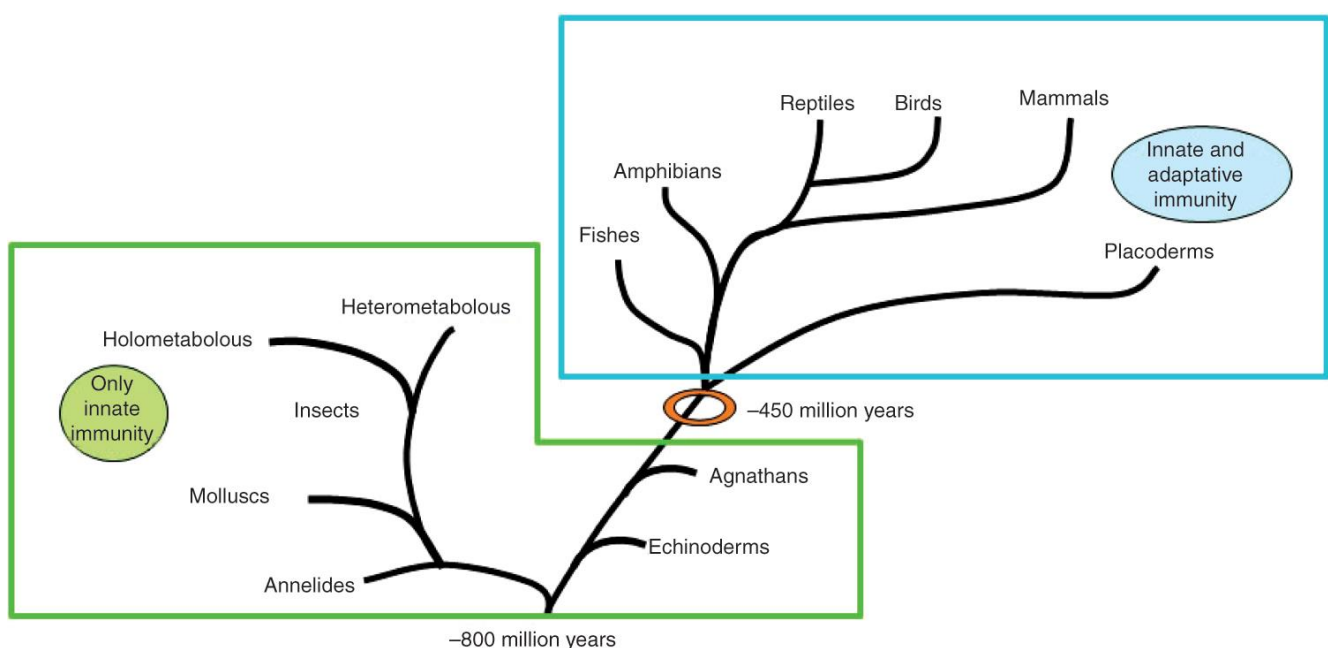
Rheumatologists commit much of their working life to the care of patients with immune mediated chronic inflammatory disease. Immune and inflammatory reactions underpin these diseases, and so it has become a priority to understand the molecular and cellular basis of the immune response in anticipation that, in the longer term, it will facilitate more accurate diagnosis and inform therapeutic decision making for this complex and heterogeneous group of patients. This module is designed to provide simple and basic knowledge of immunology of relevance to the pathogenic pathways that underpin autoimmune rheumatic disease. We have purposefully not provided a detailed description of the pathogenesis of each immune mediated inflammatory disease, since this will be discussed in depth in subsequent modules.

The inflammatory reaction brings into play both non-specific and highly specific immune mechanisms that couple innate and adaptive immune systems at an anatomical and functional level.

2 What does the immune system do?

Our immune system has evolved to protect us against attack from the universe of foreign pathogens that make up our environment. All living organisms, from the most basic plant to mankind, possess intricate self-defence systems (figure 1). Over the course of evolution, the immune system has become highly sophisticated. For example, the flies in your garden have acquired the oldest immune system (the innate immune system), while species of fish have evolved with an additional, more sophisticated system (the adaptive immune system). Depending on the species, each system has diversified to permit the organism to adapt to its environment.

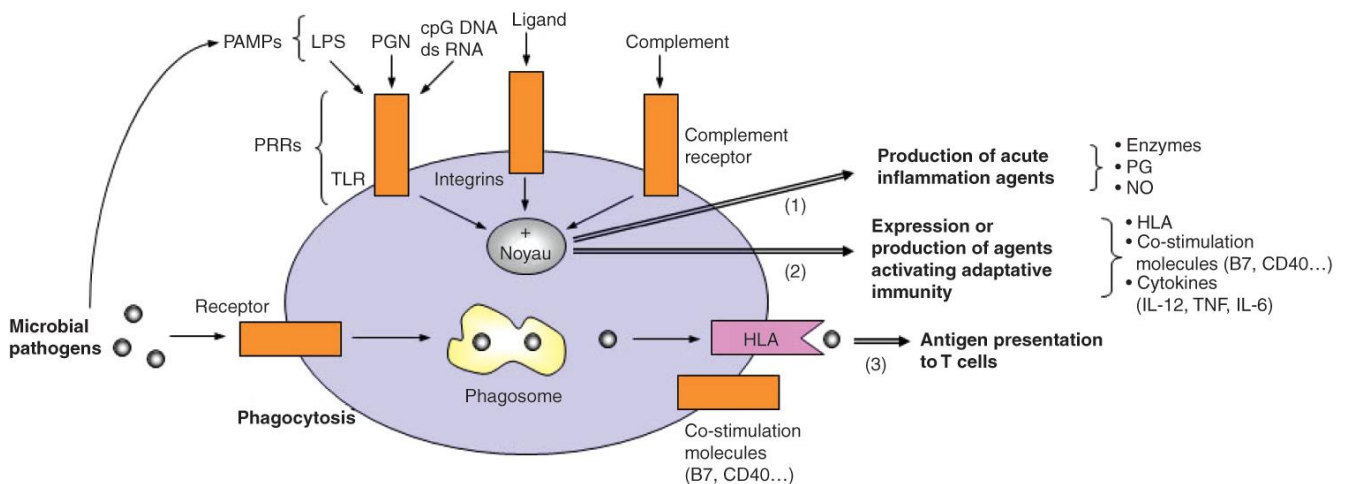
Figure 1 *Phylogeny of the immune response.*



Broadly speaking, every human has two interdependent defence systems: the innate immune system, and the adaptive immune system.

The innate immune system is a succession of immediate responses, which can eliminate external attackers rapidly. This immediate response relies on the instantaneous digestion (phagocytosis) of the 'invaders'. The innate immune system is activated when it recognises molecular patterns that are expressed by prokaryotic organisms (eg, bacteria); these patterns are not expressed by eukaryotic cells like host tissue. Such structures, such as lipopolysaccharide (LPS) or double-stranded RNA, which are only present in bacteria and retroviruses respectively, are recognised by receptors already present in flies. The innate immune system can be activated through the recognition of a variety of such highly preserved microbial constituents that are abundant and shared by numerous species of 'primitive' (prokaryotic) organisms (figure 2). This is a relatively simple and elegant way for the immune system to discriminate between self and non-self, and represents a means by which the immune system can respond rapidly and strongly to invading microorganisms. Although encounter with microorganisms can prime the activation of innate immune cells during follow-up encounters this priming of innate immune system is relatively limited and non-specific and will not result in a response to a second encounter by the same microbe in a more specific way.

Figure 2 A macrophage; as an illustration of how innate immunity senses pathogen associated molecular patterns. CpG, sequence of Cytosine and Guanine in a DNA strand; ds RNA, double stranded RNA; HLA, human leucocyte antigen; IL, interleukin; LPS, lipopolysaccharide; NO, nitric oxide; PAMPs, "pathogen-associated molecular patterns"; PG, prostaglandin; PGN, peptidoglycan; PPRs, "pattern recognition receptors"; TLR, Toll-like receptor; TNF, tumour necrosis factor.

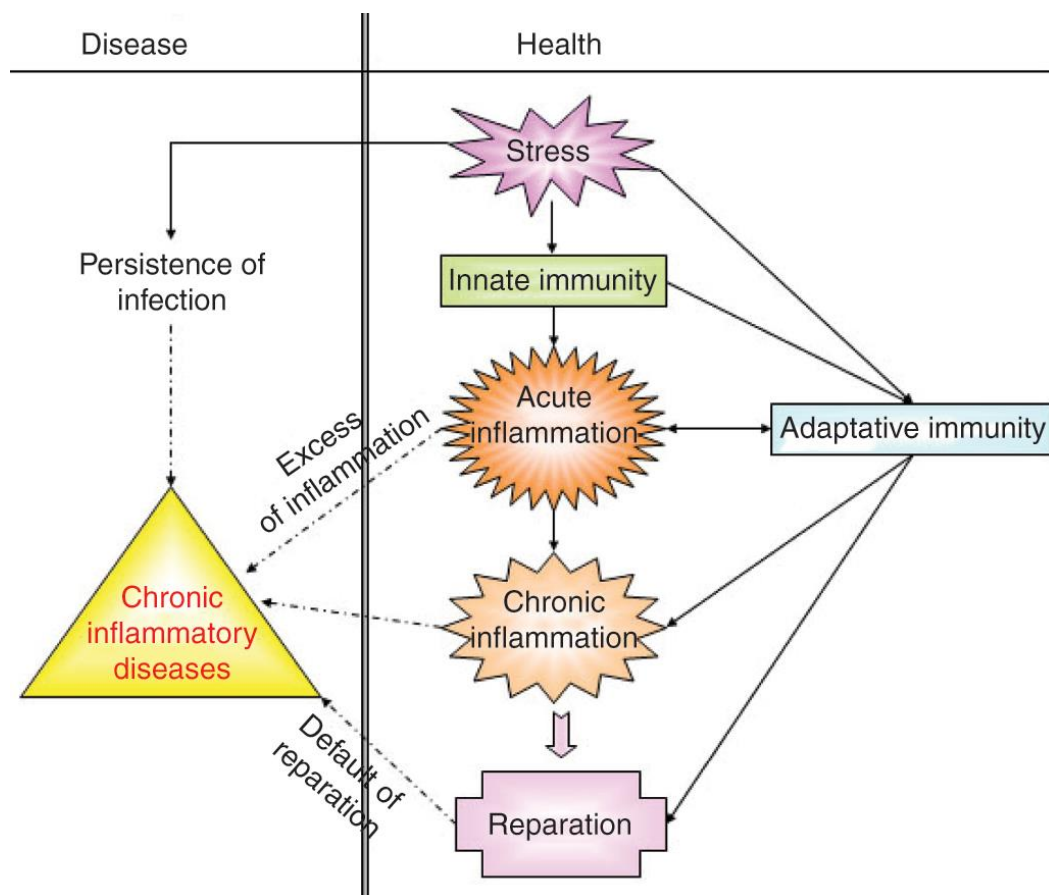


Therefore, next to the innate immune system, another 'immune arm' is present, the adaptive immune response. The adaptive immune response is relatively slow in responding to an invader when first encountered. The cause for this slow reaction is found in the fact that specific cells belonging to the adaptive immune system, the T and B cells, first need to become activated in draining lymph nodes. Here, these cells first divide before they can exert their effector functions. In contrast to the innate immune system, the cells belonging to the adaptive immune system can recognise pathogens in a highly specific fashion. Another

important difference between innate and adaptive immunity is the ability of the adaptive immune response to form a much stronger immunological memory, that allows the highly specific adaptive immune cells to respond as rapid as innate immune cells during a repeat infection. Memory T and B cells are the basis for the success of vaccination against deadly infectious diseases such as smallpox, as they can respond in a highly specific and rapid fashion upon encountering the pathogen, once they have been activated upon vaccination. In doing so, they can eradicate the invading pathogen before it can exert its devastating effects.

Analogous to many living systems, the immune system must function to achieve an equilibrium that will favour host defence against foreign pathogens, while protecting host tissues from collateral damage. To this end, immunity has both strengths and weaknesses. Therefore, a loss in this delicate equilibrium may induce modifications that are likely to become pathological. As an example, an immune deficiency, while seemingly subtle, may promote the emergence of serious infection (often due to a particular species of organism) or, occasionally, neoplastic disease. Conversely, a sustained and unbridled immune response, or a 'badly adapted' immune reaction, may trigger allergic inflammatory and autoimmune disease. The yin and yang of the immune system are the two facets of a complex system that must remain in equilibrium (figure 3).

Figure 3 Sensing environmental cues in health and disease.



3 Molecular and cellular basis of the immune system

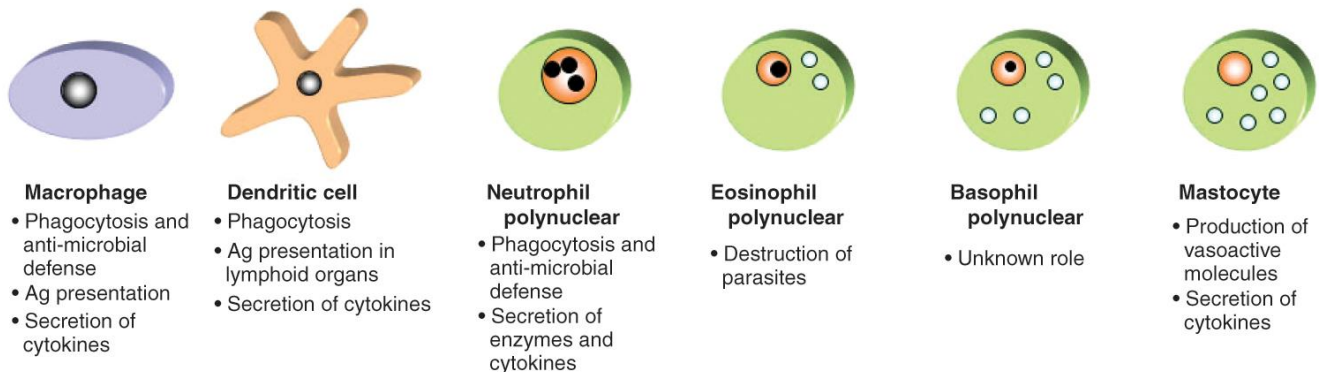
3.1 The cellular players in immunity

Before demonstrating how the score is 'set to music', it is appropriate to first mention the partners required for this 'immune symphony'.

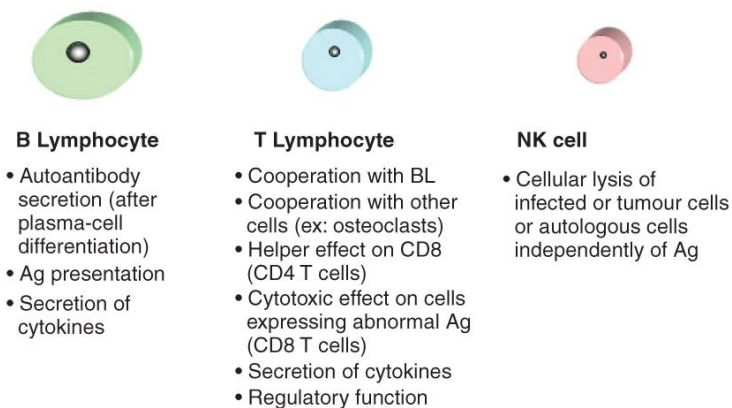
The 'conductor(s)' are those who set the musical score by adding a personal note to this system. These are the central lymphoid organs (thymus, bone marrow), where the immune cells (T and B cells) undertake basic training, and secondary central lymphoid organs (spleen, lymph node, mucous membranes), where 'remedial courses' are conducted. The 'musicians' are the innate immune cells (polymorphonuclear leucocytes, monocyte/macrophages, dendritic cells, mast cells, and natural killer (NK) cells) and those of the adaptive immune system (T and B cells) (figure 4). Only cells of the adaptive immune system require training, whereas innate immune cells have pre-programmed functions. Cells of the immune system are differentiated from each other by different surface molecules. The molecules used for this purpose are described in a protocol termed 'cluster of differentiation' (CD). Every immune cell has specific CD molecules—for example, a cytotoxic T cell is CD3+ CD8+ CD45+.

Figure 4 The cellular basis of immunity. Ag, antigen; NK cell, natural killer cell.

A. Myeloid-derived cells



B. Lymphoid-derived cells



The ‘instruments’ could be viewed as substances synthesised in a highly coordinated manner that enable communication between cells. Communication is received through high affinity receptors that are capable of interacting with specific ligands, such as soluble molecules (cytokines and chemokines) that exercise different functions.

This symphony is performed in a grand concert hall—the human body—which consists of main pathways (circulatory and lymphatic systems), ‘special dressing rooms’ (lymphatic organs), ‘sanctuary’ areas (eg, the eye, testicle), and ‘dedicated organs’ that are specific (eg, skin, joints and kidney).

Next, it is appropriate to discuss in a little more detail, some of the partners required for this ‘immune symphony’.

3.2 The immune cells have one common cellular ancestor

The bone marrow is the ‘progenitor generating centre’ of the immune system since most immune cells originate there before migrating to the peripheral blood, lymphoid organs and thymus.

In the bone marrow, pluripotent precursor cells give rise to:

- myeloid progenitor cells that give rise to the majority of innate immune cells, including polymorphonuclear cells (various types of granulocytes), cells of monocyte/macrophage lineage and dendritic cells, and
- lymphoid progenitor cells that give rise to T and B cells and a specific cell population called NK (natural killer) cells (figure 5A).

3.3 Education of the immune cells in the central lymphoid organs

The maturation of T and B cells occurs, respectively, in the thymus and bone marrow, hence their description as T cells (thymus) and B cells (bone marrow; originally the ‘B’ was derived from the bursa of Fabricius, an organ described in chickens). This maturation consists of stages described as a process of selection of lymphocytes intended to preserve only those cells likely to respond robustly to environmental ‘aggressors’ without attacking the components of the host organism. This latter point is fundamental. In fact, this phenomenon of ignorance or non-responsiveness to self, termed immunological tolerance, is indispensable for avoiding ‘auto-aggression’, which is thought to be the process that underpins autoimmune diseases. The suppression of ‘undesirable’ lymphocytes occurs by a number of processes, including the induction of programmed cell death (apoptosis). Mature lymphocytes, after having received their education in bone marrow and thymus, then leave the central lymphoid organs via the bloodstream in search of their antigen in the peripheral lymphatic organs.

However, as not all antigens recognised by T cells and B cells are expressed in the thymus and bone marrow, respectively, a second system is in place that prevents the induction of potentially harmful responses against self-antigens. Here, dendritic cells play an important role. Dendritic cells are cells with an exquisite capacity to take up antigens in organs and tissues for presentation to T cells in draining lymph nodes. Under normal, homeostatic conditions, the dendritic cells will stay immature and will present antigens under non-inflammatory conditions. Under these conditions, dendritic cells instruct the T cell not to react to the antigens they present either by forcing the T cells to die, or by instructing them to become regulatory T cells—T cells with immune-suppressive functions. The ability of immature dendritic cells to educate the T cells to be tolerant towards antigens of the host (auto-antigens) is vital to the host as many antigens we encounter should not elicit inflammatory reactions. For example, antigens expressed during pregnancy (from the child) or present in the food we eat are in this way prevented from an undesired immune attack.

4 The immune system in action

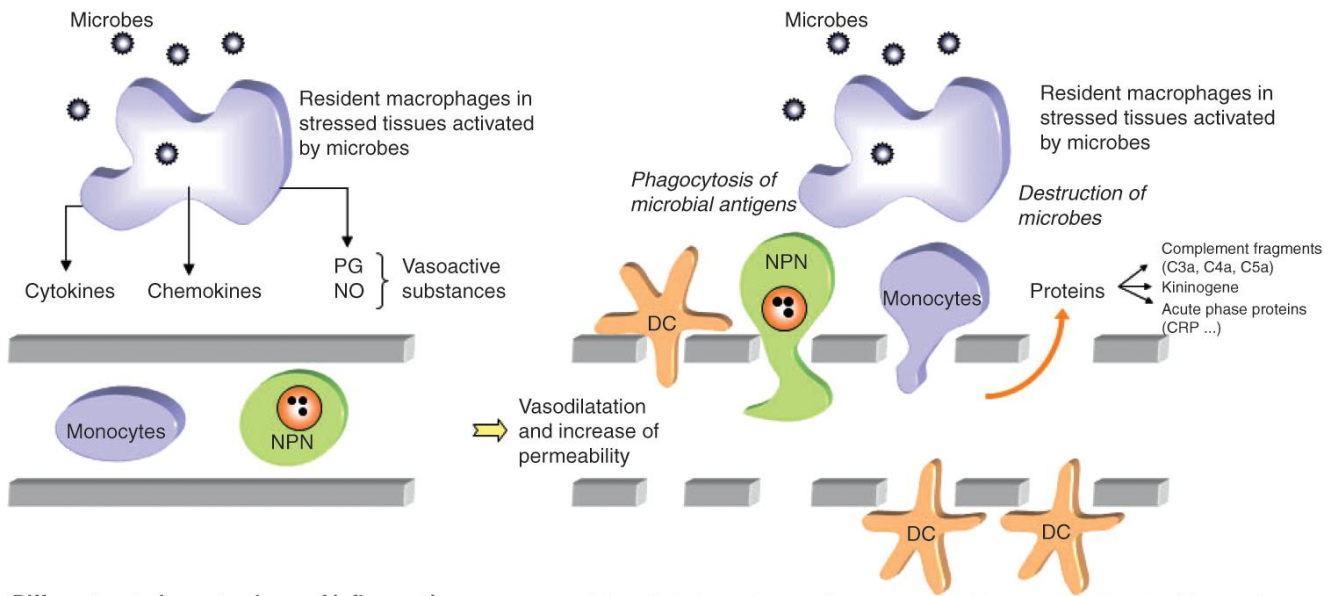
One way to understand the function of the immune system is to analyse how the most fundamental of responses—defence against pathogens—comes about.

4.1 What happens when a pathogen gains access to the body?

In a patient that is infected by a pathogen, the first line of defence is formed by the innate immune system (figure 5). Firstly, it involves a mechanical defence represented by epithelial barriers, such as skin and mucous membranes. When microbes encroach this barrier, they can induce an inflammatory reaction characterised by a wide range of different inflammatory mediators and selective cell types.

For tissues 'under attack', activation of stromal cells such as epithelium and fibroblasts and resident immune cells (macrophages) is the first step. These cells are activated through recognition of microbe associated molecules known as pathogen-associated molecular patterns (PAMPs), by specific receptors termed pattern recognition receptors (PRRs) (figure 6). These PRRs include well characterised sensors such as those of the Toll-like receptor (TLR) family and NOD-like receptors. Activation of stromal cells and resident macrophages leads to the release of numerous substances, which serve to induce vasodilatation, an increase in the capillary permeability, an influx of additional phagocytic blood cells (dendritic cells, monocytes and polymorphonuclear cells), as well as the generation of inflammatory mediators (box 1).

Figure 5 Initiation of the innate immune response. Ag, antigen; CRP, C reactive protein; DC, dendritic cell; NO, nitric oxide; NPN, normal polymorphonuclear neutrophils; PG, prostaglandins; TL, T lymphocytes.



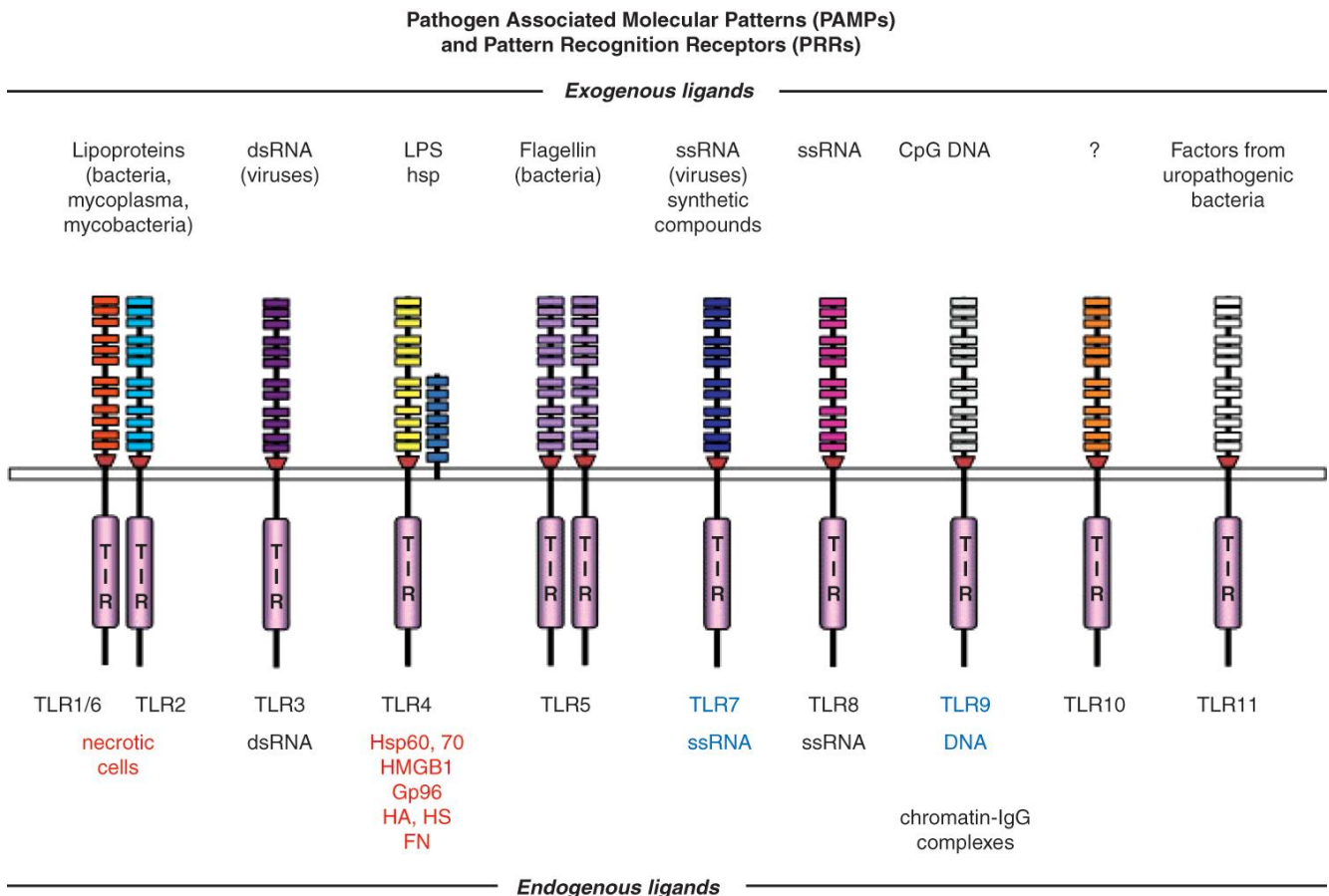
Different parts in acute phase of inflammation:

1) Microbes activate tissue macrophages by different mechanisms (figure 2). These macrophages secrete different substances vasoactive and pro-inflammatory (cytokines) and other substances (chemokines) attracting other phagocytosis cells (NPN ...)

2) Vasodilatation and increase of vascular permeability allow transfer in infected tissues of proteins (complement, kininogen ...) and of cells specialised in phagocytosis (DC, monocyte, PNN ...)

3) This phagocytosis allows destruction of microbes but also capture of antigens by DC, and macrophages which are reaching lymph nodes by efferent vessels. In these lymph nodes, these Ag-presenting cells (APC) educate and stimulate specific TL.

Figure 6 The different Toll-like receptors (TLRs) and their ligands. LPS, lipopolysaccharide.



These resident and infiltrating innate immune cells and their released substances exert potent antimicrobial effects. Microbes are killed by a variety of mediators, such as proteases (protein cleaving enzymes), lysozyme (an enzyme disrupting the bacterial cell wall) and lactoferrin (a protein that disrupts bacterial metabolism by sequestering iron), in a process assisted by reactive oxygen species (box 1). These mediators can become active after bacteria are taken up inside cells in a process called phagocytosis. They can also be active against microbes as part of DNA networks extruded by innate immune cells in a process called 'extracellular trap formation'. Other mediators, such as natural antibacterial peptides, alarmins and complement, all enhance bacterial killing, activate the surrounding stroma and attract infiltrating immune cells (figure 7). Mast cells, present in tissues together with their products, can also make significant contributions to increasing vascular permeability during the immediate/early phase of the inflammatory response. NK cells kill cells infected by virus.

Box 1 Inflammatory mediators

All these mediators are secreted to defend the organism by eliminating pathogens. However, when they are produced in excessive quantities or when they are hardly eliminated, they may become toxic to the organism.

- **Reactive oxygen species.** These are free radicals derived from oxygen such as superoxide anions (O_2^-) and hydrogen peroxide. In phagocytes, reactive oxygen species are produced in large quantities by the enzyme NADPH oxidase for use in oxygen-dependent killing mechanisms of invading pathogens.

- **Nitric oxide (NO)**

A constitutive NO synthase regulates certain physiological cellular phenomena by production of nitric oxide (NO). If an attack occurs, additional large NO quantities are synthesised due to an induced NO synthase (iNOS). Nitric oxide will then increase vasodilatation and capillary permeability and exert significant toxic cellular effects. The main purpose of this is to eliminate exogenous pathogenic agents.

- **Cell enzymes**

Activated polynuclear cells as well as other cells (synoviocytes, chondrocytes, etc) release numerous enzymes (collagenase, elastase, phosphatase, hydrolase, cathepsine, myeloperoxidase), which play a physiological role in tissue remodelling and homeostasis as well as antibacterial defence.

- **Natural antibacterial peptides (defensins)**

This newly discovered group consisting of highly preserved mediators (from insects to mankind) participates in the innate immune response. Their role in defence and potential involvement in inflammatory diseases is currently under investigation.

- **Vasoactive amines**

Histamine, serotonin and kinins (bradykinins) are vasodilatory, increase the capillary permeability and facilitate smooth muscle contraction.

- **Complement proteins**

The complement system is an important part of the innate immune defence, because it is activated rapidly and is able to provide a powerful answer to infection through a cascade of reactions, amplifying the activity of several functions of the complement system. These functions include chemotaxis, opsonisation and lysis of bacteria. The complement system can be activated via different routes (the classical, alternative and lectin pathway), enabling the synthesis of, for example, opsonising fragments ($C3b$) or anaphylatoxins ($C3a$, $C5a$) that induce the release of histamines (figure 9).

- Coagulating proteins

Factor XII (Hageman factor) activates kallikrein that transforms kininogen into bradykinin (a vasoactive amine).

- Lipid mediators

Different lipid substances are produced and released by various cell types resulting in e.g. immune cell activation and chemotaxis (figure 10).

- Inflammatory proteins of hepatic origin (C reactive protein, serum amyloid A, α 1-antitrypsin, haptoglobin, fibrinogen, ceruloplasmins, and other acute phase proteins)

These proteins, that are produced during the acute phase of inflammation, can mediate pro- and anti-inflammatory effects and facilitate the removal of cellular waste.

- Cytokines

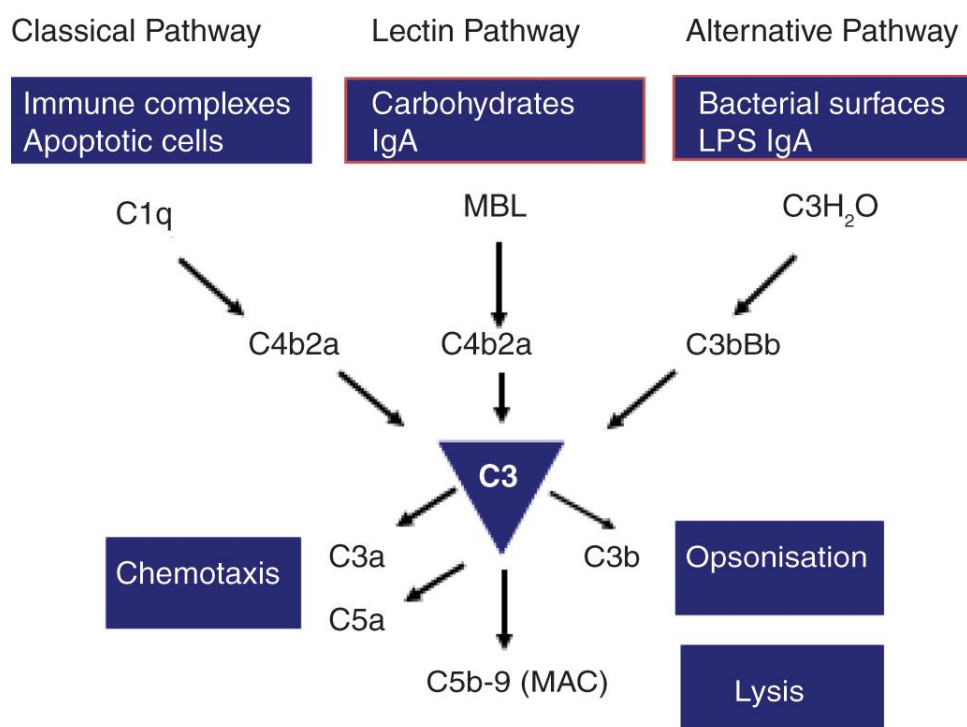
Many different cytokines, such as IL-1, IL-6 and TNF α can be released by various cell types rapidly after encounter with pattern recognition receptors (PRR)-activating microbes.

- Endogenous corticoids

This group, of which cortisol is the most important substance, consists of powerful anti-inflammatory agents that exert their action by means of different mechanisms, in particular the inhibition of pro-inflammatory cytokines.

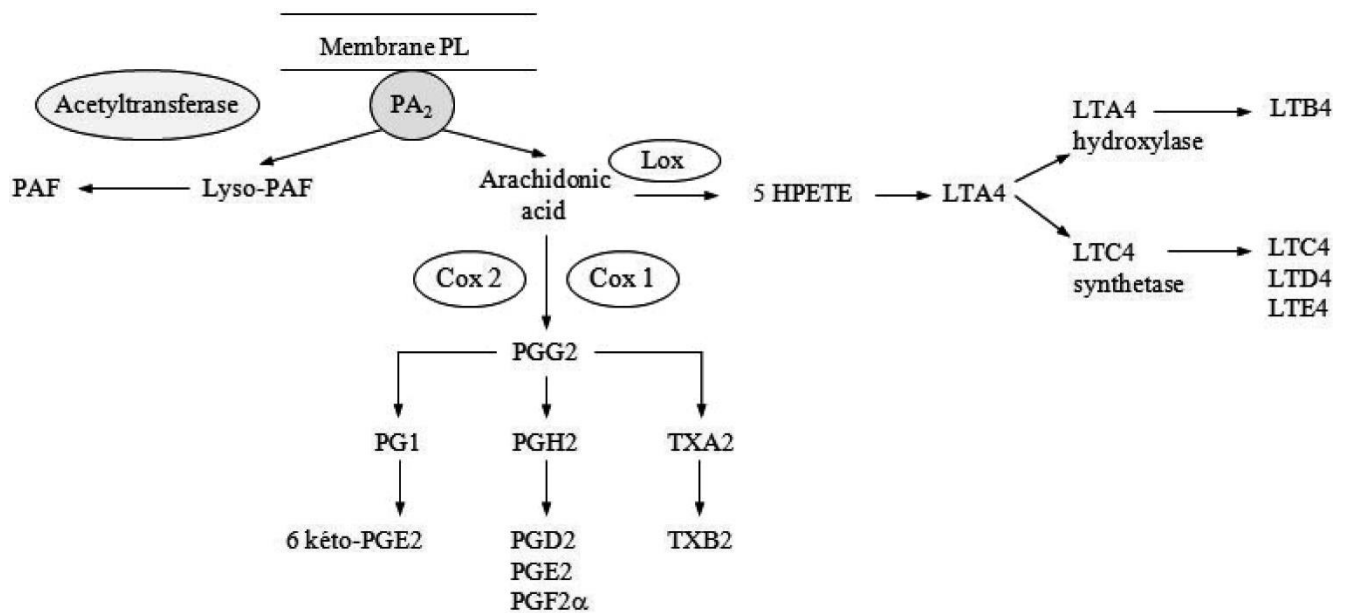
Figure 7 The complement system.

Background on complement activation



Furthermore, activated innate immune cells release mediators such as prostaglandins, nitric oxide, and pro-inflammatory cytokines and chemokines, that activate the surrounding stromal cells, attract infiltrating immune cells and induce a systemic inflammatory response (figure 8). These cytokines include TNF α , IL-6, IL-1, IL-23 and chemokines such as IL-8, MCP-1 (monocyte chemoattractant protein-1), IP-10 and MIP1 α and β , which will attract other inflammatory cells to the site of inflammation.

Figure 8 Inflammatory mediators derived from cell membrane constituents. *Cox, cyclo-oxygenase; Lox, lipo-oxygenase; LT, leukotrienes; PAF, platelet activating factor; PA2, phospholipase A2; PG, prostaglandin; PL, phospholipid; Tx, thromboxane.*



Inflammatory cells will migrate to the tissues, triggering the elimination of microbial agents, but also amplifying local inflammatory signals. These signals explain the clinical symptoms we recognise as pain, redness, swelling, heat and loss of function. The concerted attack on the infecting pathogen can induce collateral tissue destruction. Tissue degradation products together with alarmins and proteins released due to tissue stress (such as heat shock proteins) are also able to activate PRR on innate immune cells similar to PAMPs and induce these to clear cellular and tissue waste. These mediators are termed damage associated molecular patterns (DAMPs [Figure 6]). Often, this innate immune response suffices to clear a pathogen. Subsequently, innate immune mechanisms become active that resolve activated immune cells and repair damaged tissues.

However, many pathogens have evolved offense mechanisms that inhibit or skew innate immune defence responses that allow them to persist and infection to spread. This causes long-lasting infections, such as can be seen in young children and when patients do not receive antibiotic treatment. The adaptive immune system has evolved to combat these pathogens. Dendritic cells and the recently discovered innate-like adaptive immune cells, such as innate lymphoid cells (ILCs), play a key role in bridging the innate and the adaptive immune system. These cells become active as part of the early innate immune response against pathogens in a

tissue and are intimately involved in setting how the immune response evolves. Dependent on the type of pathogen specific PRR innate-like adaptive immune cells are triggered leading to the production of specific patterns of cytokines and chemokines. These cytokines and chemokines polarize the immune response towards more efficient killing of, for instance, intracellular or extracellular bacteria or intracellular viruses (polarization will be discussed below in more detail when discussing T cell subsets).

Following exposure to microbes, dendritic cells triggered through their PRR, undergo a process of maturation and migrate to the lymphoid organs where they become capable of activating T-lymphocytes. This requires a series of steps, the most important of these being the ingestion of the pathogen by phagocytosis, digestion into fragments and presentation of these fragments on their cell membrane major histocompatibility complex (MHC) molecules (encoded by human leucocyte antigen [HLA] genes). On the cell surface each MHC molecule displays a molecular fraction of a protein (i.e. a peptide), also called antigen, where it can be recognised by T cells. MHC class I is expressed on nearly all cells in the body and present peptide-antigens to CD8+ killer T cells, and MHC class II is expressed on professional antigen presenting cells, dendritic cells, B cells and macrophages and presents antigen to CD4+ helper T cells. Initially, presentation of antigen on MHC class I or II occurs mainly by dendritic cells to T cells in lymphoid tissues. Matured dendritic cells also deliver a second signal crucial to proper T-lymphocyte activation. This second signal is called co-stimulation and is provided through CD80/CD86-CD28 interaction, where CD80/86 molecules are expressed by the dendritic cells and CD28 by the T cell. Immature dendritic cells express far less CD80 and CD86 and hence cannot activate naïve T cells, but instead are thought to induce regulatory or anergic cells. Finally, dendritic cells polarize T cells towards a specific cell subset by production of cytokines. Antigen presentation by non-immune cells, macrophages and B cells to T cells occurs mostly later during an immune response (explained below). B cells in lymph nodes are also activated by antigens. In contrast to T cells, these either freely diffuse into the lymph nodes or are presented by macrophages or dendritic cells that capture and present antigens with non-MHC receptors.

4.2 Lymphocyte activation occurs in the lymph node, spleen and peripheral tissues

Peripheral lymphoid organs have multiple roles, since they:

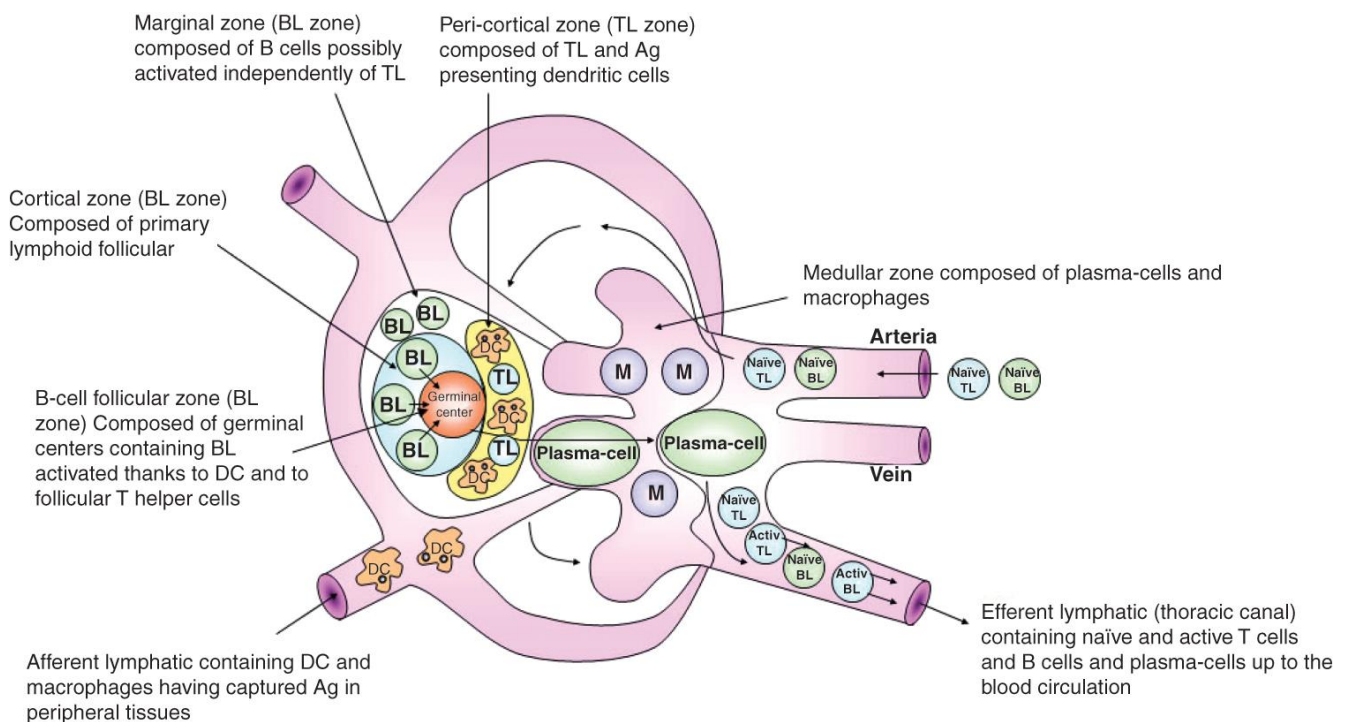
- receive dendritic cells that have captured antigens in peripheral tissues;
- facilitate activation (both proliferation and differentiation) of T and B cells;
- enable these activated lymphocytes to spread to areas where the adaptive immune effector responses are required.

These functions explain the original organisation of these peripheral lymphoid organs.

4.2.1 What is the composition of the lymph node?

Lymph nodes are highly organised structures functioning as sites of convergence of an extensive system of vessels collecting afferent lymph fluid and cells from tissues and ultimately returning it to the blood via efferent lymphatic vessels (figure 9).

Figure 9 The 'anatomy' of the lymph node. Ag, antigen; BL, B lymphocyte; DC, dendritic cell; M, macrophage; TL, T lymphocyte.



- What cells arrive in lymph nodes?
 - Antigen presenting cells, that have captured antigen in peripheral tissues, such as the skin or gut, arrive at the lymph node through afferent lymphatic vessels.
 - Naïve lymphocytes traffic to the lymph node through the blood circulation.
- What happens in the lymph node?

Lymphocyte activation and cooperation are highly organised and tightly regulated events that are temporally and spatially coordinated in the lymph node. It requires the recognition of specific antigens presented by dendritic cells on their MHC by specific T cells and antigen recognition by specific B cells. Each T and B cell express unique antigen detecting receptors, which are termed the T and B cell receptor (explained further below). To increase the chance of antigen recognition T and B cells dynamically recirculate through lymph nodes, while antigen can be retained by lymph node dendritic cells for many weeks. Activation of naïve T-cells upon antigen-recognition, results in their expansion and ability to provide help to B-cells. This “help” is

required for expansion and maturation of B cells into antibody-secreting plasma cells. This is a tightly regulated process, and the interaction of activation-induced expression of molecules on T cells (eg, CD40L), with the corresponding counter-receptors expressed on B cells (eg, CD40), plays a pivotal role in the T–B cell interplay.

These processes are reflected in the lymph node architecture (figure 9). Thus, at any one time the lymph node may be made up of:

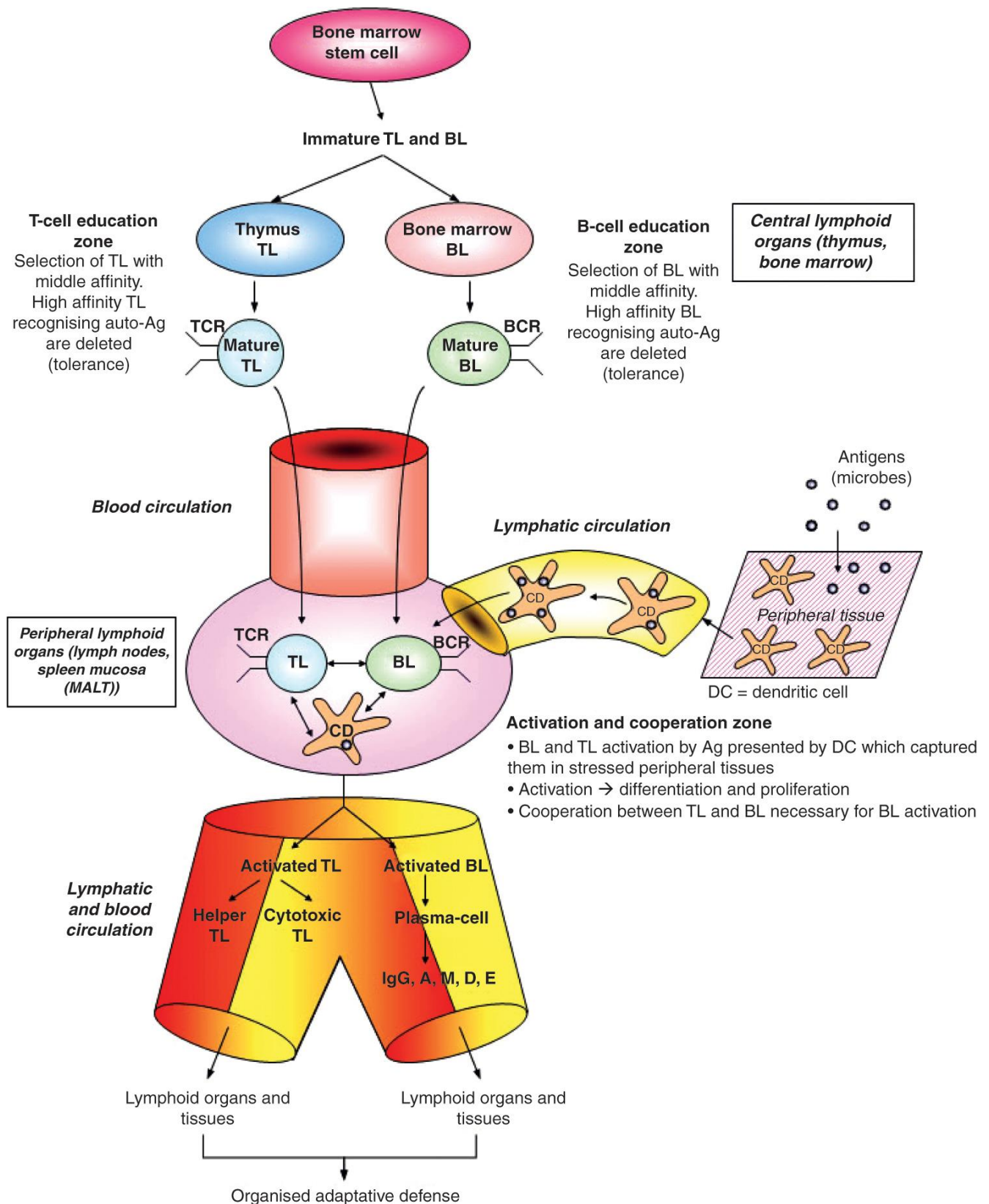
- a cortical zone where B cells recirculate to and may encounter antigens, resulting in proliferation (termed primary follicle);
 - a paracortical zone, where T cells recirculate;
 - B cell follicular structures that include germinal centres, in which B cells undergo intense proliferation, somatic hypermutation (explained below) and differentiation following encounter with specific antigen and T helper cells;
 - a marginal zone where B cells can be activated when in contact with specific B antigens, regardless of T cells;
 - a medullary zone consisting of macrophages and mature B cells that become antibody producing plasma cells.
- What are the consequences of lymphocyte activation, proliferation and differentiation?

Activated lymphocytes migrate through efferent lymphatic vessels into the blood circulation, via a main channel, the thoracic duct, which joins the systemic circulation at the left subclavian vein. These activated lymphocytes are able to migrate to peripheral tissues to participate in the immune response, as required (figure 10). Here in the inflamed tissue, lymphocytes can be further activated by MHC class I on tissue cells, leading to the elimination of e.g. virally infected cells, and by MHC class II on professional antigen-presenting cells such as macrophages leading to further control of infections

- What becomes of the lymphocytes that are not activated in the lymph node?

Those lymphocytes that are naïve (ie, they are not engaged by specific antigen) will either die or recirculate through efferent lymphatic vessels to repopulate peripheral lymphoid organs, where they may become activated upon antigen encounter.

Figure 10 Structural organisation of the lymphoid system. BCR, B cell receptor; BL, B lymphocyte; DC, dendritic cell; M, macrophage; MALT, mucosa-associated lymphoid tissue; TCR, T cell receptor; TL, T lymphocyte.



4.2.2 What is the role of the spleen?

The spleen is a lymphoid organ, with similar functions to lymph nodes, and a structure that includes lymphoid follicles. In contrast to lymph nodes, the antigens enter the spleen via the blood, more specifically via arterioles, to form a region called the white pulp. The white pulp comprises the periarteriolar lymphoid sheath (PALS) containing mainly T cells and a flanking B cell corona. As part of the immune response, germinal centres form at the interface between these T cell and B cell zones. Following activation, lymphocytes exit the spleen through the bloodstream. Although it is possible to remove the spleen without jeopardising life, the spleen does play a role in the immune protection against sepsis from polysaccharide encapsulated bacteria.

4.2.3 What is the role of lymphoid tissues associated with the mucous membrane?

Mucous membranes have a system that is particularly original and crucial for host defence, since these mucosal sites in the gut and lung form a massive surface area of tissue that is in direct contact with the environment. The lymphocyte infiltrate in these mucous membranes forms what is termed mucosa-associated lymphoid tissue (MALT). MALT exists at numerous sites, but is best characterised in the respiratory tract as bronchial-associated lymphoid tissue (BALT), and in the digestive tract as gut-associated lymphoid tissue (GALT), enriched in the tonsils, intestine and appendix. In the small intestine, antigens assemble together via a particular system comprising a network of epithelial 'multi-window' or 'M' cells, which trap antigens in the intestinal lumen. These antigens can then be presented to lymphocytes in the mucous membrane that form structures in special zones called Peyer's patches.

It is likely that lymphoid tissue of MALT contains more lymphocytes than the rest of the immune system. The MALT system functions like lymph nodes and the spleen, based on the principles of spatial interactions between the professional antigen presenting cells (dendritic cells) and lymphocytes. In contrast to lymph nodes and spleen, which may be considered 'persistent' secondary lymphoid organs, a particular characteristic of this MALT tissue is that it may appear and disappear depending on the environmental stimuli. It is now generally accepted that comparable lymphoid organisation, or lymphoid neogenesis, is observed in other tissues such as salivary glands or synovium. Under these circumstances, persistence of such structures accompany chronic immune pathological conditions such as Sjögren's syndrome and rheumatoid arthritis. Although relatively rare, malignant transformation has also been described in these tissues, leading to a group of conditions known as MALTomas or MALT lymphomas.

4.3 While lymphoid organs coordinate the generation of specific effector defence responses, they are also the sites of immune regulation

Immune regulation in the periphery, known as peripheral tolerance, is based on the induction, activation and expansion of specific subsets of T and B cells that exert regulatory properties. Their function serves to regulate and stop immune responses. The best characterised are T regulatory cells (Tregs), defined at least in part on the basis of the anti-inflammatory cytokines that they produce during an immune response (eg, IL-10 and transforming growth factor β (TGF β)). Defining the mechanisms whereby regulatory cells exert their suppressive effects on the activation and expansion of effector cells is a topic of great interest. Production of anti-inflammatory mediators such as IL-10 and TGF β are important, but cell contact dependent pathways also exist, which are less well defined.

5 The adaptive immune system in action

5.1 How are T cell effector functions initiated?

After infection of the body by a microorganism and presentation of microbial epitopes by a dendritic cell to T cells in lymphoid tissue, T cells that recognise the pathogen with their T cell receptor in a specific fashion will become activated and start dividing. The activation of T cells requires two successive signals:

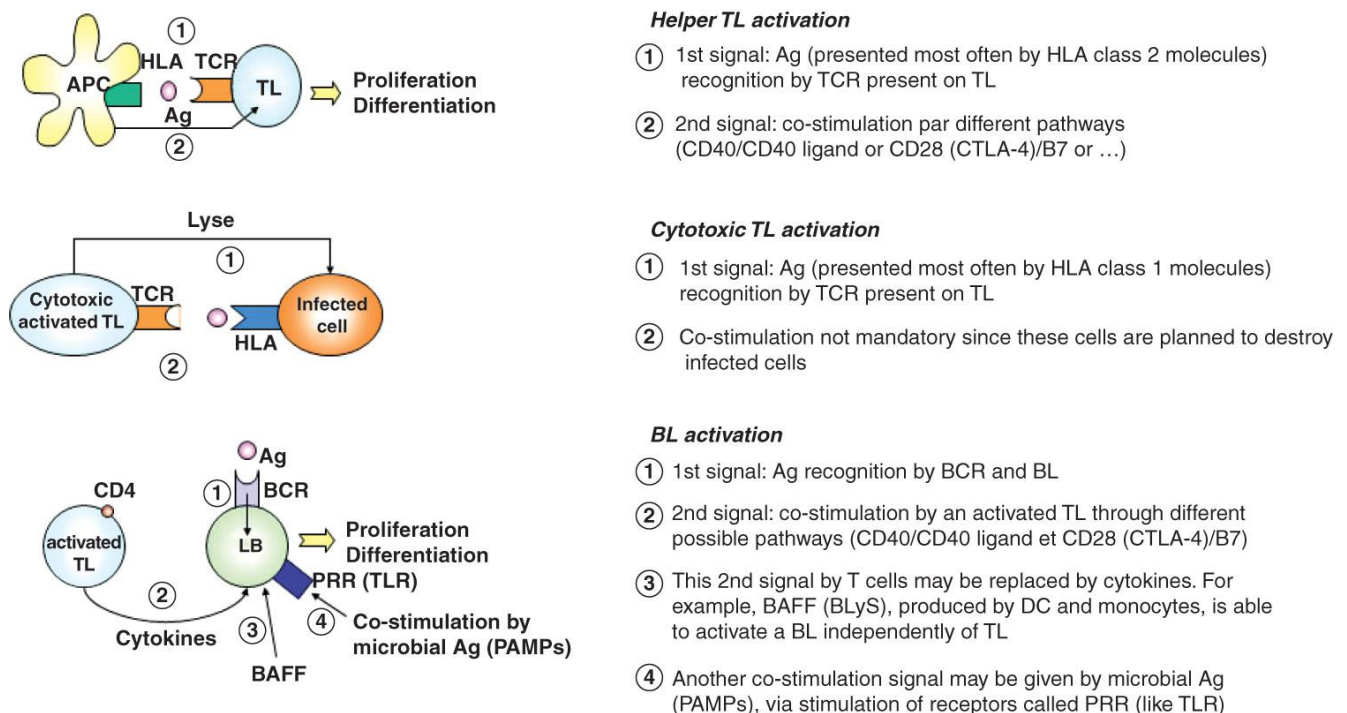
- The first signal is recognition by specific membrane receptors of the T cell. The receptor is called the T cell receptor (TCR)/CD3 complex, and is made up of variable antigen recognition subunits (TCR α and β chains, or TCR γ and δ chains), and invariant signal transducing units (CD γ , δ , and ζ chains). The TCR recognises a complex of antigenic peptide bound to MHC class I or II molecules expressed on the surface of antigen presenting cells (figure 11). MHC class I molecules present peptides from proteins synthesised in the cytosol such as viral peptides, and are recognised by CD8+ T cells. Class II molecules, recognised by CD4+ T cells, mostly display proteins that are present in intracellular vesicles that originate from the phagocytosis of pathogens (figure 11).
- While the overall structure of MHC molecules is rather similar, the antigen binding domains of MHC molecules are highly variable between individuals. This variation in MHC sequence (particularly within the peptide binding groove and pockets that accommodate antigen peptide amino acid side chains), permits the binding of a wide range of antigenic peptides. This means that different HLA molecules (encoded by different HLA genetic variants) present different fragments of a particular peptide to T cells. This process of recognition of an MHC/peptide complex by T cells is essential since T cells become activated if they recognise their matching antigen presented by an MHC molecule. Therefore, this antigenic specific response is said to be 'restricted' by the host MHC molecules. This genetic variability results in various protection and susceptibility to infections between individuals, but also variability in susceptibility to autoimmune diseases.

- TCR signals can be terminated by inhibitory receptors (eg CTLA4, PD-1).

The manner of activation of T cells by epitopes and co-stimulatory signals and cytokines delivered by antigen-presenting cells determines the specific T cell subset into which the cell will differentiate. This is termed polarization. As mentioned, CD8+ cytotoxic T cells are activated by MHC class I presented peptides and kill virus infected cells. The CD4+ helper T cell subsets are activated by MHC class II presented peptides and specific dendritic cell cytokines and have diverse functions.

T cells with helper function are, as a rule, CD4+ T cells; helper function refers to cytokine mediated activities on a range of cell targets, including not only B cells, but also cytotoxic CD8+ T cells, macrophages and granulocytes. Th cells come in different subsets (Th1, Th2, Th17 and Treg cells) that are generated from naïve precursor T cells. Over the years, a growing number of CD4+ T cells subsets have been described (figure 12), having been defined initially in the mouse based on cytokine profiles through the pioneering work of Mosmann and Coffman, first reported in 1986:

Figure 11 Lymphocyte activation. Ag, antigen; APC, Ag presenting cell (DC, macrophage, LB); BAFF, B cell activating factor; BCR, B-cell receptor; BL, B lymphocyte; BLyS, B lymphocyte stimulator; DC, dendritic cell; HLA, human leucocyte antigen; PAMPS, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; TCR, T cell receptor; TL, T lymphocyte; TLR, Toll-like receptor.



- Th1 cells function to activate macrophages (M1) in ways that enhance microbial killing. This includes intracellular infections, such as Mycobacterium and Listeria species, that are not eliminated adequately by the innate immune defence. In fact, macrophages phagocytose mycobacteria in vesicles, which cannot fuse with the macrophage lysosomes, where they would be destroyed by enzymes and lysosomal antibacterial

proteins. Th1 cells are capable of inducing fusion of macrophage vesicles with lysosomes by activating the macrophages through synthesis of cytokines, such as interferon γ (IFN γ) (figure 13).

- Th1 cells are characterised by the profile of cytokines they produce (IFN γ), and they also release chemokines, which attract other macrophages that contribute to the inflammatory immune reaction. Th1 cells also contribute help for B cells and direct the production of specific IgG isotypes that promote host defence to intracellular pathogens. Th1 cells play key roles in autoimmune diseases and syndromes associated with chronic infection.
- Th2 cells have evolved to participate in responses against parasitic infestation through the promotion of IgE antibodies that neutralise antigen, and through promoting mast cells and eosinophils. By secreting cytokines such as IL-4, IL-5 and IL-13, they provide help for B cells to produce antibody isotypes such as IgG4 and IgE. Th2 cells play key roles in atopic and allergic disease.
- Th17 cells have been identified more recently, based on their expression of IL-17A and F, and IL-22. In man, they are thought to be generated in the context of cytokines that include IL-1, IL-23, IL-6 and TGF β . Current thinking suggests that they have evolved to participate in host defence against fungal infections, such as *Candida* as well as extracellular bacteria. IL-17 is a potent chemoattractant for neutrophils, so may contribute to the early infiltration of polymorphs to sites of infection. Based on studies in the mouse, Th17 cells contribute to organ specific autoimmunity, including inflammatory arthritis and demyelinating disease.
- T helper follicular cells (TFH) likely represent a population of T cells which, in lymphoid tissues together with follicular dendritic cells, play dominant roles in the selection of B cells in germinal centres. Their origin is not fully understood.
- Specific populations of CD4⁺ T cells exert immunosuppressive or regulatory function. These are collectively known as regulatory T cells, or specifically Tregs. An extensively investigated subset is CD4⁺ CD25⁺ and expresses the master transcription factor FoxP3 (box 2). Other regulatory T cell populations, such as Th3 and Tr1 cells play a variable role in various body compartments. Tregs are necessary to maintain homeostasis of the immune system, particularly by preventing the activation and expansion of self-reactive lymphoid populations.

While the assignment of specific cell lineages is an attractive model, it is likely that there remains much plasticity and reciprocity between T cell subsets *in vivo*.

After T cells are activated by epitopes, proliferate and differentiate into a specific T cell subset in lymphoid tissue after which they are called memory T cells. They may activate B cell partners in lymphoid germinal centres. Furthermore, they leave the lymphoid tissue as effector memory T cells, mediated by sphingosine 1-phosphate. It is likely that the nature of dendritic cell activation determines the profile of integrins and chemokine receptors expressed on the T cell that permits the cell to home to the appropriate infected tissue. Adhesion (mediated by rolling, chemo attraction and firm arrest) to microvascular endothelial and migration

into tissues is a highly regulated process mediated by selectins, chemokines and integrins, such as LFA-1 and VLA-4. At the site of infection they exert their effector function that result in enhanced innate immune cell function. After clearance of the infection memory T cells persist in blood and various body compartments. Memory T cells together with memory B cells and antibodies enhance and rapidly amplify innate immune responses when similar micro-organisms infect the body at later time points (adaptive immunological memory). In adults most adaptive immune responses are directed by memory TB and T cells.

Figure 12 The subpopulations of CD4⁺ T cells. IFN, interferon; IL, interleukin; TGF, transforming growth factor; TNF, tumour necrosis factor.

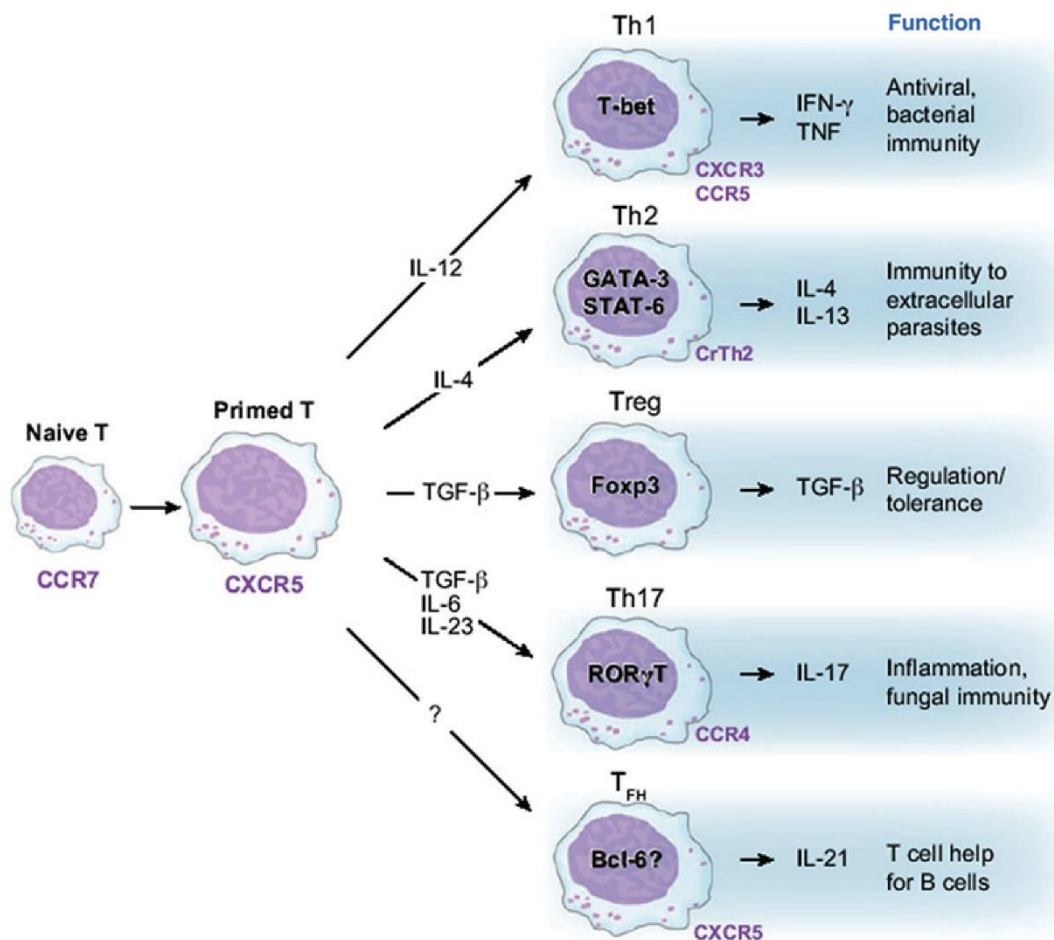
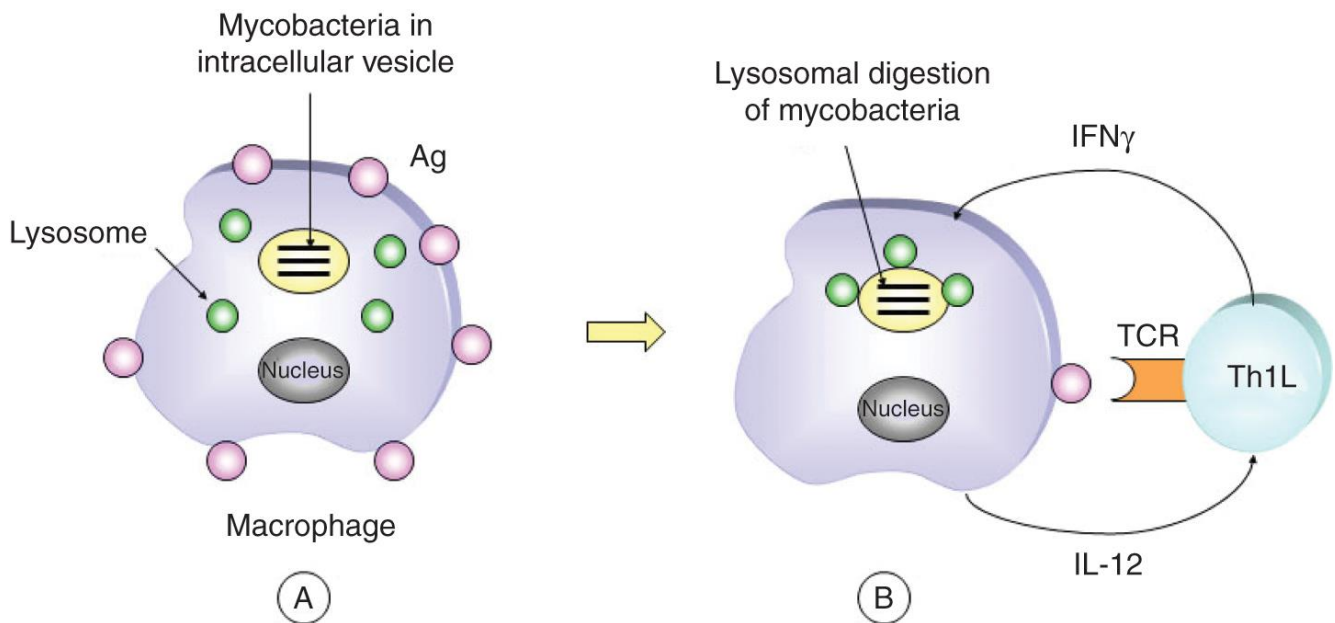


Figure 13 Mechanism of defence against an intracellular mycobacterial infection. Ag, antigen; IFN, interferon; IL, interleukin; TCR, T cell receptor; Th, T helper.



5.2 What are the effector functions of B cells?

5.2.1 Antibodies

An important part of the adaptive immune system combatting invading pathogens is mediated by antibodies (humoral immunity). Antibodies are glycoproteins produced by B cells. Antibodies bind to the molecules of pathogens that provoked the immune reaction and are able to activate various other molecules of the immune system (such as the complement system) in order to eradicate the pathogen.

Binding of an antibody to a virus can, for example, prevent the infection of other cells. At the same time, the virus is marked for destruction by phagocytes and the complement system. Antigen recognition and effector function are structurally separated within the antibody molecule; one part binds specifically to the antigen, whereas the other end of the molecule is involved in recruiting immune effector systems. The antigen-binding part is highly variable between different antibodies and is therefore also known as the variable part or the V-region of the antibody. This variability of antibodies allows the antibody system to bind to many different antigens, where one antibody is always specific for one antigen. The region of the antibody that is involved in the 'recruitment' of effector functions of the immune system is rather constant and hence this region is called the constant region or C-region. The membrane-bound form of an antibody, which is present on naïve and memory B cells, cannot recruit effector mechanisms as it is anchored in the B cell membrane (termed the B cell receptor). It is, however, involved in the activation of the B cell after it has bound antigen through its

variable part. This leads to proliferation of this B cell (a process termed clonal expansion) and the production of specific antibodies that can be measured in serum of individuals.

Antibodies can exert several different effector functions: neutralisation of viruses or toxic products from pathogens, complement-mediated lysis of microorganisms, opsonisation of microorganisms for phagocytosis and antibody-dependent cellular cytotoxicity (ADCC). In case the antibody is directed against molecules expressed by cells (for example, rituximab which recognises CD20, a molecule expressed by B cells) it can also lead to killing of cells through complement-mediated lysis or ADCC. ADCC can be mediated by several immune cells, such as NK cells to kill virally infected cells, or granulocytes to combat parasites. Recognition of antibody–antigen complexes in general and ADCC in particular is dependent on the recognition of the immune complex by specialised receptors on immune cells—the Fc-receptors (which recognise the constant region (the Fc-region) of antibodies). To which extent an antibody can recruit these different immune effector functions depends on its type of constant region that can vary in subclass (or isotype) (ie, IgM, IgD, IgA1, IgA2, IgG1, IgG2, IgG3, IgG4 and IgE).

5.2.2 B cells

After invasion of the body by a microorganism, and presentation of microbial antigens to B cells in lymphoid tissue, B cells that recognise the pathogen with their B cell receptor in a specific fashion will become activated and start dividing. These B cells differentiate subsequently to plasma cells that produce and secrete antibody. The antibodies produced by the offspring of a single B cell (a B cell clone) have the same specificity as the membrane-bound antibody receptor that is expressed by the precursor of that given B cell clone. The production of antibodies, that can bind and neutralise pathogens and their toxic products in the various body compartments, is one of the most prominent functions of B cells as part of the adaptive immune system.

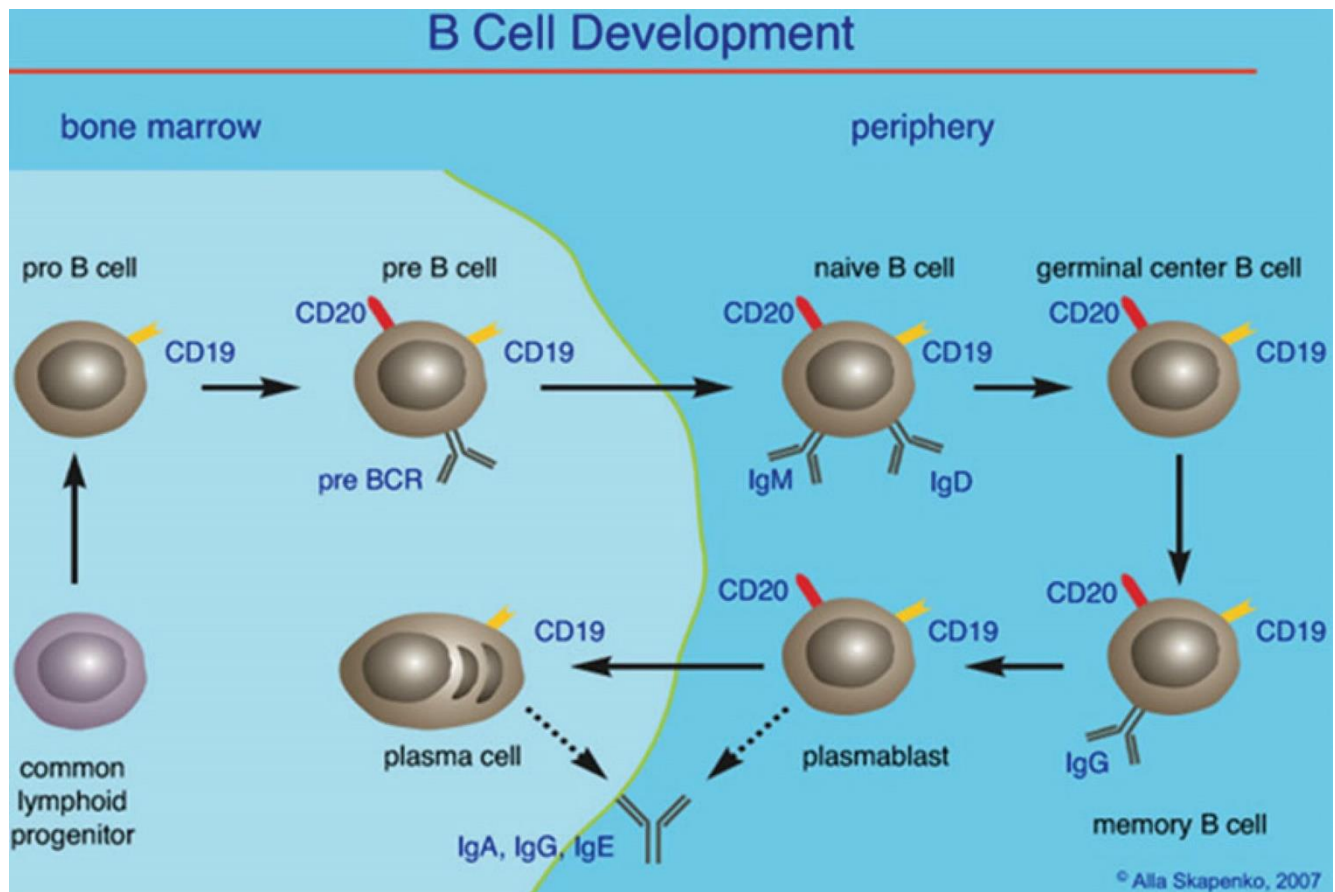
Mature B cells are activated after antigen recognition in lymphoid organs. After initial activation of mature B cells, short-lived plasmablasts that are responsible for the production of the first wave of antibodies are immediately formed (figure 14). These antibodies circulate to the site of infection and enhance microbial killing through their various effector functions. Next to the formation of relatively short-lived plasmablasts, also memory B cells are formed recognising the same inciting antigen. In general, memory B cells against T cell dependent antigens have undergone isotype switching (ie, express another Fc region, most often an IgG- instead of an IgM-tail) and express a mutated immunoglobulin variable region. The latter is a result of a process called somatic hypermutation and results in an increase in avidity of the overall antigen-specific B cell response as it selects for (memory) B cells that have been able to increase the strength of antigen recognition by the B cell receptor. Both isotype switching and somatic hypermutation result in the formation that improve microbial killing in prolonged infections. Activated B cells can also migrate to sites of inflammation. Here they can then also differentiate into plasmablasts, produce and secrete the required antibodies to combat the

infection locally. B cells also have other functions that contribute to the immune response. They contribute to activation of T cells at the site of infection since the B cell expresses HLA and co-stimulatory molecules and so function as an antigen-presenting cell. B cells also produce abundant pro- and anti-inflammatory cytokines, as well as chemokines.

Furthermore, memory B cells can differentiate further to long-lived plasma cells. These cells can migrate to special niches in the bone marrow where they keep on secreting antibody for years. Also memory B cells persist after clearance of the infection similar to memory T cells. The size of the effector memory T and B cell pool during and persistent memory pool after infection is determined by growth factors such as IL-7 and B cell activating factor (BAFF) for T cells and B cells, respectively. Together with the antibodies secreted by long-lived plasma cells, memory B and T cells form adaptive immunological memory. It is this phenomenon that forms the rationale for vaccination.

The human immune system has evolved several hurdles to prevent occurrence of autoimmunity. These are called 'tolerance checkpoints'. A crucial checkpoint is that, as explained above, for optimal B cell differentiation, antibody production and memory formation, most B cells need help from CD4⁺ T helper (Th) cells. CD4⁺ Th cells can give an additional signal to B cells via the production of cytokines such as IL-4 and direct cell–cell contact, required for activation of the enzymes involved in somatic hypermutation and isotype switching. Likewise, the help of T cells is often also required for the formation of memory B cells. Thus, by recruiting the help of T cells, B cell responses can mature and remember. In order to provide help to B cells, CD4⁺ Th cells need to see antigen in the context of HLA molecules. B cells that acquire antigen through their membrane-bound antigen receptor (the membrane-bound antibody) can take up the antigen inside the cell, digest it, and present it subsequently in the context of HLA class II molecules on their cell surface for recognition by T cells. Only T cells recognising this antigen become activated and can provide help to this particular B cell. There, high affinity antibodies, memory B cells and IgG antibodies against a particular antigen will only be formed in case B cells and T cells recognise the same antigen/pathogen. This is often the case when a pathogen invades the body because such a pathogen is 'foreign' to the body. Therefore, there is a relatively high chance that both a B cell as well as a T cell are present in the body that can recognise the invading pathogen. In contrast, however, a B cell that would recognise a self-molecule is far less likely to be able to attract helper activity from CD4⁺ Th cells, as these T cells are likely not present (and vice versa). Therefore, the requirement of T cell help for the generation of optimal antibody responses is an additional protective measure against the development of (B cell mediated) autoimmunity.

Figure 14 B cell differentiation.



6 How is the immune system measured?

6.1 Detection of humoral immune responses

In clinical practice, analysis of immunoglobulin levels (abnormal in autoimmune conditions, paraproteinaemias, globinopathies and primary immune deficiencies) has become routine. Identification of ongoing, recent or past infections (bacterial or viral) and evaluation of vaccine responses is also common practice. In addition, immunoassays have, for many years, become central to the repertoire of clinical laboratories, providing key diagnostic information for a wide range of conditions including organ specific autoimmune diseases, connective tissue diseases, the vasculitides and rheumatoid arthritis. Dynamic assays of B cell function are, to a large extent, the domain of the research laboratory.

Examples of the more common assays employed to evaluate components of humoral immunity include:

- quantitative analysis, where the amount of immunoglobulin protein is determined (adult values): IgG 7–15 g/l, IgD 0–150 mg/l, IgA 0.6–4 g/l, IgE 3–190 U/ml, IgM 0.6–3 g/l;

- serum electrophoresis, providing a global picture of immunoglobulin levels in the context of other abundant serum proteins such as albumin and α -macroglobulin;
- serum or urine immunofixation to confirm the presence of a monoclonal immunoglobulin when it is suspected by the presence of a peak on electrophoresis;
- detection of cryoglobulins;
- enumeration and phenotyping of B cells, according to expression of B cell lineage markers CD19 or CD20 (eg, evaluation of therapeutic B cell depletion; normal range 200–1250/mm³);
- analysis of light chain subunits (2/3 kappa and 1/3 lambda)—these proportions may be deranged in autoimmune disease and haematological malignancies;
- functional analysis, including studies of antigen specific responses and evaluation of neutralising titres (eg, to influenza, pneumococcal antigens and tetanus toxin), and B lymphoblast transformation (in response to mitogens; of limited value in the clinical setting).

6.2 Evaluation of cellular immunity

A family history may provide clues as to the possibility of cellular immune deficiencies. Although rare, these lead to susceptibility to specific infections, manifest in early life, and may be X-linked. Neoplastic complications and, paradoxically, autoimmunity also may be a manifestation of an immune defect.

Components of cellular immunity are commonly evaluated by:

- enumeration and phenotyping of total T cell numbers, and T cell subsets by flow cytometry. Normal values in adults are: total number of lymphocytes (CD45) 1500–5000/ml, CD3+ 1400–4000/ml, CD4+ 600–2500/ml, CD8+ 350–1500/ml, CD4/CD8 ratio 0.98–3.20, NK cells (CD56+ CD16+) 150–1000/ml;
- evaluation of antigen specific responses in vivo, such as following intradermal injection of tuberculin or candida antigens. This is also known as a delayed type hypersensitivity reaction.
- in vitro proliferative responses to antigens (candida, tuberculin/PPD (purified protein derivative), tetanus toxin) or to mitogens (phytohaemagglutinin, concanavalin A, pokeweed mitogen) or following cross-linking of the TCR/CD3 complex with anti-CD3, with or without anti-CD28 for co-stimulation.

6.3 Detection of innate immune responses

There are few assays employed in routine practice that provide a robust or dynamic analysis of innate immunity. The following could be viewed as screening assays that may provide important clues:

- functional assessment of complement activity (CH50). CH50 (total haemolytic complement) measures the lysis of sheep red blood cells sensitised with rabbit IgM, by a patient's serum. All nine components of activation of complement by the classical pathway are necessary to achieve a normal CH50. If CH50 is abnormal, specific tests can be used to find the absent component;

- evaluation of complement components and breakdown fragments;
- quantitative enumeration, by flow cytometry, of innate immune cells: monocytes, neutrophils, eosinophils, basophils and mast cells;
- in vitro assays of phagocytosis.

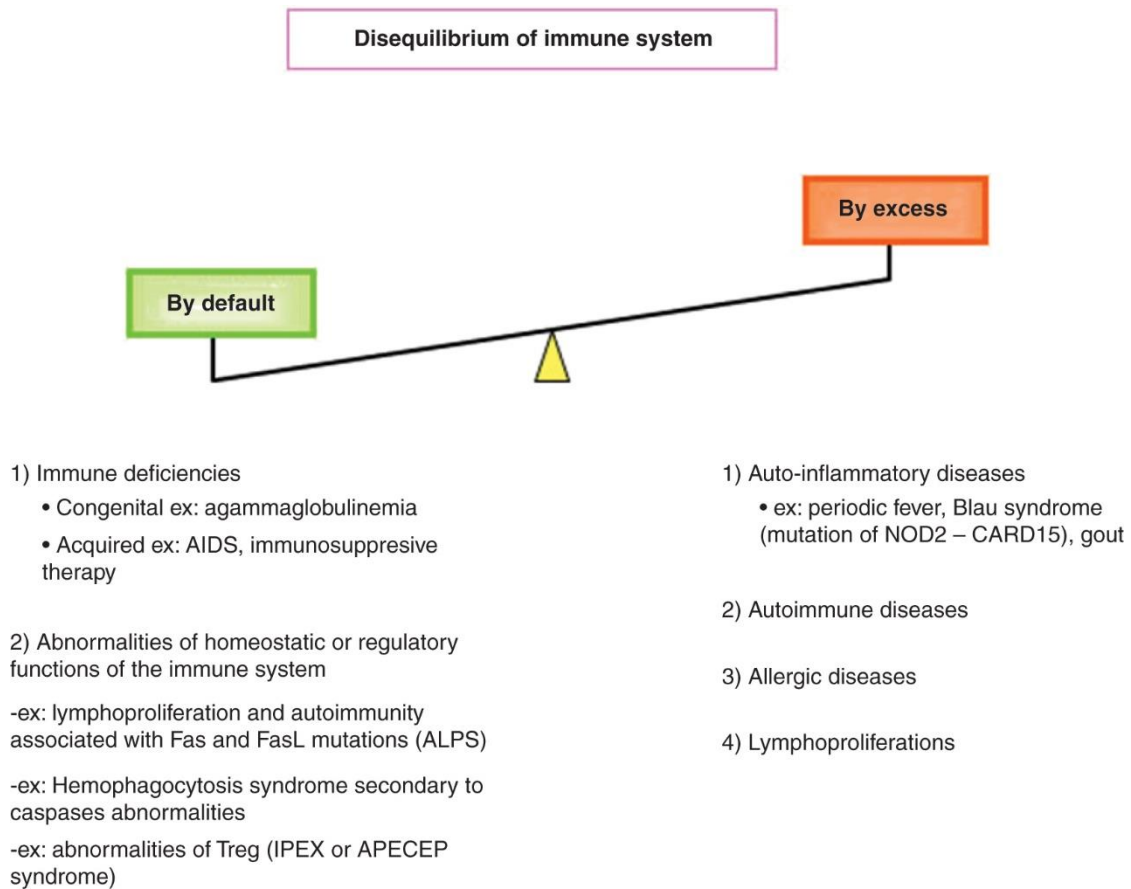
6.4 New techniques

While many studies of immune function lie more within the scope of the research laboratory, new technologies now permit the unbiased and systematic evaluation of large numbers of analyses such as gene variants (genomic techniques such as SNP Chips), gene expression/mRNA (transcriptomics, applying DNA microarrays) and proteins (proteomics, applying medium to low density protein arrays; protein analysis using bead-based protein arrays). Determination of TLR-induced cytokine production by monocyte subsets is just one example. Analysis of cells at a single cell level, by flow cytometry (pioneered by Herzenberg, Stanford, California, USA), are likely to continue to play a major part in immune phenotyping, as this approach becomes more applicable in the clinical setting. Flow cytometry is highly adaptable, and can analyse mixed populations of live cells, accommodating assays of cell protein expression, cell division, expression of secreted proteins as well as analysis of T cells specific for self, foreign and tumour antigens (using tetramer technology), and analysis of the state of activation of specific signalling pathways (PhosphoFlow). Nonetheless, cell-based functional assays remain a challenge.

7 Aberrations of immunity

Dysregulation of the immune response is a key element that underpins pathogenicity of multiple immune and inflammatory diseases (IMIDs). Taken at the most fundamental level, there are two broad categories of disease that reflect the two extremes of immune dysregulation (figure 15). The first group is characterised by deficiencies of the immune system. The second group of diseases includes those in which there are features of an excessive, overactive or inappropriately persistent immune response.

Figure 15 The main diseases linked to a dysfunction of the immune system. *ALPS*, autoimmune lymphoproliferative syndrome; *APECEP*, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *IPEX*, immune dysfunction, polyendocrinopathy, and enteropathy, X-linked.



7.1 Immune deficiencies

7.1.1 Inherited immune deficiency syndromes

The prototype immune deficiencies, first described in 1952, are inherited (the majority being monogenic and recessive, with a subset being X-linked), of which there are >100 in man. Gene knockout technology in rodents has added greatly to our knowledge of immune deficiencies. Each of these forms is characterised by a specific clinical disease entity, imposed by the genetic anomaly and the cellular or molecular component of the immune system that is affected. A few examples are included below.

- Deficiencies in the adaptive immune system, arising commonly through defects in lymphocyte development, may lead to a complete lack of T and/or B cells (severe combined immune deficiency—SCID). SCID arises due to specific deficiencies in adenine deaminase (ADA), purine nucleotide phosphorylase (PNP), the cytokine receptor common γ chain subunit or enzymes involved in DNA repair. More selective defects, such as those that target humoral deficiencies (Bruton's X-linked agammaglobulinaemia, due to a deficiency of protein tyrosine kinase—Btk—required for B cell development) are defined by the absence of B cells, low levels of immunoglobulin and impaired clearance of extracellular bacteria. Subjects with X-linked hyper-IgM

syndrome have normal numbers of T and B cells, but have high IgM levels and generate limited levels of Ig isotypes other than IgM and IgD in response to pathogens. The defect is in CD40L expression, which is normally expressed on T cells, as opposed to B cells which express CD40. This defect is explained by the CD40ligand-CD40 interaction which is crucial in the help to B cells given by CD4⁺ Th cells. In case a defect in CD40L is present, the antibody response is severely affected in its ability to undergo somatic hypermutation and isotype switching. Hence a reduced level of IgG is present which, in part, is compensated by higher IgM levels. The hampered antibody response makes patients susceptible to infection with extracellular bacteria but also to opportunistic organisms such as *Pneumocystis carinii*.

- Innate immune deficiencies also exist, in particular anomalies of phagocytosis or phagocyte function (eg, chronic granulomatous disease), defects in cytokines and their receptors, and deficiencies of specific components of complement. Complement deficiencies cause syndromes associated with persistence of immune complexes, which activate phagocytes, causing inflammation and tissue (eg, renal) damage. Recently, more specific deficiencies of some molecules belonging to the innate immune system have been described, such as those that target elements of receptor signalling pathways (eg, IRAK4 mutations, leading to pneumococcal infections).

Immune deficiencies are characterised by a fundamental defect in the host response to specific pathogens leading to chronic or recurrent infections; before the antibiotic era, it is likely that most individuals would have died from these infections during infancy. This is especially true of those defects in innate immunity, since defects in the adaptive immune system, with the possible exception of the most severe forms, are in general better tolerated. For example, defects in the IFN γ pathway predispose to recurrent infection with intracellular pathogens such as *Mycobacterium* and *Listeria* species. Paradoxically, immune deficiencies are commonly complicated by autoimmune disease (in particular thyroid autoimmunity and haemolytic anaemia), as well as lymphoproliferative or neoplastic syndromes (associated with persistent viral infection, such as Epstein-Barr virus (EBV)).

7.1.2 Acquired immune deficiencies

The most famous example of acquired immune deficiencies is AIDS. First reported in 1981, AIDS is caused by the human immunodeficiency virus that destroys the T cells, dendritic cells and macrophages, gaining access to these cells through high affinity interactions with cell surface receptors such as the CD4 co-receptor and chemokine receptors (eg, CCR5). There are other acquired deficiencies that arise as a consequence of immunosuppressive treatment (high dose glucocorticoids, cell depleting biological therapies, therapies used to maintain tolerance to tissue allografts), that increase the risks of infection and, in some very particular situations, of neoplasia.

7.1.3 Conditions determined genetically (through Mendelian inheritance) may lead to loss of homeostatic equilibrium in the immune system

These conditions are often classified as immune system deficiencies, but they are manifested clinically by signs and symptoms ordinarily attributable to lymphoproliferative and autoimmune syndromes. The conditions are characterised by constitutional deregulation of apoptosis that leads to a homeostatic deficiency of the immune system. Examples include:

- Lymphoproliferative syndromes coupled with autoimmunity (also known as the autoimmune lymphoproliferative syndrome—ALPS). This group of diseases is characterised by genetic mutations in pathways promoting cell death—specifically apoptosis. The prototype ALPS arises through loss of expression/function mutations in the Fas receptor or its ligand, which leads to the inhibition of apoptosis and therefore persistence of peripheral lymphocytes. Affected individuals develop autoimmune symptoms, associated with lymphoproliferation and expansion of a subset of mature $\alpha\beta$ TCR T cells that lack CD4 or CD8 (double negative T cells). Variants of this syndrome have led to a better understanding of the role of apoptosis in maintaining immune homeostasis.
- Haemophagocytic syndromes, which are also the consequence of genomic anomalies that target caspases (enzymes that participate in intracellular death receptor signalling pathways).
- APECED syndrome (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome), an autoimmune T cell dependent polyendocrinopathy that targets the parathyroid, thyroid, adrenal and pancreas endocrine glands. This syndrome is the consequence of a genetic deficiency of autoimmune regulator (AIRE), a transcription factor involved in thymic expression of self-antigens that, when presented in the context of HLA class I or II, regulate the selection (negative selection or deletion) of autoreactive T cells during T cell development in the thymus.
- IPEX syndrome (immune dysregulation polyendocrinopathy-enteropathy X-linked) is an autoimmune T cell dependent disease that targets the endocrine system and intestines. This syndrome is linked to a genetic defect of Foxp-3, the master transcription factor of CD4⁺ CD25⁺ regulatory T cells.

7.2 Excessive immune activity

In the context of conditions associated with a pathologically overactive immune system, one might consider three broad groups of conditions, occurring with varying frequency.

7.2.1 Auto inflammatory syndromes

These inherited diseases are characterised by persistent, systemic, chronic inflammatory responses. These are monogenic and arise through poorly understood aberrations of inflammatory signalling pathways. These

syndromes are discussed in more detail in a subsequent module. Briefly, there are two groups of auto inflammatory syndromes:

- Recurrent hereditary fevers that comprise familial Mediterranean fever (or periodic disease), the hyper IgD syndrome and other diseases, such as periodic syndromes associated with cryopyrin (called CAPS for cryopyrin-associated periodic syndrome), Muckle-Wells syndrome, cold urticaria and CINCA or the TRAPS syndrome (a syndrome related to the mutations of the TNF receptor). These diseases are considered as inherited disturbances of the innate immune response.
- The other group of inflammatory diseases comprises certain forms of Crohn's disease, Blau's syndrome and, in all likelihood, other related granulomatous diseases. In these diseases, mutations of subunits of the inflammasome (an intracellular pathway that processes responses to the IL-1/IL-18 family of cytokines, as well as endogenous and exogenous stimuli), including the NOD2/CARD15 gene, lead to an abnormal cellular response to bacterial components. (The inflammasome is discussed further in the 'in-depth discussion'.) These diseases are also considered as inherited disturbances of the innate immune response. Excess production of uric acid, and precipitation to form urate crystals, may stimulate similar intracellular pathways leading to the inflammatory syndrome we recognise as gout.
- The mechanism of other auto inflammatory syndromes, such as adult Still's disease or PFAPA syndrome (which associates periodic fever, mouth ulcer, pharyngitis and cervical adenopathy), remains unknown, but may turn out, at least in part, to be inherited polygenic disorders. It is likely that in the years to come, we will discover numerous other auto inflammatory diseases, thus permitting re-classification of groups of known diseases, such as juvenile idiopathic arthritis.

7.2.2 Autoimmune diseases

Autoimmune diseases such as type I diabetes and rheumatoid arthritis are most likely caused by a response of the cells of the adaptive immune system (ie, T cells and B cells) to tissue of the host. It is, therefore, no surprise that in many autoimmune diseases auto-antibodies are found that can be more or less specific for a given disease. Also an association with the HLA system is often found, indicating that T cells are involved in the process leading to disease. Because B and T cells can form memory cells, and because the autoimmune response is directed against an antigen expressed by the person's own body, it is often difficult to cure autoimmune diseases such as type 1 diabetes and rheumatoid arthritis. The cause of most of the autoimmune diseases is not known but they are likely to arise through multiple mechanisms, some of which are shared across disease states. (Pathogenesis of several specific autoimmune diseases will be discussed in the following chapters.)

7.2.3 Lymphoproliferative disease

These syndromes can also be viewed as a consequence of excessive function of the immune system. This excess may be related to the deregulation of an elementary mechanism, such as apoptosis, as well as to chronic stimulation that may arise through persistent infection (eg, EBV infection). Examples include:

- Autoimmune diseases (eg, Sjögren's syndrome) in which there is an increased incidence of B cell lymphoma considered to be the result of chronic immune stimulation linked to persistent antigenic stimulation. Initially, this stimulation could be induced by an environmental agent as demonstrated by the example of lymphoma that complicates cryoglobulinaemia linked to the hepatitis C virus.
- ALPS, a rare but extreme example of genetically determined defects in immune homeostasis as a result of impaired apoptosis. There are other examples, such as follicular lymphoma, in which translocation (t14-18) leads to deregulation of the expression of Bcl-2, an anti-apoptotic gene. Therefore, in these two situations, the 'malignant' lymphocytes proliferate since the immune system no longer eliminates them.

7.2.4 Allergic and atopic inflammation

These conditions are excluded from this review, but they form a particularly important and common field.

8 Therapeutic agents as molecular scalpels for dissecting disease pathways

Increased knowledge of the immune system has underpinned the development of new immunomodulators such as 'biological' therapies, in particular, monoclonal antibodies and fusion proteins that inhibit the function of inflammatory mediators. These agents have become molecular scalpels for studying disease pathways.

Good examples include:

- the inhibition of pro-inflammatory cytokines, such as TNF α , IL-1 and IL-6 by monoclonal antibodies, soluble receptors or receptor antagonists (eg, infliximab, adalimumab, tocilizumab, etanercept, anakinra). These cytokines are produced in large quantities by both innate and adaptive immune cells in the response to various triggers and are therefore applicable in a broad spectrum of auto inflammatory and autoimmune disease;
- the use of an agent (such as the monoclonal antibody rituximab) that is capable of depleting populations cells such as B cells through recognition of lineage specific surface molecules such as CD20;
- the interruption of interaction between antigen presenting cells and lymphocytes by means of an inhibitor of co-stimulatory molecules, such as abatacept (CTLA4-Ig);
- the application of inhibitors of intracellular signal transduction pathways such as the Janus kinase (JAK)/signal transducer and activation of T cells (STAT) that transduce cytokine signals from the cell surface receptor to the nucleus (inhibitors of JAK-1, 2 and 3);

- the inhibition of adhesion of inflammatory cells to endothelium of inflamed tissues, using, for example, an anti-integrin monoclonal antibody (eg, natalizumab or efalizumab);
- the promotion of a regulatory mechanism, such as apoptosis, and, in particular, enhancement of peripheral regulation by the regulatory T cells (eg, anti-CD3 immunotherapy, or IL-2 therapy are currently being analysed in systemic lupus erythematosus and cryoglobulinaemic vasculitis).

In conclusion, it is tempting to speculate that as the cellular and molecular basis of immune mediated diseases become better defined, these clinical disease entities may be reclassified according to the specific pathological pathways involved, as opposed to the patterns of clinical signs and symptoms. This is likely to facilitate diagnosis and the identification of better targeted therapies.

Summary points

- The immune system is a sophisticated machine consisting of a first-line defence barrier called the innate immune system and an acquired arm, termed the adaptive immune system, capable of requiring a memory for specific antigens.
- The innate immune system relies on soluble mediators (eg, complement proteins) and cells (macrophages, dendritic cells, polymorphonuclear cells, mast cells). The latter have the capacity of phagocytosing pathogens and produce inflammatory mediators rapidly. This phase comprises inflammatory mediators (enzymes, antimicrobial peptides, free radicals) as well as vasoactive and chemotactic factors required to facilitate the influx of immune cells.
- The activation of innate immune cells occurs mainly through recognition of microbial products called PAMPs, by receptors called PRRs, among which TLRs and NOD-like receptors. PAMPs induce cellular activation, production of acute inflammatory mediators (enzymes, prostaglandins, nitric oxide) and upregulate molecules on the surface of antigen-presenting cells that activate the adaptive immune system.
- Innate immune cells are programmed to induce an immediate response to the pathogen, whereas the adaptive immune cells (lymphocytes) require training that occurs in the central lymphoid organs (thymus and bone marrow), followed by activation in the peripheral lymphoid organs (spleen, ganglions, bone marrow, mucous membranes).
- Maturation of T cells (in the thymus) and B cells (in the bone marrow) is a fundamental step designed to select 'good' lymphocytes that are highly efficient in destroying pathogens, but incapable of reacting against self-tissue/host proteins. Therefore, these lymphocytes must be tolerant; otherwise, an autoimmune disease will occur.
- The activation of T and B cells in the peripheral lymphoid organs occurs when in contact with the antigen presenting cells of the innate immune system, the 'job' of which is to trap the pathogens in the peripheral tissues in order to present these to lymphocytes. The major antigen presenting cell for T cells is the dendritic cell; the most important intermediate to couple the innate and adaptive immune systems. This antigenic activation occurs mainly in the lymph node, but also in the spleen as well as in cutaneous tissues and mucous membranes.
- 'Professional' antigen presenting cells, such as dendritic cells and macrophages, are a major link between the innate and adaptive immune systems. They play a fundamental role in the induction of immune responses to pathogens as well as the prevention of immune responses to host tissues.
- Humoral immunity plays an important role in the extracellular adaptive immune response. It is characterised by the production of antigen-specific antibodies (immunoglobulins) by antibody-secreting B cells, also called plasma cells. B cells recognise (unprocessed) antigens by means of their BCR. Antibodies are able to bind antigen in order to neutralise or opsonise antigens for lysis by complement or cellular responses.
- Intracellular immune mechanisms are orchestrated through T cells and NK cells. T cells recognise (processed) antigens in the context of HLA, by means of their TCR. HLA molecules, present on the surface of cells, display a molecular fraction of a protein, called a peptide.

- Prevention of an unwanted immune response against self-proteins by T cells occurs through a central tolerance mechanism, initiated during T cell development in the thymus as well as peripheral control systems, including regulatory T cell populations.
- Pro-inflammatory (IL-1, IL-6, TNF α , IL-17) and anti-inflammatory (IL-10, TGF β) cytokines and chemokines provide molecular signals for communication between cells, and play significant roles in sustaining and regulating inflammatory reactions.
- Anomalies of the immune system may arise through functional defects (immune deficiencies and deranged homeostasis) or through excessive functioning (autoimmune diseases, auto-inflammatory syndromes and allergies).
- Listed among the immune deficiencies are congenital diseases (Mendelian inheritance), which can be distinguished from those that can be acquired (most important: HIV infection or immunosuppressive treatment).
- Loss of homeostatic equilibrium in the immune system linked to gene mutations can be manifested as lymphoproliferative and autoimmune diseases, such as the ALPS syndrome that is linked to mutations in the Fas/Fas ligand system.
- Auto-inflammatory diseases are often characterised by genetically acquired deregulation of inflammation. Periodic fever syndromes can be defined among these and comprise the familial Mediterranean fever, hyper-IgD syndrome and other diseases linked to anomalies of the NOD-like receptor genes, such as certain forms of Crohn's disease and Blau's syndrome.
- Autoimmune diseases are mostly characterised by aberrant immune responses of the adaptive system against self-molecules and are often associated with the presence of certain HLA molecules and specific auto-antibodies.

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IN-DEPTH DISCUSSION I

NOD-Like receptors as innate sensors involved in auto-inflammatory disorders.

Auto-inflammatory diseases are caused by the activation of the innate immune system. These disorders are often characterized by intense episodes of inflammation leading to symptoms like fever, rash and swelling of the joints. Auto-inflammatory disorders are not associated with the HLA-system and no auto-antibodies are present.

Many auto-inflammatory disorders are caused by mutations in proteins that are intimately involved in the activation of immune cells through the release of pro-inflammatory molecules. These proteins belong to the NOD-like receptor (NLR)-family and have in common that they, once activated, can proteolytically process several protein substrates including pro-interleukin-1 into their biologically active forms through a caspase-1-mediated process. NOD-like receptors, or NLRs, play a prominent role in the innate immune defence against pathogens, but are also involved in normal tissue homeostasis. Prominent members of the NLR-family are the NOD-2 (nucleotide-binding oligomerization domain) proteins, as well as inflammasomes.

The investigation into the biology of these proteins has been intense in the last years as they are linked to several inherited auto inflammatory syndromes, but are also playing a role in diseases like inflammatory bowel disease (IBD). For example, one of the most prominent genetic risk factors for IBD is found in NOD2, where mutations in the gene that encodes NOD2 predisposes to IBD. NOD2 has an important role in innate immunity as sensor of microbial components derived from bacterial peptidoglycan such as muramyl dipeptide. Apparently, when mutated, it can give rise to aberrant immune response to (gut) bacteria leading to a predisposition for IBD.

NLR-family members have as common feature that they are expressed in the cytosol and when activated through direct- or indirect recognition of a “danger-associated signal” can quickly activate downstream signalling pathways such as those dependent on NF- κ B, or the caspase-1 triggered cleavage of pro-IL-1, pro-IL-18 or pro-IL-33. The latter will lead to the quick activation and release of IL-1 and thereby to immediate inflammation.

Several mutations in NLR-family members, which together consists of 22 proteins, are intimately associated with monogenic and autosomal dominant inflammatory disorders that are characterized by an excessive production of IL-1. For example, mutations in NLRP3 are strongly associated with rare, monogenic and autosomal inflammatory diseases such as neonatal-onset multisystem inflammatory disease (NOMID), familial cold auto inflammatory syndrome (FCAS), Muckle–Wells syndrome and cryopyrin-associated periodic syndrome (CAPS). Similarly, mutation in NOD-2 are not only associated with IBD, but also Blau syndrome, whereas other mutations located in other NLR-family members are associated with familial psoriasis (PSORS2) or CARD14-mediated pustular psoriasis (CAMP5) (please see also figure below for overall structure of NLRs).

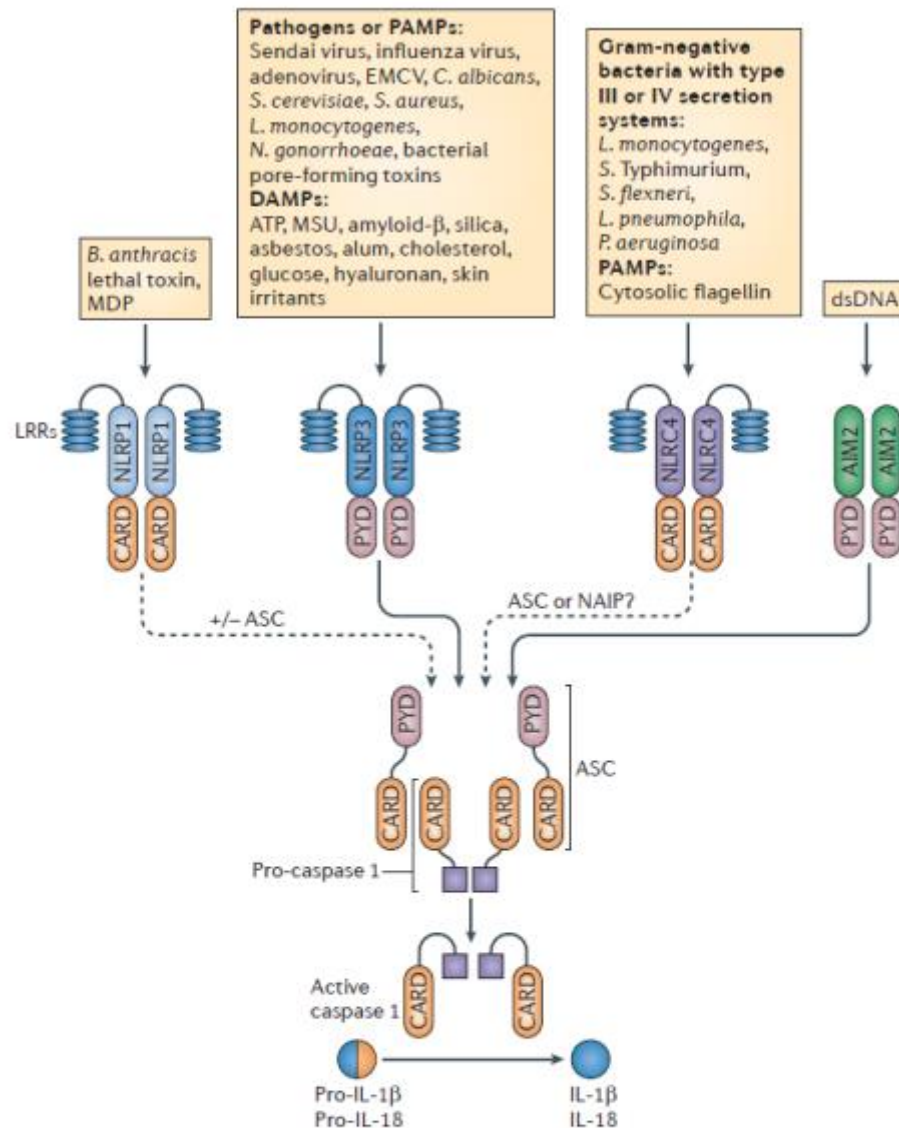


Figure 3 | The NLRP1, NLRP3, NLRC4 and AIM2 inflammasomes. The NOD-, LRR- and pyrin domain-containing 1 (NLRP1) inflammasome is activated by *Bacillus anthracis* lethal toxin and muramyl dipeptide (MDP). The NLRP3 inflammasome is activated by exposure to whole pathogens, pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs) and environmental irritants. The NOD-, LRR- and CARD-containing 4 (NLRC4; also known as IPAF) inflammasome is activated by Gram-negative bacteria with type III or IV secretion systems, and the absent in melanoma 2 (AIM2) inflammasome senses double-stranded DNA (dsDNA). Other complexes (not shown) — such as NLRP6-containing complexes that regulate interleukin-18 (IL-18) production — also exist²⁴, and pyrin probably regulates an inflammasome complex containing ASC but not NLRP3 that activates IL-1 β processing⁶⁹. CARD, caspase recruitment domain; EMCV, encephalomyocarditis virus; LRR, leucine-rich repeat; MSU, monosodium urate; PYD, pyrin domain.

Obviously, not all auto-inflammatory disorders are caused by genetic defects such as exemplified by gout. Gout is a disease characterized, like many inherited inflammatory disorders, by recurrent attacks of acute inflammation, in this case caused by crystals deposit in joints, tendons and surrounding tissues. However, like

the inherited inflammatory disorders, also the deposition of crystals lead ultimately to the activation of the NLR-family, and hence the acute and rapid activation of the IL-1 pathway, subsequently followed by the signs and symptoms characteristic for gout.

Together, recent research into the basic activation of the innate immune system has revealed the relevance and importance of NLRs in the recognition of microbial ligands and danger-signals leading to the production of IL-1- and IL-1-related cytokines. NLR-family triggering can, therefore, lead to an acute inflammatory reaction leading to the control of infection. However, when going uncontrolled, either by genetic aberrations or response to the innocent triggers, they can also be at the basis of several auto-inflammatory disorders such as gout, CAPS or NOMID.

Taken from: Park et al. Nature Reviews Immunology, page 570-580, 2012

For further reading:

Activation and regulation of the inflammasome by Latz, Xiao and Stutz. Nature reviews Immunology, page 397-411, 2013.

Lighting the fires within; the cell biology of auto-inflammatory disorders by Park et al. Nature Reviews Immunology, page 570-580, 2012.



5

module

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IN-DEPTH DISCUSSION II

Autoantibodies in Rheumatoid Arthritis

1. Rheumatoid Factors

1.1 Introduction

Rheumatoid factors (RF) are antibodies that are usually directed against the Fc portion of the immunoglobulin G (IgG) molecule (antibodies to the Fab portion have also been described, but their clinical significance is unclear). Although RF may be of any immunoglobulin class, it is the RF of IgM class that are measured in diagnostic laboratories. IgG rheumatoid factors have been associated with vasculitis, but have not, so far, found a useful role in diagnosis and management in routine clinical practice. On the other hand, IgA RFs have in the past been considered to be more closely associated with cartilage loss and bone erosion in RA. First documented 60 years ago, IgM RF still remains the commonest assay used for the diagnosis of RA (and the sole serological parameter included in the 1987 American College of Rheumatology RA classification criteria for rheumatoid arthritis). Although IgM RF has a sensitivity of ~70%, it has a relatively low specificity as it may be detected in other rheumatic diseases, acute and chronic infections, and at low titre in the elderly healthy population [1]. Indeed, IgM rheumatoid factor is not specific for RA, being found at high titres in Sjögren's syndrome, in a subset of patients with cryoglobulinaemia and in ANCA-associated vasculitis, among others. Lower levels may also be found in SLE, systemic sclerosis, polymyositis and in patients with infections. The RF detected in diseases other than RA is indistinguishable from that detected in RA. The diagnostic specificity of IgM rheumatoid factor is therefore quite low, and, when the appropriate healthy and disease control groups are taken into account, may only be around 50%.

From the work of Schlomchik's group (Leadbetter et al Nature 2002), we know that our IgG become immunogenic when they are part of immune complexes (IC). It is the consequence of the presence of a second signal given by PAMPS present in the antigenic part of the IC to PRR of quiescent B cells with an anti-Fc activity. This explains that RF may appear in all situations when there is an excess of IC: chronic viral infection like HCV infection, acute infections like endocarditis and all the systemic autoimmune diseases.

1.2 Clinical Significance

The commonest finding in RA is the detection of IgM RF, but as described above this finding is not restricted to RA. The finding of both IgM and IgA RF has a higher specificity for RA [2], but is also found in ~25% of patients with primary Sjögren's syndrome. In the context of RA, IgM and IgA RF seem to be indicative of a more severe form of the disease and it has been proposed that these specificities, together with anti-CCP, are useful prognostic markers of RA [3]. However, there is no close correlation between the levels of IgM and IgA RF and markers of disease activity such as ESR and CRP [4]. There has been a report documenting high IgA RF titres associated with inadequate clinical responses to TNF blockade [5], but this association requires confirmation, and as yet no clear mechanism is apparent for such a correlation. The levels of IgM rheumatoid factor may fall

following treatment with TNF-blocking agents or with anti-B cell therapy, although there remains no clear relationship between these changes in titre and clinical response to drug.

1.3 Methodology

RFs may be measured by particle agglutination, nephelometry, turbidometry or by ELISA, and methodological variation may lead to conflicting results being obtained when two different technologies are used in parallel. Most of these techniques have been clinically validated but it is important to interpret the results of any assay in conjunction with the levels found in a normal population as well as in disease profiles relevant for the technology used. It is also important to ascertain whether the assay detects specific RF isotypes, as opposed to RF activity (i.e. IgG binding activity). The commonest methodology has traditionally been passive agglutination of IgG coated beads. However, in recent years these techniques have increasingly been replaced by the use of immunochemical techniques on high throughput analytical platforms.

2. Antibodies to Citrullinated Protein Antigens (ACPA)

2.1 Introduction

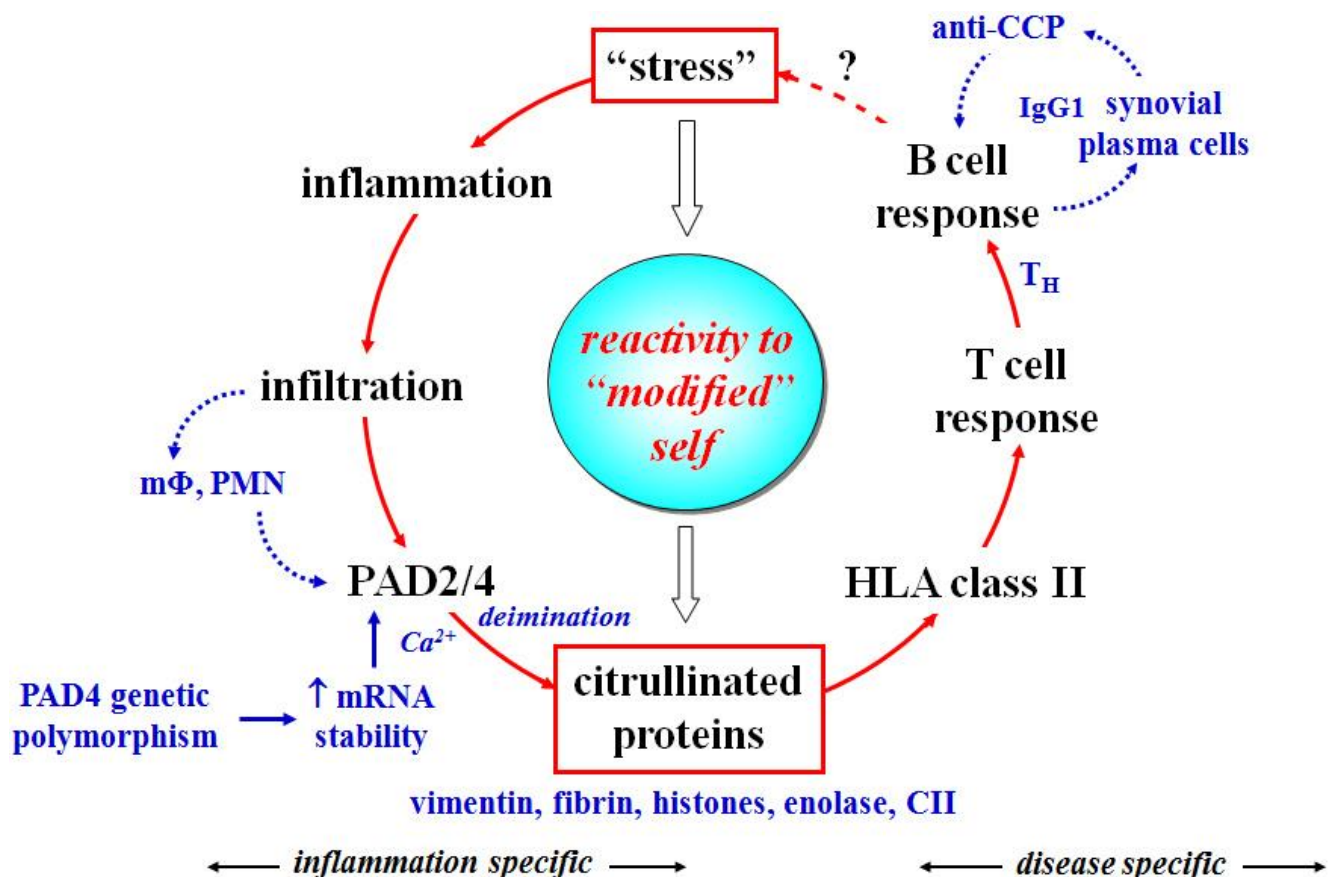
Over the last decade there has been an explosion of interest in research into antibodies to citrullinated protein/peptide antigens (ACPA; reviewed in ref 6). Initially, the fine specificity of ACPA, besides the original study of anti-filagrin antibodies first described in 1998, was poorly defined. Today many ACPA specificities have been documented, perhaps the best documented being antibodies to citrullinated (or de-aminated) filagrin, fibrinogen, vimentin, type II collagen and alpha-enolase. The first commercially available anti-cyclic citrullinated peptide (CCP) antibody assay was launched on the market in 2001.

The history of ACPA is of interest. Anti-perinuclear factor antibody (APF) was first described in 1964, detecting granules around the nucleus of differentiating buccal mucosal epithelial cells by indirect immunofluorescence. However, this cellular source of antigenic substrate was only reliable in ~5% of donors and so the assay was not used routinely in clinical laboratory practice. The APF antibody had a sensitivity of 55-70% and a specificity of ~95% for RA. In 1979 [7], anti-keratin antibody (AKA) was noted by its staining of the epithelial cells of rat oesophagus stratum corneum; these autoantibodies had a sensitivity of 40-60% and a specificity of 90-99% for RA. In 1993, the antigen was identified as filagrin [8]. The molecular basis for the strong correlation between AKA and APF antibody positivity became clearer in 1995, when it was discovered that these autoantibodies recognised the same antigen, namely filagrin [9]. However, technical problems associated with the protein used in the anti-filagrin antibody (AFA) assay, which only had ~ 50% sensitivity for RA, again prohibited routine use in the clinical setting. It was subsequently determined that AFA actually targeted not native amino acid epitopes but citrullinated residues on the filaggrin polypeptide [10]. Antibodies to the citrullinated (or deiminated) alpha and beta chains of fibrin have also been documented as markers of RA. Thus, in early RA,

the autoantibody has a sensitivity of 56-61% (rising to ~70% in late RA), a specificity of 93-99%, PPV ~94%, and may also be detected in a subset (~ 10-15%) of seronegative (i.e. RFneg) patients [11].

Citrulline is not a naturally occurring amino acid. Thus, citrullination (deimination) arises through post-translational protein modification through the conversion of a positively charged arginine amino acid residue into a neutrally charged citrulline. When arginine is oxidised, a terminal nitrogen of the arginine side chain is replaced by an oxygen molecule, with the reaction using one water molecule and releasing ammonia (NH₃) as a by-product. This process is catalysed by a family of calcium-dependent enzymes called peptidylarginine deiminases (PADs), with certain subtypes of PADs being expressed in monocytes (PAD4) and macrophages (PAD4 and PAD2) [12], cells playing a key role in the pathogenesis of RA and whose synovial numbers correlate with rheumatoid joint inflammation [13]. A thought provoking hypothesis for the role of cell death, PAD enzymes and anti-CCP antibodies in RA has been proposed by Zendmen et al [14]. A schematic of citrullination in the context of inflammation is illustrated in Figure 1.

Figure 1 - immune response to CPA is more disease specific



Recent studies have shown that the anti-CCP response in RA is made up of a number of antibodies which react with different citrullinated peptides. These include antibodies to citrullinated forms of filaggrin, fibrinogen, fibronectin, vimentin, type II collagen and alpha-enolase. The repertoire of reactive specificities is

heterogeneous and varies from patient to patient [15]; extensive profiling has not identified to date any correlation between the repertoire of APCA and either clinical phenotype or outcome. Antibodies to citrullinated vimentin and to citrullinated alpha enolase have been shown to be very tightly linked to the genetic-environmental complex of shared epitope, PTPN22 and smoking which is known to be a significant risk factor for the development of RA [16]. Despite this finding there has been little association found between the presence of a specific antibody subtype and disease features such as erosions. As has been reported with anti-CCP antibodies, these specific ACPA can be detected years before the clinical onset of the disease, and one study has shown that maturation of the ACPA repertoire, in terms of both antigenic specificity and immunoglobulin isotype usage, occurs predominantly before the onset of clinical disease [17].

2.2 Clinical Significance

The most commonly used anti-CCP antibody (termed anti-CCP2) assay exploits a mixture of synthetically derived cyclic citrullinated peptides with no known homology to tissue proteins, and was generated with RA sera after screening large libraries of derivatised peptides. As such, CCP2 is not an antigen in the conventional sense of the term, but the benefit of synthetic peptide production and purification is that it is cheap and reproducible, with uniform citrullination of the peptides.

The anti-CCP2 assay has been reported to have a sensitivity as high as 80% and a specificity of 95-99%. Its production is independent of RF and so there exist subsets of anti-CCP positive patients (~ 10-15%) who are negative for IgM RF. Interestingly, the association between HLA-DRB1 and patients with RA appears to be intimately linked with anti-CCP, independently of RF, suggesting that SE+ HLA-DRB1 alleles predispose not to RA per se, but to immunity to citrullinated proteins [18]. While IgM RF levels have been found to decrease with treatment, anti-CCP antibody concentrations do not appear to change significantly, limiting the use of anti-CCP as a marker of disease activity or as an indicator of response to treatment. There is also no correlation between the levels of anti-CCP and markers of disease activity such as ESR and CRP [4]. There is increasing evidence that anti-CCP antibodies are also detected at a low frequency in patients with other connective tissue diseases including Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease and idiopathic inflammatory myositis. A common clinical denominator, which could account for these findings, may be the presence of joint erosions in patients that have these other conditions, since anti-CCP positive RA has been associated with a more aggressive disease course, with respect to radiographic progression [19]. In a cross-sectional study of patients enrolled in the British Society of Rheumatology Biologics Register, the presence of anti-CCP antibodies was associated with a poorer response to anti-TNF agents at 6 months [20]. However, a model comprising both clinical and serological predictors could only account for a small proportion of variance in drug response ($R^2=0.17$) and would be of no value in predicting an individual patient's outcome. Recently, a novel subtype of antibodies that recognise homocitrulline have been identified [21]. These arise through carbamylation of self-proteins and are termed anti-CarP

autoantibodies. They appear to be specific for RA, distinct from anti-CCP (since they do not cross react) and can be found in a proportion of RA patients who are negative by anti-CCP2 testing. The full clinical utility of this subset await further investigation. Autoantibodies to PAD have also been described.

2.3 Methodology

Assays detecting antibodies to citrullinated peptides or proteins use conventional ELISA methodology. It has also become common research laboratory practice to screen for the presence of citrullinated specificities by de-aminating recombinant antigens in vitro, and comparing the reactivity of RA serum to both unmodified and modified antigen by Immunoblotting or ELISA. A number of the commercially produced assays use a range of different antigenic targets from varying sources, and this has led to some variations in specificities and sensitivities from those recorded with the prototype anti-CCP2 test. Somewhat confusingly, some of these newer generation assays are also referred to as 'CCP'.

3. Future Developments

The advent of ACPA has defined a new era in understanding autoimmunity in RA. Whether they reflect autoimmunity to “inflammation”, or arise as a consequence of cell stress and death remain topics of much debate [22]. Following these discoveries, and influenced by the recognition of the heterogeneous nature of the disease and the advent of costly biological therapy, much time and energy is currently being invested in the finer classification of the autoantibody response in RA as a potential method of sub-classifying RA patients. It may be that, among other immunological parameters, ACPA profiles will turn out to be most helpful in identifying those subjects with joint pains (arthralgia) at most risk of developing RA. For example, in blood bank serum samples, one study showed that 34% of the RA patients were positive for ACPA up to nine years prior to diagnosis (23). Whilst another study showed that 49% of the RA patients tested positive for IgM- RF and/or ACPA at a median of 4.5 years before symptom onset (24). Using banked sera from the Nurses' Health Study, anti-CCP antibodies were detected up to 12 years prior to diagnosis (25). ACPA may also inform outcome, disease severity, as well as response to therapy. In addition to IgM, IgA RF and anti-CCP it is likely that other autoantibody markers will emerge in the coming years. It will prove be challenging for both the clinician and the pathology laboratory to provide robust, clinically informative assays. It would seem likely that one productive way forward will be to use multi-parametric assay systems where a panel of the dominant specificities are measured in a single assay, perhaps combined with an algorithm which enables the clinician to interpret the results obtained with respect to the sub-classification of disease, the clinical phenotype and longer term outcome for that disease subset.

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Spondyloarthritis: Pathogenesis, clinical aspects and diagnosis

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LEARNING OUTCOMES

- ➔ Discuss the concept of spondyloarthritis (SpA)
- ➔ Describe the pathophysiology of these disorders and the role of genetic and environmental factors
- ➔ Explain the different hypotheses for the role of HLA-B27 in the pathogenesis of these disorders
- ➔ Explain the approach to the diagnosis of SpA
- ➔ Improve assessment of patients with SpA, especially disease 'activity', 'severity' and 'refractory' characteristics of the disease
- ➔ Present treatment strategies for patients with ankylosing spondylitis
- ➔ Describe the use of the different tools allowing better patient monitoring

1 The concept of spondyloarthritis

Spondyloarthritis (SpA) is a heterogeneous group of chronic inter-related inflammatory arthropathies affecting mainly the spine but also showing peripheral symptoms in the joints, entheses and certain extra-articular sites. The SpA group includes axial SpA (axSpA ; incorporating non-radiographic axSpA and ankylosing spondylitis (AS)), peripheral SpA, reactive arthritis (ReA), psoriatic arthritis (PsA), enteropathic-related arthritis and juvenile SpA (box 1). AS is termed the prototype of SpA. The introduction of the new ASAS classification criteria for axSpA and peripheral SpA has facilitated understanding of the concept of SpA and incorporated this into clinical practice and trials.

Box 1 Clinical presentation of SpA

Disease subgroups

- AxSpA including AS and non-radiographic axSpA
- Peripheral SpA
- PsA
- Reactive arthritis
- Inflammatory bowel disease/enteropathic-related arthritis
- Juvenile SpA

Clinical features

- Rheumatological manifestations
 - o Axial involvement
 - o Peripheral arthritis
 - o Enthesopathy
- Extra-articular features
 - Acute anterior uveitis
 - o Psoriasis
 - o Inflammatory bowel disease
 - o Cardiac involvement (e.g., heart block, aortic insufficiency)
- Genetic background
 - o Family history
 - o HLA-B27 antigen
-

AS, ankylosing spondylitis; axSpA, axial spondyloarthritis ; PsA, psoriatic arthritis; SpA, spondyloarthritis.

Adapted from Dougados and Hochberg, Best Pract Res Clin Rheumatol 2002;16:495–505.

SpA occurs primarily in genetically predisposed individuals, particularly those who are positive for the major histocompatibility complex (MHC) class I molecule HLA-B27. However, additional genetic and environmental factors play a role in its pathogenesis. It can be difficult to differentiate these disorders because their clinical features may overlap, which is why undifferentiated forms of SpA are also recognised.

The monitoring and treatment of these diseases is related more closely to the clinical presentation (axial versus peripheral) than to the precise diagnosis. The rheumatic manifestations include inflammation of the spine and sacroiliac (SI) joints, peripheral arthritis and enthesitis (inflammation at the entheses, the sites of attachment of tendons, ligaments, fasciae or joint capsules to bone). Enthesitis is the distinguishing pathological feature of SpA. The extra-articular manifestations of the disease may be similar whatever the SpA subgroup or may be specific to a SpA subgroup, such as skin lesions in PsA, gut involvement in inflammatory bowel disease-related arthritis and the oculo-urethro-synovial triad in classic ReA.

1.1 Subtypes

SpA can present with a wide spectrum of clinical features. Certain features occur more commonly in some subtypes of SpA. Table 1 shows typical patterns of SpA subtypes. However, symptoms overlap and so it is possible for any of the principal clinical features to be present in any of the distinct diseases.

Table 1 Prevalence of clinical features/disease in spondyloarthritis (SpA)

Clinical features/diseases	AxSpA	Psoriatic arthritis	Enteropathic arthritis	Reactive arthritis	Juvenile-onset SpA	Peripheral SpA
Axial involvement	+++	++	+	+	+	+
Peripheral arthritis	+	+++	++	++	++	+++
Enthesitis	+	++	+	+	+	++
Extra-articular features:						
Uveitis	++		+	+	+	+
Psoriasis		+++				+
Diarrhoea	+		+++	+		+
Conjunctivitis, urethritis				+++		
Aortic insufficiency	+		+	+	+	+

1.1.1 AxSpA including AS

AS is the prototype of axSpA. It is characterised by the presence of spinal pain, resulting in limitation of spinal mobility and radiological evidence of structural changes in the SI joints and the spine. Nevertheless, other manifestations can also be seen, such as enthesitis (40–60%), acute anterior uveitis (30–50%) and colitis (15% symptomatic, 60% microscopic). The disease course of axSpA is highly variable and characterised by ongoing axial inflammation and radiographic progression associated with restricted mobility of the spine and decreased function. Since axSpA usually starts in early adulthood, the lifetime impact of the disease can be considerable, resulting in stiffness, fatigue, limitation of social activities and participation.

The modified New York criteria (see box 7, section 6.1 Plain radiographs) have been widely accepted in clinical practice and in clinical trials to classify patients as having AS. Although they work well in established disease,

they require evidence of structural radiographic changes, so are limited for capturing the early disease stages and not all patients with suggestive clinical features develop radiographic changes. This was the reason why the Assessment of SpA international Society (ASAS) developed new classification criteria for patients with axSpA (with and without radiographic changes) and also for those with peripheral SpA (for further details see boxes 8 and 9, section 7. Classification).

1.1.2 Psoriatic arthritis

Psoriasis is a common skin disease among Caucasian subjects (1–3% prevalence), but uncommon in some other ethnic groups, such as Afro-Caribbean and Native American populations (0–0.3%). It affects men and women equally. About 10–20% of patients have associated PsA. Psoriasis usually predates the appearance of arthritis, but the onset is simultaneous in 20% of patients, and in up to 15% the arthritis may precede the onset or diagnostic recognition of psoriasis. The arthritis usually starts between 30 and 50 years of age, but may also begin in childhood. In most patients, exacerbations and remissions of skin and joint involvement occur with little or no apparent relationship. PsA is a heterogeneous disease that may involve the peripheral or axial skeleton. Recognisable PsA phenotypes include: asymmetric oligoarthritis; predominantly distal interphalangeal disease; peripheral polyarthritis (rheumatoid-like); predominantly enthesal disease; or dominant axial disease (~5%). Many patients also develop sausage-shaped swelling of digits called dactylitis. Occasionally patients present with a mutilating type of disease affecting mainly the digits with osteolysis, called ‘arthritis mutilans’. PsA is characterised radiologically by juxta-articular new bone formation and erosions (in contrast to rheumatoid arthritis which is not associated with new bone formation). Treatments were historically adapted from those used in rheumatoid arthritis, but increasingly new biologic therapies are adapted from psoriasis.

The CASPAR (Classification Criteria for Psoriatic ARthritis) criteria were developed by an international study group and have a sensitivity of 91% and a specificity of 99% (box 2).

Box 2 CASPAR (Classification Criteria for Psoriatic ARthritis)

A patient must have inflammatory articular disease (joint, spine or entheses) AND ≥3 points from the following:

- Current psoriasis (score 2) or a personal or family (1st or 2nd degree relative) history of psoriasis (score 1)
- Dactylitis—score 1
- Juxta-articular new-bone formation on x-ray—score 1
- Rheumatoid factor negativity—score 1
- Nail dystrophy—score 1

Adapted from Taylor et al, Arthritis Rheum 2006;54:2665–73.

The SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis) syndrome also presents with skin and musculoskeletal features that suggest it may belong in the SpA spectrum.

It shares many clinical and radiological similarities with SpA and in particular with PsA, including lesions similar to pustular psoriasis (Figure 1), sacroiliitis and enthesopathy. Furthermore, the possible role of IL-17 in the pathophysiology of SAPHO has been recently appreciated, suggesting shared pathophysiology.

Figure 1: palmar pustulosis in a patient with SAPHO syndrome. [Source: CRI (Club Rhumatismes et Inflammation, <http://www.cri-net.com>)]



On the other hand, SAPHO does not exhibit a strong HLA-B27 association or familial predisposition and is not associated with uveitis or inflammatory bowel disease (IBD). The scarcity of the disease and lack of large-scale clinical studies have precluded the in-depth exploration of the disease and its optimal treatment.

Hidradenitis suppurativa is an inflammatory skin condition of hair follicles in areas of friction in the body (e.g. axilla, groin) that has also been reported to be associated with IBD and SpA. Hidradenitis suppurativa is also strongly associated with obesity and the metabolic syndrome. Interestingly, the arthritis seen in association with hidradenitis suppurativa is HLA-B27 negative and may often flare up in conjunction with flares of the skin disease.

1.1.3 Enteropathic arthritis

Enteropathic arthritis describes the occurrence of inflammatory arthritis in patients with ulcerative colitis or Crohn's disease. The prevalence of arthritis in IBD ranges from 17% to 20%, with a higher prevalence in Crohn's disease.

The most common manifestation of enteropathic arthritis is inflammation of the knee and ankle joints as part of a peripheral oligoarthritis. The peripheral arthritis may be transient, migratory and non-deforming, although in some cases the arthritis may become chronic and destructive. Axial involvement and enthesitis may also be found, often as incidental findings on imaging such as abdominal CT scans. Intestinal symptoms usually antedate or coincide with joint manifestations, but arthritis may precede the intestinal symptoms by years.

1.1.4 Reactive arthritis

ReA describes an episode of aseptic peripheral arthritis that occurs within 1 month of a primary infection elsewhere in the body, usually a genitourinary infection with *Chlamydia trachomatis* or enteritis due to Gram-negative enterobacteria such as *Shigella*, *Salmonella*, *Yersinia* or *Campylobacter* species. Genitourinary tract infection with *Chlamydia trachomatis* is the most commonly recognised initiator of ReA in developed countries, whereas infections with enterobacteria are the most common triggers in developing parts of the world (box 3). In about 25% of cases, however, the triggering organism is unknown.

Box 3 Bacteria that trigger reactive arthritis

- *Chlamydia trachomatis*
- *Shigella flexneri*
- *Salmonella* spp
- *Yersinia enterocolitica*
- *Yersinia pseudotuberculosis*
- *Campylobacter fetus jejuni*
- *Clostridium difficile*
- Intravesical injection of bacilli Calmette–Guérin (BCG) to treat bladder cancer
- *Chlamydia pneumoniae* (unconfirmed)

Adapted from Smith et al, Best Pract Res Clin Rheumatol 2006;20:571–92.

ReA is typically an acute, asymmetrical oligoarthritis and is often associated with one or more characteristic extra-articular features, such as ocular inflammation (conjunctivitis or acute iritis), enthesitis, mucocutaneous lesions, urethritis and, on rare occasions, carditis. Conjunctivitis occurs in one-third of patients, usually at the same time as arthritis flares, and acute anterior uveitis may occur at some time in about 5% of patients. The triad of arthritis, conjunctivitis and urethritis is called classic ReA. However, most patients with ReA do not present with this triad. The average duration of arthritis is 4–5 months, but two-thirds of patients have mild musculoskeletal symptoms that persist for more than 1 year. Recurrent attacks are more common in patients with chlamydia-induced ReA. About 15–30% of patients develop chronic or recurrent peripheral arthritis, sacroiliitis or spondylitis. Most patients with chronic ReA have a positive family history of SpA or are HLA-B27 positive.

1.1.5 Juvenile-onset SpA

Juvenile-onset SpA usually manifests initially as peripheral arthritis or enthesitis in children aged 8–12 years, but onset at younger or older ages has been reported. There is a striking predominance of male subjects, particularly in the prepubertal stage. Juvenile-onset SpA clinically resembles adult SpA. Nonetheless, there are a few differences. Oligoarthritis affecting the knee, ankle and/or mid-foot is the typical initial presentation, and dactylitis is commoner in children. Systemic manifestations such as fever and weight loss occur more often in children, and enthesitis is prominent early on in the disease course.

The disease pattern often changes throughout childhood, adolescence and adulthood (e.g., from monoarthritis to a more complex form of disease, comprising axial, peripheral and extra-articular manifestations).

There are undifferentiated and differentiated forms of juvenile-onset SpA, which can be classified according to the International Association for Rheumatology criteria in the enthesitis-related arthritis subgroup. The adult Amor and European Spondyloarthropathy Study Group criteria have been validated in children and may also be used. Prognosis seems to be less favourable in juvenile-onset SpA than in adults. Structural damage, particularly in the feet, hips and spine, may lead to long-term functional impairment. Nearly 60% of patients have moderate-to-severe limitations 10 years after disease onset. The probability of remission is only 17% after a disease duration of 5 years.

2 Epidemiology

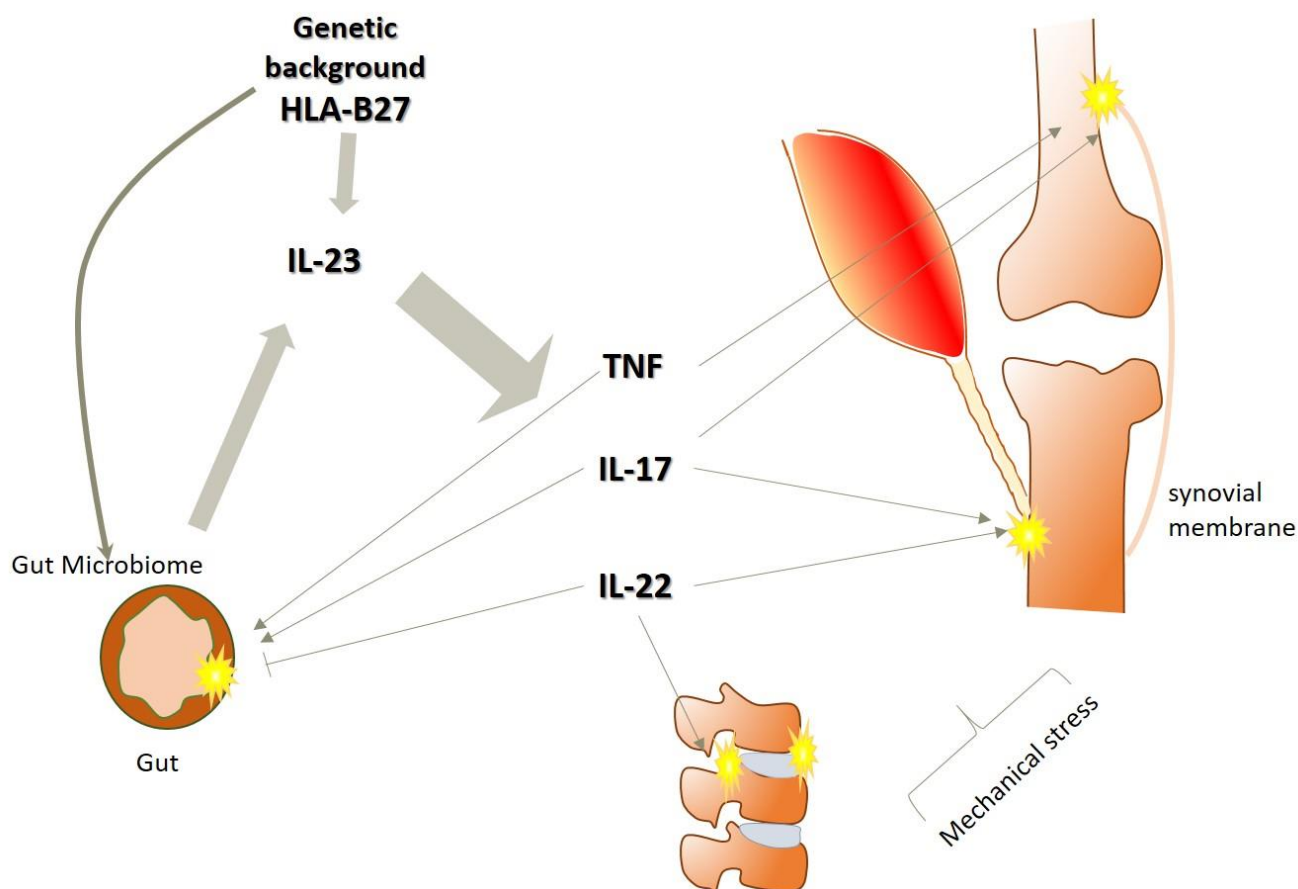
There is a paucity of good epidemiological studies to define the true incidence and prevalence of AS, axSpA and SpA, with wide variation as a result of geographic, demographic and methodological factors. Furthermore, most of the published epidemiological studies pre-date the development of the ASAS criteria for axSpA, and therefore most of the data relates to AS rather than axSpA. The prevalence varies significantly among different ethnic populations, being higher in white and certain Native American subjects and lower in African American and Asian subjects. The estimated global prevalence of AS ranges between 0.01% and 0.2%, with estimates of around 0.3% in European populations. Estimates for the prevalence of the broader axSpA population range from 0.3% up to 1.4% in Caucasian populations. The prevalence of AS parallels that of the HLA-B27 gene. Eight per cent of the healthy white population is HLA-B27 positive, while 4% of the healthy African American population is HLA-B27 positive. Ninety-two per cent of the white AS population is HLA-B27 positive, while 50% of the African American AS population is HLA-B27 positive. Up to sixty per cent of patients with ReA, PsA and enteropathic spondylitis are HLA-B27 positive, while 25% of patients with undifferentiated SpA are HLA-B27 positive. The chance of developing AS if one is HLA-B27 positive is 1–5%, increasing to 15–20% for people with an affected first-degree relative.

AS is more common in male subjects, with the male: female ratio being 2:1 to 3:1. However, in recent cohort studies of axSpA, this ratio has been found to be more equally distributed between genders. The reasons why male patients seem to progress more frequently than female patients towards development of AS are still unclear. The mean age of diagnosis is 26 years, but it can present from late adolescence to 45 years of age. There is often significant delay in diagnosis, especially in HLA-B27-negative patients. A shorter time to diagnosis was observed in patients with inflammatory back pain (IBP) or a positive family history because clinical suspicion tended to be higher.

3 Pathogenesis

The exact aetiology of SpA is still unknown but is likely to be a complex interplay of genetic and environmental factors with the microbiome and/or biomechanical stress (Figure 2)

Figure 2: SpA pathogenesis at a glance. A complex interplay of genetic, environmental factors, biomechanics and microbiome. Genetic alterations (including HLA-B27) and changes in the intestinal microbiota (dysbiosis) may produce aberrant immune responses, including activation of IL-23/-17 axis. Synovitis and gastrointestinal inflammation have been associated with IL-17 and TNF. Mechanical stress has been proposed also to associate with enthesitis and new bone formation in animal models of SpA. The involvement of IL-23, IL-17 and IL-22 can help explain the combination of erosive and osteoproliferative musculoskeletal changes seen in SpA.



3.1 Genetics

The involvement of genetic factors in determining susceptibility to SpA has long been suspected owing to frequent familial clustering of cases. The first genetic factor identified was gene encoding the surface antigen HLA-B27. Further genetic studies have led to the discovery of other genes important in disease susceptibility, including various HLA-B27 subtypes as well as non-HLA-B27 MHC and non-MHC genes, although it is not clear how these cause the disease. Studies are still in the early phase but potentially might provide further insight into disease pathogenesis and translate into future diagnostic and prognostic tools.

3.1.1 Methodology of genetic studies

The genetic analysis of complex, multifactorial diseases such as SpA is difficult owing to numerous factors. The model underlying the inheritance of the disease is unknown, although several genes are likely to be involved, which may be different from patient to patient (genetic heterogeneity). Moreover, the molecular variants of a gene (alleles) associated with disease susceptibility may be present in healthy subjects, suggesting that exposure to specific environmental factors is probably required to cause the disease to develop (incomplete penetrance). Discovering genes through family-based or candidate gene methods has not been successful. Using high-throughput microarray-based single nucleotide polymorphism (SNP) genotyping techniques has made it easier to identify genes associated with SpA more rapidly.

3.1.2 Family and twin studies

Twin studies in AS have shown a monozygotic concordance rate of around 70%. The genetic risk determines the risk of developing the disease and also the age of onset, clinical disease severity and radiographic severity, although to date, no genes have been consistently identified that are associated with the ankylosis process. Family and modelling studies have indicated that heritability contributes more than 90% to the overall susceptibility of developing AS, with <50% of the genetic risk due to HLA-B27. First-degree relatives have a 5–16% risk of developing the disease, while only 1–5% of HLA-B27 individuals develop AS, suggesting that other genes and environmental factors are involved. HLA-B27-positive relatives of patients with AS have a risk of developing AS that is 5.6–16 times greater than in HLA-B27 individuals in the normal population.

3.1.3 HLA-B27 gene

In 1973, the association of HLA-B27 with the development of AS was reported by two separate groups. Nevertheless, despite extensive investigation, the precise role of HLA-B27 in the pathophysiology of the disease remains unknown.

Three major theories have been proposed to explain how HLA-B27 contributes to the pathophysiology of AS:

1. Arthritogenic peptide theory

This theory proposes that HLA-B27 presents self-peptide complexes, thereby eliciting an autoreactive inflammatory response. However, to date, no arthritogenic peptides have been identified and the HLA-B27 animal model of SpA has been shown to be dependent upon CD4+ (helper) and not CD8+ (cytotoxic) T cells.

2. Endoplasmic reticulum stress and unfolded protein response theory

This theory proposes that HLA-B27 chains misfold and remain in the endoplasmic reticulum for longer. This in turn is proposed to result in endoplasmic reticulum stress and precipitate the pro-inflammatory unfolded protein response in an attempt at homeostasis. Recent data have however raised doubt about endoplasmic reticulum stress and the unfolded protein response model in AS.

3. Homodimerisation theory

HLA-B27 heavy chains have a propensity to self-associate and homodimerize, resulting in the expression of homodimers on the cell surface which are recognized by receptors on Th17 and natural killer cells, resulting in IL-17 production.

It should be noted that there are over 50 subtypes of HLA-B27 and that not all subtypes are associated with AS, while some even appear to be protective.

3.1.4 Non-HLA-B27 MHC genes

The MHC consists of about 220 genes, many of which have immunoregulatory functions. Other non-HLA-B27 MHC genes have been implicated in AS, but in many cases these have been confounded by linkage to HLA-B27, lack of sufficient marker density or not been replicated in other cohorts.

3.1.5 Non-MHC genes

More recently, large genome-wide association studies have identified a number of non-MHC genes which are associated with AS. The first study was carried out by the Wellcome Trust Case Consortium and the Australo-Anglo-American Spondyloarthritis Consortium (TASC, 2010*) which identified disease associations with interleukin 23 receptor (IL-23R) and endoplasmic reticulum aminopeptidase 1 (ERAP1). IL-23R is also linked with IBD and PsA. This may partially explain the frequent coexistence of these diseases.

The second study carried out by TASC was a complete genome-wide association study, which confirmed the above and identified new associations with IL-1R2, ANTXR2 and gene deserts (regions of the genome lacking protein-encoding genes) at chromosomes 2p15 and 21q22. Strong evidence to support association with the disease has also been demonstrated for the TNFSF15 and TNFR1 genes and a region on chromosome 16q,

including the TRADD gene. The exact role of these genes in AS remains to be determined, but of interest, many implicate innate immunity, antigen-presentation and the IL-23/17 pathway. ERAP-1 is of particular interest as the related protein also involved in antigen-processing (as a molecular ruler) and the ERAP-1 association with AS is only seen in patients who are HLA-B27 positive, indicating a gene-gene interaction.

3.2 Infections

Abnormalities in gut microbiota are increasingly implicated in rheumatic diseases including AS. The B27-transgenic (Tg) rats develop a SpA-like disease when housed in a probiotic (non-germ free) environment, but not, when raised under entirely germ-free conditions. Interestingly, colonisation of the gastrointestinal tract with normal gut flora, in particular *Bacteroides* spp, is sufficient to trigger inflammation. The severity of the SpA-like disease developed by B27-Tg rats correlates with levels of HLA-B27 expression.

Several gastrointestinal or genitourinary pathogens have been strongly implicated as triggers of HLA-B27-associated ReA in humans, including *Campylobacter* spp, *Chlamydia* spp, *Salmonella* spp and *Shigella* spp (box 2). While DNA from these organisms has been found by polymerase chain reaction in synovial cell and fluid samples, this remains controversial but does point towards a potential link between gut infection and joint inflammation. Recent studies have reported altered gut microbiota signatures in patients with AS or PsA, compared to healthy individuals, suggesting a potential role for alterations in the microbiome in the pathogenesis of SpA.

3.3 Inflammation

The most common sites of inflammation in AS include the SI joints, entheses, vertebral bodies adjacent to intervertebral discs, peripheral joint synovium, gastrointestinal tract and the eye. As many of these lesions are poorly accessible, information on histopathology is limited. In early sacroiliitis, synovitis with myxoid-appearing bone marrow and subsequent formation of granulation tissue is seen. Destroyed bone is eventually replaced and endochondral ossification results in bony ankylosis. Histologically, there is infiltration of T cells (CD4+ and CD8+) and CD68+ macrophages, proliferation of fibroblasts, and neovascularisation as well as tumour necrosis factor blocker (TNF α) and transforming growth factor β mRNA overexpression.

Synovitis in SpA displays features of other types of inflammatory arthritis, such as increased vascularity and endothelial cell activation, with increased expression of adhesion molecules and chemotactic factors. Relevant differences with rheumatoid arthritis include a tendency towards greater vascularity, greater CD4+ T cell and CD20+ B cell infiltration and few lymphoid aggregates. A recent study in a TNF α overexpressing mouse model suggested that mesenchymal stromal cells are the main target activated by TNF α signalling. These mice spontaneously develop an inflammatory disease characterised by Crohn-like arthritis, sacroiliitis, peripheral arthritis and enteritis (Armaka et al, 2008).

TNF α , but also other proinflammatory cytokines, are directly connected with Dickkopf-1, which leads to an upregulation of Dickkopf-1, a key target gene of TNF and an inhibitor of osteoblast differentiation and activation. AS is associated with reduced levels of Dickkopf-1 and sclerostin which has been proposed to result in increased new bone formation, the hallmark radiographic sign of AS.

Enthesitis is a hallmark of SpA. Inflammatory lesions are characterised by soft tissue inflammation and bone marrow infiltration with CD8 and CD4 T cells, B cells, macrophages and osteoclasts. This is more common at peripheral sites subject to biomechanical stresses and rich in fibrocartilage containing type II collagen and aggrecan proteoglycan, such as at the insertion of the Achilles tendon into the calcaneum. In the early phase of enthesitis, CD68+ and macrophages (1 month to 1 year of disease) seem to predominate, while abundant lymphocytes tend to be found in established disease. Recent animal models (covered in section 3.3.1) have started to help explain the link between systemic IL-23 and enthesitis.

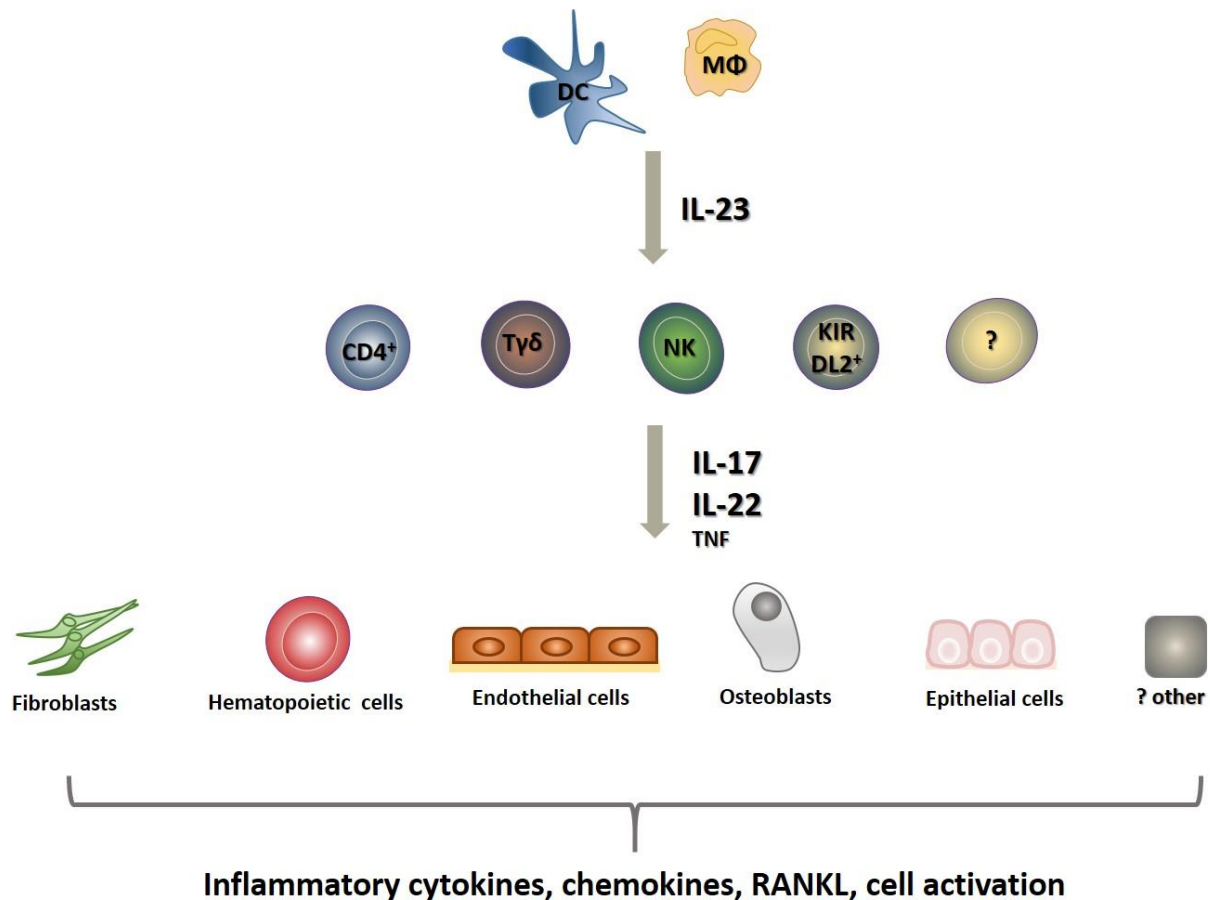
3.3.1 The Interleukin 23/Interleukin 17 (IL-23/-17) axis

The IL-23/-17 pathway appears to play a crucial role in the pathogenesis of SpA. IL-23 is thought to be the main regulator of the axis. It consists of the p19 and p40 subunits, sharing the latter with IL-12. IL-23 is mainly secreted by activated macrophages and dendritic cells, and acts through the IL-12R β 1 and IL-23R receptors, driving a Th17 response. Ligation of IL-23 to its receptor upregulates the transcription factor ROR γ t leading to the production of various chemokines and cytokines including TNF α , IL-21, IL-26 and most importantly in SpA, IL-17 and IL-22 (Figure 3).

There are 6 forms of IL-17 (IL-17 A-F) with IL-17A and IL-17F being the best characterised. Activated CD4⁺ T (Th17) cells were initially thought to be the primary cells for IL-17 production, but, it is now recognised that many other cell types, including subpopulations of natural killer cells (NKp46+), CD8+ NK (NKT) cells, $\gamma\delta$ T cells, KIRDL2+CD4+, innate lymphoid cells, Paneth cells and neutrophils, can also express and possibly produce significant amounts of IL-17 (Figure 3).

The IL-17 cytokines are able to act in a plethora of cells since their receptors are expressed by hematopoietic cells, epithelial cells, endothelial cells, fibroblasts, keratinocytes, osteoblasts and monocytes/macrophages. The triggering of IL-17 receptor can lead to the expression of various pro-inflammatory cytokines (IL-6, IL-8, TNF α and IL-1 β), metalloproteinases, chemokines (CXCL8, CXCL1, CXCL5, CXCL2 and CXCL10) and RANKL by osteoblasts (Figure 3).

Figure 3: IL-23/-17 axis. IL-23 drives IL-17 and IL-22 production, which act on a number of target cells to produce inflammatory cytokines, chemokines and other molecules which lead to the phenotype seen in SpA. DC: Dendritic cells, MΦ: Macrophages, NK: Natural Killers, KIR: killer immunoglobulin-like receptor



There is now substantial evidence indicating that IL-23, IL-17 and IL-22 are central players in the pathogenesis of SpA (Smith and Colbert, 2014). Firstly, genetic studies in AS patients have revealed nucleotide polymorphisms in genes that are directly (*IL-23R*) or indirectly (e.g. *STAT3*) involved in this pathway. Some of these SNPs have been also found to associate with Crohn's disease and psoriasis. Secondly, data from animal models suggest a prominent role of the IL-23/-17 axis in SpA, including enthesitis. A recent study has reported a novel class of IL-23R positive (IL-23⁺RORγt⁺CD4⁺CD8⁻) T cells in enthesal sites in a mouse model which develops enthesitis in response to overexpression of IL-23, suggesting that not only can mechanical stresses trigger inflammatory responses, but that systemic IL-23 can lead to inflammation at these sites ([Sherlock JP et al, 2012](#)). Thirdly, human in-vivo and in-vitro studies, have shown that IL-17 is increased in the serum and the synovial fluid of SpA patients. In line with these finding, IL-17 producing cells are also found to be increased in the peripheral blood of patients with SpA, compared to healthy individuals; however, there are some discordances between studies. Surprisingly, in non-radiographic AS, CD4⁺ T cells producing IL-17 have been reported to be decreased in patients' peripheral blood, reflecting the possible differences among the phenotypes of axSpA. There are reports of increased IL-17 expression at the tissue level IL-17 in SpA patients,

although there is some inconsistency in the cells reported to express IL-17 and these studies require further validation.

Finally, a close association between the HLA-B27 and IL-17/-23 axis has been described. In HLA-B27/human β 2-microglobulin-transgenic (B27-Tg) rats, which display skin disease, arthritis and colitis suggestive of the SpA phenotype, Th17 cells were found to be expanded in lymph nodes and with increased frequency of IL-17-producing cells reported in their joints. Furthermore, misfolding of HLA-B27 in the endoplasmic reticulum leads to the formation of dimers and oligomers. One theory of HLA-B27 pathogenesis in AS that has received significant attention recently suggests that HLA-B27 homodimers are able to directly trigger CD4⁺ and NK cells expressing KIRDL2⁺, leading to IL-17 production. The efficacy of agents that inhibit IL-17 in recent clinical trials is further support that this is an important pathway in SpA and suitable target for therapeutic intervention.

4 Clinical features

4.1 Rheumatological manifestations

4.1.1 Inflammatory back pain

IBP is the first clinical manifestation in 75% of patients with axSpA. Classically, the pain starts in the lumbar region or at the lumbosacral junction. It is typically a dull pain of insidious onset, becoming persistent after a few months. The pain worsens with inactivity and improves with exercise and non-steroidal anti-inflammatory drugs (NSAIDs). Morning stiffness is often prolonged (>30 min) and nocturnal pain may awaken patients from sleep. On imaging, sacroiliitis or spondylitis is the dominant finding. If there is progression to ankylosis over time, the inflammatory pain usually lessens but is replaced by relevant functional impairment. Symptoms may be mild with intermittent flares and remission. An acute onset of pain, worsening symptoms with activity and radicular pain are more suggestive of a mechanical or degenerative cause, but both pathologies may also occur in the same patient. Three different sets of IBP criteria with similar sensitivities and specificities have been proposed (boxes 4, 5 and 6).

Box 4 Calin inflammatory back pain criteria

At least four of the following:

- Insidious onset
- Onset before the age of 40 years
- At least 3 months' duration
- Morning stiffness \geq 30 min
- Improvement with exercise

If four of these five criteria are fulfilled, sensitivity is 95% and specificity is 85%.

Adapted from Calin et al, JAMA 1997;237:2613–4.

Box 5 Berlin inflammatory back pain criteria

These require a patient to be aged <50 years with chronic back pain (>3 months duration) and at least two of the following:

- Morning stiffness ≥ 30 min
- Improvement with exercise but not with rest
- Awakening because of back pain during the second part of the night
- Alternating buttock pain

If two of these four criteria are fulfilled, sensitivity is 70% and specificity is 81%. If three out of four criteria are fulfilled, sensitivity is 33% and specificity is 98%.

Adapted from Rudwaleit et al, Arthritis Rheum 2006;54:569–78.

Box 6 ASAS expert criteria for inflammatory back pain

These require a patient to have chronic back pain (>3 months duration) and at least four of the following:

- Improvement with exercise
- Pain at night
- Insidious onset
- Age at onset <40 years
- No improvement with rest

The criteria are fulfilled if at least four of these five parameters are present.

Adapted from Sieper et al, Ann Rheum Dis 2009b;68:784–8.

IBP is the one of the main symptoms in SpA, but its value in diagnosis/classification and screening in primary care has still not been validated. It is estimated that about 10-15% of patients presenting with chronic back pain have IBP but only about 5% will have SpA. The sensitivity and specificity of IBP criteria are directly related to the pre-test probability of the patient having the disease and the stringency of the IBP criteria used. This is important, since the prevalence of IBP is much higher in rheumatology practices (25–50%) than in the primary care setting (5-15%), where the IBP criteria are probably less useful. Another important observation is that not all patients with axSpA have IBP. These observations have led to the removal of IBP as the first entry criterion in the current ASAS classification criteria for axSpA.

4.1.2 Ankylosis

One of the major concerns of patients with axSpA is progression towards ankylosis of the axial skeleton, which results from ossification of the ligaments and of the costovertebral and sternocostal joints. The first sign of an abnormal posture is loss of lumbar lordosis, followed by thoracic hyperkyphosis and, in severe cases, forward stooping of the neck. Spinal movement is restricted in all planes. The restriction of motion may not be proportionate to the degree of ankylosis because of secondary muscle spasm and other mechanical factors. It is important to detect these abnormal features as early as possible, so that physiotherapy or other appropriate treatments can be initiated.

In patients with restricted chest wall motion, airflow measurements are normal, but vital capacity is decreased and functional residual capacity is increased. Respiratory failure can occur in severe cases. However, ankylosis in the thoracic and lumbar spine is not necessarily linked to severe physical limitations unless the hips are

affected, in which case bending forward is a major problem. Ankylosis at the cervical level often has major physical consequences—for example, in driving, as patients cannot turn their head to view cars alongside them.

4.1.3 Fractures and neurological complications

Although SpA is associated with new bone formation at sites of inflammation, spinal osteoporosis is commonly seen in longstanding SpA, resulting in increased fracture risk (OR = 3.26, 95% CI 1.51 to 7.02). Together with altered biomechanics, this contributes to the high prevalence of fractures, which may occur after even very minimal trauma to the rigid, ankylosed spine (figure 4). The risk of any clinical fracture is increased especially in patients with a history of IBD. Most spinal fractures occur in the lower cervical spine, followed by the thoracic spine and a significant proportion may develop multilevel fractures. Spinal fractures in AS are typically horizontal and may occur through the ossified disc (transdiscal) or the vertebral body (transcorporal) as a result of extension-distraction forces, usually hyperextension injuries. If there continues to be persistent motion at the fracture site, a pseudoarthrosis may develop. The risk of spinal cord injury following spinal fractures in AS is significantly increased and can lead to paraparesis or quadriparesis. One needs to have a high index of suspicion for the possibility of fracture in patients with SpA who present with acute onset of back or neck pain or sudden increased movement range, especially if this follows trauma, even if this sounds trivial. Plain radiography is poorly sensitive due to existing changes from AS and CT and/or magnetic resonance imaging (MRI) may be needed to make the diagnosis.

Spinal osteoporosis is partly due to the lack of mobility as a consequence of the disease, as well as a result of proinflammatory cytokines. Assessment of biochemical markers of bone metabolism has shown diminished bone formation and enhanced bone resorption. Osteoporotic fractures of the thoracic spine contribute to thoracic kyphosis and increased occiput-to-wall distance.

The majority of neurological manifestations of AS are related to spinal cord or nerve compression due to spinal fractures. Neurological involvement may rarely result following atlanto-axial subluxation, although this is far less common than in rheumatoid arthritis. Rarely cauda equina syndrome can present in patients with longstanding AS due to marked ankylosis or dural ectasia. The mechanisms causing dural ectasia (also known as mega dural sac) in AS are not fully understood but may relate to adhesions and fibrosis, likely due to a chronic arachnoiditis, leading to dilation of the dura. Dural ectasia is usually detected on MRI scan and may require surgery in cases with significant neurological compromise.

Figure 4: A) Fracture of the lower part of the thoracic spine (12th thoracic vertebra) and also of the lumbar spine (fourth lumbar vertebra), the latter with an additional aspect of spondylitis and fusion with the third lumbar vertebra in a patient with longstanding ankylosing spondylitis and osteoporosis. (B) Fracture of the middle part of the thoracic spine in a patient with ankylosing spondylitis, causing additional hyperkyphosis to the patient.



4.1.4 Peripheral arthritis

Peripheral arthritis is typically asymmetrical, oligoarticular and involves the lower limbs. Upper limb involvement is typically associated with PsA. A bilateral symmetrical polyarticular presentation is possible, which differs from rheumatoid arthritis in that the distal interphalangeal joints are often affected (the various PsA phenotypes are covered in section 1.1.2).

4.1.5 Dactylitis (sausage digit)

Dactylitis is characteristic of SpA, although not entirely specific and also seen in other rheumatic conditions. It is not as common in AS but is more typical of ReA, PsA or undifferentiated SpA. Unlike synovitis, the swelling is not confined to a joint but involves the whole digit (sausage digit). It is a combination of synovitis, enthesitis, tenosynovitis and soft tissue swelling (figure 5).

Figure 5 Sausage-like digit (dactylitis). (Source: CRI (Club Rhumatismes et Inflammation, <http://www.cri-net.com>).)



4.1.6 Anterior chest wall pain and axial joint involvement (hips and shoulders)

Anterior chest wall pain occurs in about 15% of patients with SpA and up to 45% with axSpA. It is usually the result of sternoclavicular, manubriosternal or costochondral arthritis. As stated above, this can lead to reduced chest expansion.

Arthritis of the hips and shoulders often occurs early in the first 10 years of the disease and affects a third of patients. Hip involvement is commonly bilateral. It is important to check for hip and shoulder joint involvement, as there may be limited range of movement and flexion deformities. Hip involvement often leads to severe destruction and disability. Total hip replacement might be needed at an earlier stage in patients with axSpA who usually also have a reduced range of spinal movement resulting in a severe functional disability (virtually complete loss of forward flexion).

4.1.7 Enthesitis

Painful inflammation of entheses (the sites of attachment of tendons, ligaments, fascia or joint capsules to bone) is the distinguishing pathological feature of SpA. The most typical enthesitis symptom is heel pain (posterior or inferior) related to inflammation of the Achilles' tendon or the plantar fascia insertion. Achilles tendon swelling can be better observed in the standing position from behind. Pain appears in the morning as soon as the patient sets their foot on the floor and slowly improves with ambulation. Heel enthesitis is not painful during sleep but can be very disabling and resistant to standard antirheumatic treatment. Other clinical signs include tenderness of the lateral epicondyles, iliac crest, anterior tibial tuberosity or anterior chest wall. Enthesitis is best visualised by MRI (figure 6) or ultrasonography. It is only detected by radiography after the

ossification process has occurred but it should be noted that calcaneal spurs are not specific for SpA and occur in many otherwise healthy people (figure 7).

Figure 6 Heel enthesitis (MRI findings). (Source: Cofer, <http://www.lecofer.org>.)



Figure 7 Heel enthesitis (ossification). (Source: Cofer, <http://www.lecofer.org>.)



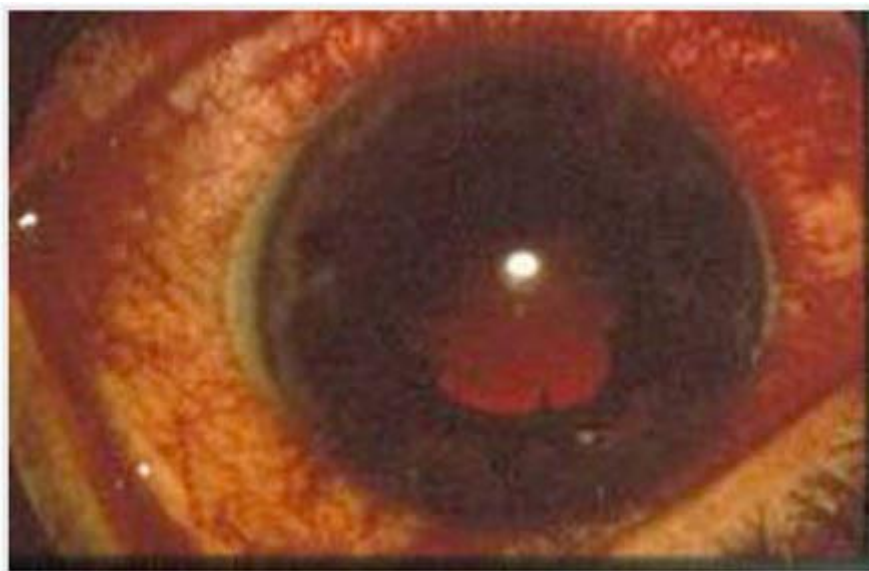
Evaluation of enthesopathy can be undertaken in various ways, traditionally using enthesitis scoring systems such as the Mandel Enthesitis Index, Stoke Enthesitis Index, University of San Francisco Enthesitis Score, Maastricht Ankylosing Spondylitis Enthesitis Score, the Spondyloarthritis Research Consortium of Canada Enthesitis Index, the Berlin Enthesitis Score or the Leeds Enthesitis Index. However, these scoring systems have been criticised for being time consuming and having poor interobserver reliability and face validity. In clinical practice, evaluation generally involves assessment of tenderness at enthesal insertion, MRI and/or ultrasound scans.

4.2 Extra-articular features

4.2.1 Uveitis (iritis or iridocyclitis)

Acute anterior uveitis is the most common extra-articular manifestation of AS, occurring in about 20–30% of patients, with 25–40% of these patients experiencing more than one episode. The incidence is higher in HLA-B27-positive patients. It is important to detect and treat acute anterior uveitis rapidly as visual loss may be irreversible. The condition typically presents with unilateral eye pain, redness, photophobia and increased lachrymation (figure 8). Patients with these signs require urgent examination by an ophthalmologist, and may need specialised treatment (e.g., retro-orbital injections of glucocorticoids in severe cases). With treatment, attacks usually resolve after several weeks- months. The main complication is the occurrence of synechiae. Uveitis that develops with PsA or enteropathic SpA tends to be more chronic and bilateral and often involves posterior elements.

Figure 8 Acute anterior uveitis.



4.2.2 Cardiac manifestations

Cardiac features are rare but may be severe. Heart block is the most frequent manifestation. Aortic insufficiency secondary to an aseptic endocarditis can also be a severe cardiac manifestation of the disease.

4.2.3 Pulmonary involvement

Restrictive lung disease may occur in end-stage disease, as a result of costovertebral and costosternal fusion and limited chest expansion. Apical fibrosis may occur in severe disease and this may become colonised with bacteria or fungi such as *Aspergillus*.

4.2.4 Renal involvement

IgA nephropathy has been reported in AS in a few case reports. Amyloidosis is a very rare complication in severe longstanding disease. Renal deficit is more commonly a result of NSAID related toxicity.

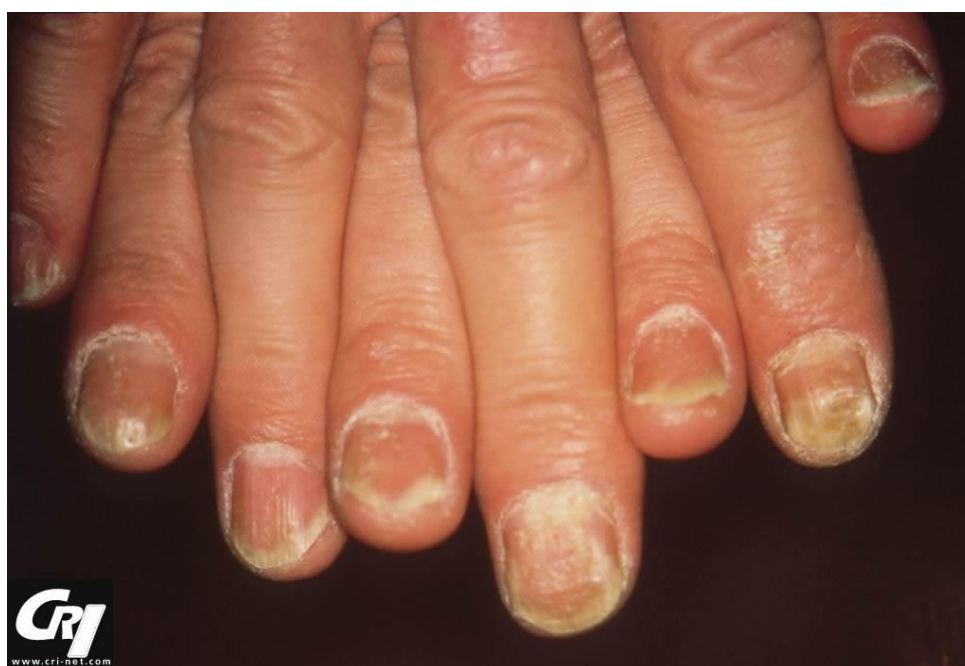
4.2.5 Gastrointestinal involvement

Inflammatory lesions in the gut are common and can cause diarrhoea, which is usually accompanied by blood and mucus. Loss of weight is common. IBD may or may not have already been diagnosed in these patients. The prevalence of IBD in AS has been reported to range between 6-15%. Furthermore, colonoscopic mucosal biopsy shows that subclinical microscopic inflammatory lesions are seen in about 60% of SpA patients who have no gastrointestinal symptoms or clinically obvious IBD. Follow-up studies of such patients indicate that 6% will develop IBD. About 28–35% of patients with enteropathic arthritis have axial disease: 10–20% have sacroiliitis alone, 7–12% have spondylitis and 10% have the classic features of SpA. The axial radiology is similar to that of AS, characterised by symmetrical bilateral sacroiliitis. The onset of axial involvement often precedes that of bowel disease.

4.2.6 Dermatological manifestations

Dermatological manifestations are common but are usually related to a specific disorder such as psoriasis or ReA. Psoriasis is seen in 20–40% of patients with SpA. Nail lesions are a common feature in patients with rheumatological manifestations (Figure 9).

Figure 9: Nail lesions in a patient with psoriatic disease. Oil dyschromias, onycholysis and pitting can be observed. [Source: CRI (Club Rhumatismes et Inflammation, <http://www.cri-net.com/>)]



4.3 Comorbidities

When considering comorbidities one has to consider mainly cardiovascular (CV) disorders, hypertension and osteoporosis (see section 4.1.3 Fracture). The mortality rate in patients with AS is increased twofold in comparison with that in the general population, mainly owing to an increased CV risk. Although specific CV disorders (valvular disease and conduction disturbances) occur more frequently in AS, accelerated atherosclerosis disease due to chronic systemic inflammation probably also contributes to the increased CV risk of these patients. AS is also associated with an increased risk of hypertension.

5 Laboratory features

No laboratory tests are diagnostic for SpA. Erythrocyte sedimentation rate and C-reactive protein (CRP) are raised in 40% of patients. Increased CRP is one of the features of SpA used in the ASAS classification for axSpA, but must be present with other features. Patients with non-radiographic axSpA who have increased CRP levels have an increased risk of further structural progression in the SI joints, and developing AS. On the other hand, increased CRP levels are also predictors for a good response to treatment with TNF α blockers (OR = 2.8, 95% CI 1.3 to 5.7).

A mild normochromic normocytic anaemia of chronic disease may be present in patients with axSpA. Alkaline phosphatase may also be raised but this does not correlate with disease activity.

HLA-B27 is present in >90% of patients with AS. However, HLA-B27 by itself has no diagnostic value since it is found in up to 8% of healthy European individuals; it is therefore more helpful in populations with lower HLA-B27 prevalence. Determining HLA-B27 status is not mandatory in clinical assessment but is especially helpful for classifying patients who have negative imaging. With the new ASAS classification criteria for axSpA, a patient with a 3-month history of back pain that started before the age of 45 years can be classified as having SpA if HLA-B27 is positive and two other SpA features are present. The diagnosis of SpA is unlikely when imaging and HLA-B27 are both negative.

6 Imaging

EULAR has recently published recommendations for the use of imaging in the diagnosis and management of SpA in clinical practice (Mandl et al. *Ann Rheum Dis.* 2015;74:1327-39).

6.1 Plain radiographs

Plain radiographs of the spine, SI joints and peripheral joints can show various structural changes. However, they are unhelpful in the early, 'non-radiographic' stage because structural changes reflect the consequences of inflammation rather than inflammation itself (see section 6.2 MRI). Radiographic sacroiliitis is the hallmark

of AS and takes several years to become visible on plain radiographs. While a number of specific sacroiliac views have been proposed, these x-rays can be difficult to interpret for those unfamiliar with these views. Therefore, standard antero-posterior views of the pelvis are generally recommended for imaging the SI joints as this modality also allows assessment of the hip joints, which are frequently affected in AS. The earliest visible changes include blurring of the cortical margins of the subchondral bone, erosions and sclerosis (figure 10). As erosions progress, the joint space appears wider and then fibrous, until bony ankylosing obliterates the joint. Joint changes usually become symmetrical during the course of the disease. Radiographic sacroiliitis can be graded according to the New York grading system as follows: grade I, suspicious; grade II, evidence of erosion and sclerosis; grade III, erosions, sclerosis and early ankylosis; and, finally, grade IV, total ankylosis.

The modified New York criteria for classification of AS (box 7) combine different clinical criteria with evidence of definite structural changes on conventional radiographs. However, these criteria focus mainly on the SI joints (both clinically and on radiographs) and the spine (only clinically) and do not include any extra-articular manifestations of the disease. The sensitivity of the modified New York criteria increases with disease duration (sensitivity 0% for a disease duration of 2 years vs 60% for a disease duration of >10 years). The delay before detecting radiological sacroiliitis might explain these results. As stated above, although the modified New York criteria are sensitive, they cannot detect mild, undifferentiated or early forms of the disease.

Figure 10 Radiological sacroiliitis in ankylosing spondylitis.



Spinal X-ray findings typically show squaring of the vertebrae secondary to erosions of the superior and inferior margins of these bodies (figure 11). Vertebral enthesitis may cause sclerosis of the upper and lower vertebral bodies, which appears as the formerly called 'shiny corners'. Annulus fibrosus ossification leads to

syndesmophyte formation and over time bridging of these syndesmophytes results in a bamboo spine (figure 12). Structural damage of the spine can be scored using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (figure 13).

Figure 11 (A) Radiological lumbar spinal ankylosis; (B) normal spine. (Source: Cofer, <http://www.lecofer.org>.)



Figure 12 Syndesmophytes.



Figure 13 Radiological spinal scoring system in ankylosing spondylitis (AS) (modified Stoke AS Spine Score). (Reproduced with permission from Wanders *et al*, *Arthritis Rheum* 2004;50:2622–32.) Based on the Outcome Measures in Rheumatology Clinical Trials (OMERACT) (2004).

Radiological evaluation of AS

- **Modified Stoke Ankylosing Spondylitis Spine Score (M – SASSS)**
- **M – SASSS**
 - Anterior site of the vertebra
 - C2 to T1, T12 to S1
 - Score =
 - 0 = normal
 - 1 = erosion, sclerosis or syndesmophyte
 - 2 = syndesmophyte
 - 3 = bridging syndesmophytes
 - Range 0 - 72



Wanders A *et al*. *Arthritis Rheum* 2004;50:2612-32
Wanders A *et al*. *Ann Rheum Dis* 2004;63:1601-4

AS and enteropathic arthritis typically exhibit bilateral symmetrical sacroiliitis and continuous syndesmophytes, while ReA and PsA characteristically exhibit asymmetrical sacroiliitis and discontinuous spondylitis.

Radiographs of other areas such as the heel or hip might show evidence of enthesitis.

6.2 MRI

MRI can detect inflammatory lesions long before definite lesions are visible on plain radiographs. The ASAS criteria for axSpA include inflammation in the SI joints seen on MRI as one of the major entry criteria. When clinical suspicion of early SpA is high but standard radiography of the SI joints is normal or shows only equivocal changes, MRI can produce excellent evidence of sacroiliitis and enthesitis (figure 14). The preferred imaging sequences are T2-weighted fat-suppressed fast spin-echo, for chronic fatty changes, and short-tau inversion recovery (STIR) sequences for assessment of bone marrow oedema (BMO), which represents a sign of inflammation. The regular use of gadolinium or contrast is no longer recommended for routine diagnostic scans in axSpA.

Figure 14A Sacroiliitis (MRI findings on STIR sequence). STIR, short-tau inversion recovery. (Source: Cofer, <http://www.lecofer.org>.)



Figure 14B Spondylitis (left image, STIR MRI) and fatty degeneration (postinflammatory, right image, T1-weighted MRI). STIR, short-tau inversion recovery.



Box 7 Modified New York criteria for ankylosing spondylitis (AS)

Diagnosis

- Clinical criteria
 - Low back pain and stiffness for more than 3 months which improves with exercise but is not relieved by rest
 - Limitation of motion of the lumbar spine in both the sagittal and the frontal planes
 - Limitation of chest expansion relative to normal value, corrected for age and sex
- Radiological criterion (x-ray)
 - Sacroiliitis grade ≥ 2 bilaterally or sacroiliitis grade 3–4 unilaterally

Grading

- Definite AS if the radiological criterion is present with at least one clinical criterion
- Probable AS if:
 - Three clinical criteria are present
 - The radiological criterion is present without any signs or symptoms fulfilling the clinical criteria

Adapted from van der Linden et al, Arthritis Rheum 1984;27:361–8.

Box 8 ASAS classification criteria for axSpA

Patients with back pain ≥ 3 months and age at onset <45 years

- **Imaging arm:** *Sacroiliitis on imaging** plus ≥ 1 SpA feature** or
- **Clinical arm:** *HLA-B27* plus ≥ 2 other SpA features**

*Sacroiliitis on imaging = definite radiographic sacroiliitis according to the modified New York criteria *or* positive sacroiliac MRI

**SpA features:

- Inflammatory spinal pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's/colitis
- Good response to NSAIDs
- Family history of SpA
- HLA-B27
- Elevated CRP

ASAS, Assessment of SpondyloArthritis international Society; CRP, C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis.

Source: Sieper et al, Ann Rheum Dis 2009a;68(Suppl II):ii1–44.

Box 9 ASAS classification criteria for peripheral SpA

Arthritis or enthesitis or dactylitis
(without current back pain)

Plus ≥ 1 of:

- Uveitis
 - Psoriasis
 - Crohn's/colitis
 - Preceding infection
 - HLA-B27
 - Sacroiliitis on imaging
- OR*

≥ 2 of:

- Arthritis
- Enthesitis
- Dactylitis
- IBP (ever)
- Family history of SpA

ASAS, Assessment of SpondyloArthritis international Society; IBP, inflammatory back pain; SpA, spondyloarthritis.

MRI evidence of sacroiliitis has been incorporated in the ASAS classification criteria for axSpA (Box 8) that are covered in more detail in Section 7. The ASAS/OMERACT (Outcome Measures in Rheumatology Clinical Trials) MRI working group has proposed a definition of a 'positive' MRI (Rudwaleit et al, 2009a*). This definition should be applied for the imaging feature 'sacroiliitis by MRI' of the ASAS classification criteria for axSpA.

According to this definition the following findings are required:

- Active inflammatory lesions of the SI joints, BMO (on STIR) must be clearly located in typical anatomical areas (subchondral or periarticular bone marrow).
- When a solitary BMO lesion is seen, this should be present on at least two consecutive slices.
- When more than one BMO lesion is seen on one slice, documentation of inflammation by using one single slice only is sufficient.
- The presence of synovitis, enthesitis or capsulitis without concomitant BMO/osteitis is not sufficient for diagnosis.

However, since BMO can also be found in patients with mechanical low back pain, but moderate or severe lesions are only found in patients with IBP, there is definite need for experience and consideration of pre-test probability when interpreting MRI of the SI joints. Also, further study is needed to specify the size and severity of the lesions in order to improve the specificity of MRI, so these definitions are likely to evolve in future.

Furthermore, a definition of a 'positive' MRI of the spine, has been also recently proposed by ASAS (Hermann et al, 2012*). According to this definition, evidence of spondylitis in three or more vertebral sites is highly suggestive of inflammatory lesions related to axSpA, while evidence of fatty deposition in several vertebral

sites (at least 5) is highly suggestive of post inflammatory lesion-related axSpA. These lesions should preferably be located at the edges of the vertebrae, independently of whether these edges are in the anterior or the posterior part of the vertebral body.

6.3 Other imaging modalities

Bone scintigraphy is not recommended for identification of sacroiliitis or spondylitis in the context of axSpA owing to the associated radiation exposure and its low sensitivity (50–55%) and specificity (<80%).

Furthermore, ultrasound of SI joints is also not frequently used in daily practice owing to lack of standardisation of both its use and interpretation of findings, while computed tomography (CT) seems to have only an additional value in detection of structural changes but is also associated with higher radiation exposures, which is an important limiting factor for its use in daily routine.

6.4 Differential diagnosis of the radiographic findings

The differential diagnosis of low back pain includes various situations. Some of these, like osteitis condensans ilii (OCI) and diffuse idiopathic skeletal hyperostosis (DISH) share similar radiographic characteristics with AS.

OCI affects mainly but not always women who have given birth and its prevalence is estimated to be about 0.9–2% of the general population. Its aetiology remains largely unknown but mechanical stress seems to be the main factor. It is a non-inflammatory condition and typically the patients are HLA-B27 negative. Radiologically, it is characterized by triangular sclerosis – usually, but not always, bilaterally - in the iliac bone on x-ray, without erosions or sacroiliac joint narrowing. Lack of involvement of the sacrum or joint space narrowing is usually diagnostic.

DISH (also known as Forestier's disease) is most common among middle-aged/elderly people and rare before the age of 40. DISH is characterised by ossification of soft tissues, including ligaments and tendons, of joint capsule and of contiguous vertebrae, leading to bony bridges in the spine. Despite the often striking radiographic changes, which may resemble those seen in the spine in AS, patients with DISH often have disproportionately mild symptoms or functional impairment. The aetiology of DISH is unknown but it is correlated with obesity and metabolic disorders like diabetes mellitus. There are currently no treatments available for this, apart from standard analgesia for back pain, if required. Differentiation of DISH from AS is based on clinical (milder symptomatology) and radiological features. There are a number of radiographic criteria used to diagnose DISH which include flowing ossification/calcification of the anterior longitudinal ligament, preservation of intervertebral disc height in affected areas (differentiating this from pure degenerative spinal disease) and relative sparing of the SI joints (differentiating this from AS). While SI joint capsule ossification and mild narrowing or sclerosis may be observed in DISH, this is usually in the upper portion of the joint with no erosions or bony ankylosis as typical for AS.

7 Classification criteria

The SpA conditions are heterogeneous multisystem disorders with no single ‘gold standard’ clinical, laboratory, pathologic or radiologic feature to confirm the diagnosis. A number of criteria have therefore been developed to support clinical practice and research. It should however be noted that there are currently no diagnostic criteria (i.e. to be applied in clinic where the *a priori* diagnosis is unknown) for SpA and that all the current criteria for axSpA and SpA are classification criteria (designed to be applied where the *a priori* diagnosis is suspected in order to create more homogenous cohorts for research purposes). There are many important differences between diagnostic and classification criteria. Therefore, while classification criteria can be useful in clinical practice, they cannot simply be applied using a “check box” process as a diagnosis of axSpA and SpA in clinic also requires exclusion of other potential causes for symptoms and findings, which is usually best done by a clinician with expertise in these conditions.

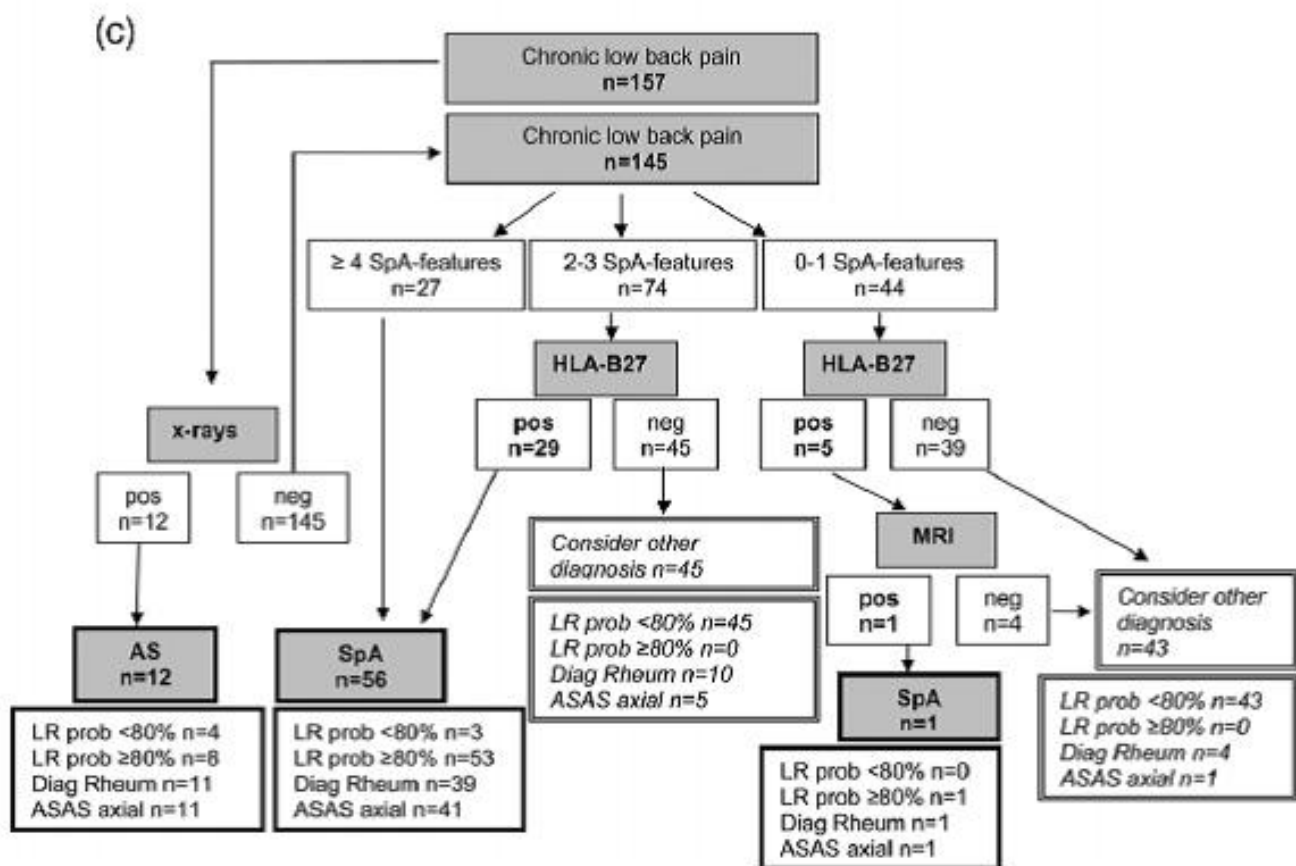
The new validated ASAS classification criteria for axSpA (box 8) and for peripheral SpA and SpA in general (box 9) are a major step forward (Rudwaleit et al, 2009b*; Rudwaleit et al, 2011*). It is now possible to diagnose axSpA earlier. The ASAS criteria for axSpA are applied in patients with predominantly axial symptoms with or without peripheral manifestations, while the criteria for peripheral SpA in general have been developed for patients who present with predominantly symptoms of peripheral arthritis, enthesitis or dactylitis. The ASAS classification criteria for axSpA require a history of chronic back pain (pain duration ≥ 3 months) and an age of onset of < 45 years as entry criteria. Patients can then fulfil the axSpA criteria either via the imaging arm, with evidence of sacroiliitis on X-ray or MRI in addition to at least one typical clinical SpA feature, or via the clinical arm with the presence of HLA-B27 in addition to at least two other typical clinical SpA features. With this set of criteria, patients can be still classified as AS when they present with established radiographic changes in the SI joints, or as non-radiographic axSpA when such changes have not yet occurred but other entry criteria (see above and box 8) are present. The introduction of this new concept has led to an increasing interest in patients with non-radiographic axSpA, leading to clinical trials and subsequent licensing of therapies for this indication. The ASAS classification criteria have a sensitivity of 82.9% and a specificity of 84.4%.

The most significant change in the criteria, as compared with former criteria sets, is the inclusion of inflammatory activity detected by MRI. On the other hand, normal MRI results do not necessarily exclude a classification as SpA, which can still be made on the basis of clinical findings. In such a case, and as mentioned above, the presence of HLA-B27 plus two other SpA features is useful for classification. Another important difference of the new ASAS criteria is that IBP is no longer a compulsory criterion but is being considered as one of the typical clinical SpA features, among all others.

Patients with peripheral symptoms without major axial involvement can be classified with the ASAS classification criteria for peripheral SpA (Box 9). These require a history of arthritis, enthesitis or dactylitis in addition to SpA features.

As mentioned previously, there are no diagnostic criteria for SpA, which means that in daily clinical practice one might have to adopt a more flexible approach. A proposed clinical diagnostic tree is shown in figure 15.

Figure 15 Diagnostic pathway for ankylosing spondylitis and spondyloarthritis in patients presenting with chronic back pain (decision tree). AS, ankylosing spondylitis; ASAS, Assessment of SpA international Society; LR, likelihood ratio; SpA, spondyloarthritis. (Reproduced from van den Berg et al, *Ann Rheum Dis* 2013;72:1646–53.)



8 Treatment

Treatment with NSAIDs and exercise is recommended as first-line therapies in patients with SpA. For those patients who still have active disease the introduction of TNF inhibitors (TNFi) was a major advance in the management of axSpA. The main principles of the treatment of patients with SpA is published by ASAS in the ASAS/EULAR recommendations for the management of AS (Braun et al, 2011*). One important principle in the treatment of patients with SpA is the need for a combination including pharmacological and non-pharmacological treatment options. The treating physician should tailor the treatment of patients according to

prognostic factors (see section 9.3, Can we predict the further course of the disease?) and to the general clinical status, including comorbidity.

8.1 NSAIDs

NSAIDs are recommended as first-line drugs for patients with axSpA. If taken in appropriate dosages, they are efficacious for the relief of pain and stiffness in up to 60–70% of the patients. Long-acting NSAIDs could be prescribed at bed time to relieve early morning stiffness. There is no significant difference in efficacy between short-acting and long-acting agents or between Cox-2-selective and non-selective agents. Up to 15% of patients with active AS treated with a full dose of an NSAID may even reach a status of partial remission. The question of whether it is advisable to recommend continuous treatment with NSAIDs even in, or after reaching, a status of low disease activity is still a matter of discussion. The effect of NSAIDs on inflammatory activity (CRP, BMO) or on the radiographic progression of patients with axSpA is still not clear.

8.2 Anti-TNF therapy

The major advance in the treatment of patients with AS was the approval of anti-TNF blockers at the beginning of the 21st century. Anti-TNF blockers should be prescribed according to the international ASAS recommendations (van der Heijde et al, 2011*) (table 2) in conjunction with national guidelines. These recommendations give detailed information for patient selection, assessment of disease and assessment of response when using these compounds. It is important to note that these recommendations specifically relate to patients with axSpA. For treatment with anti-TNF agents, patients need to have increased disease activity, which is defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 (on a 0–10 scale) despite previous treatment with at least two NSAIDs over a period of 4 weeks. There is no evidence to support the obligatory use of disease-modifying antirheumatic drugs (DMARDs) before starting anti-TNF therapy.

It is recommended that the response to anti-TNF therapy is assessed 3 months after starting treatment. A decrease of disease activity (as measured by the BASDAI) of at least 50% as compared with previous treatment (BASDAI-50 response) or an absolute BASDAI change of ≥ 2 units (on a 0–10 scale) in addition to an expert opinion (based on improvement in CRP, MRI inflammation or clinical examination) are considered parameters for continuing treatment. Currently adalimumab, etanercept, certolizumab and golimumab are licensed for use in both AS and non-radiographic axSpA (with positive MRI and/or elevated CRP) while infliximab (and therefore also its biosimilar) is only licensed for AS. The exact role and positioning of biosimilars in the treatment of axSpA in clinical practice remains to be seen and will ultimately be influenced by cost, demonstration of sustained efficacy and long-term safety.

Table 2 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with SpA

Patient selection	Recommendation
Diagnosis	Patients fulfilling modified New York criteria for definitive AS or the ASAS criteria for axSpA
Active disease	<ul style="list-style-type: none"> • Active disease for ≥ 4 weeks • BASDAI ≥ 4 (0–10) and a positive expert opinion
Treatment failure	<ul style="list-style-type: none"> • All patients should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as at least two NSAIDs over a 4-week period in total at a maximum recommended or tolerated anti-inflammatory dose unless contraindicated • Patients with predominantly axial manifestations do not have to take DMARDs before anti-TNF treatment can be started • Patients with symptomatic peripheral arthritis should have an insufficient response to at least one local steroid injection if appropriate and should normally have had an adequate therapeutic trial of a DMARD, preferably sulfasalazine • Patients with symptomatic enthesitis must have had appropriate local treatment which has failed
Assessment of disease	ASAS core set for daily practice and BASDAI
Assessment of response	
Responder criteria	BASDAI: 50% relative change or absolute change of 2 units (on 0–10 scale) and expert opinion in favour of continuation
Time of evaluation	After at least 12 weeks

AS, ankylosing spondylitis; ASAS, Assessment of SpA international Society; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; TNF, tumour necrosis factor.

Patients with high disease activity, short disease duration, no structural lesions and increased CRP are more likely to benefit from anti-TNF medication than patients with longstanding disease, extensive structural changes and poor functioning before treatment initiation. Overall, the response rates to anti-TNF treatment in clinical practice appear better than those reported in the phase III clinical trials, which may relate at least in part to differences in outcome measures used in these settings. Even in patients with complete ankylosis of the spine, this treatment has substantial clinical efficacy on symptoms. There is no evidence of differences in the efficacy of the various TNFi approved so far. The initial phase III open-label extension studies in AS did not report any reduction in radiographic progression when compared to historical AS controls. However, more recent observational studies and longer follow-up of study participants, have suggested that TNF inhibitors may indeed slow radiographic progression, particularly in earlier disease. There is now also increasing data from registries and observational studies to support the use of sequential TNF blockers for axSpA where patients fail to respond to a particular TNF inhibitor. Withdrawal of TNF inhibitors in patients in apparent remission is not recommended as several studies have shown that the majority of patients will relapse rapidly,

with most flaring up within the first 4-10 weeks of discontinuation. Intermittent or 'on-demand' dosing has been shown to only marginally reduce costs, at the expense of worse clinical outcomes, so is also not recommended. However, there is increasing interest in reducing or tapering the dose or frequency of TNF inhibitors in patients in remission, with several ongoing studies evaluating this approach.

8.3 Anti-IL-23/-17 drugs

The IL-23/-17 axis has been increasingly implicated in the pathogenesis of SpA, leading to the development of therapeutic agents targeting IL-23 and IL-17. Amongst them, the best studied are: Ustekinumab, a fully human monoclonal antibody against the p40 subunit of both IL-12 and IL-23, and Secukinumab, a fully human monoclonal antibody against IL-17A.

Both ustekinumab and secukinumab are already licensed and established in clinical practice for the treatment of active psoriasis and PsA. The skin responses in the skin with IL-17 inhibition have been particularly impressive. Both these agents have demonstrated efficacy in PsA in both TNF-naïve and TNF-experienced patients.

Recent phase III studies have demonstrated the efficacy of secukinumab in active AS, leading to approval by the regulatory agencies. Several other anti-IL-17 agents are also in development for AS and a range of other SpA conditions. Early phase studies suggest potential efficacy of ustekinumab in AS, with the results of phase III studies awaited. Agents specifically targeting IL-23, but not IL-12, directly or via the p19 subunit, are also in development. Overall, these agents appear to have an acceptable safety profile, although their long-term safety in SpA remains to be established.

8.4 DMARDs

Data on the use of DMARDs in patients with AS did not show an effect on axial symptoms, so their use for axial disease is not recommended where biologic agents are available. The majority of the studies suggest a limited efficacy of sulfasalazine in patients with peripheral SpA and in the prevention of anterior uveitis. One head-to-head trial comparing sulfasalazine with a TNF blocker showed that TNF blockade is more efficacious in achieving an ASAS20 response at week 16 than sulfasalazine (75.9% vs 52.9%, $p < 0.0001$)

8.5 Non-pharmacological treatment

The cornerstone of non-pharmacological treatment is regular exercise and patient education. It has been shown that regular exercises are effective in reducing pain and preserving functioning. Overall, supervised exercises are more effective than home exercises.

8.6 Surgery

Surgery might be required in patients with AS with hip involvement, severe spinal deformity or vertebral fracture. Around 5% of patients will undergo a total hip arthroplasty, while around 50% of these patients will need bilateral hip replacement during the course of their disease. Chronic knee disease may also necessitate knee replacement in a minority. The restricted mobility and hyperkyphosis of the spine may lead to loss of the ability to keep the eyes and head upwards, or being able to look horizontally. Patients with such severe deformities can benefit from a spinal corrective osteotomy. Such procedures should only be performed in experienced centres. As stated above, patients with AS have an increased risk of vertebral fractures but not of non-vertebral fractures. In most cases the occurrence of a spinal fracture is an acute clinical situation that may be associated with neurological symptoms. Although not all patients need to be operated on, physicians should consider consulting an experienced surgeon when even 'silent' fractures are suspected.

9 Assessment/monitoring

For both assessment and monitoring, one has to consider systematically the four potential clinical presentations of axSpA: axial involvement, peripheral arthritis, enthesopathy and extra-articular features. According to the variable disease course, the clinical presentation of the patient should be the key feature for disease monitoring. Monitoring is based on the clinical presentation, and the tools used for evaluating the severity of axial involvement are similar, and independent of the SpA subgroup. Principles for monitoring patients with AS are defined in the ASAS core set (table 3). The ASAS recommendations for the management of AS do not specify the time frame in which patients have to visit the treating physician. It is advisable that a patient with a new diagnosis or with a high disease activity should be seen more often than a patient with a low disease activity. In general, spinal X-ray examinations do not need to be repeated more frequently than every 2 years unless indicated in individual cases as a result in altered symptoms, such as concern about a fracture. Each change in the disease course should be evaluated carefully by the treating physician.

Table 3 ASAS core set (Adapted from van der Heijde D et al, *J Rheumatol* 1999;26:951–4)

Domain	Instrument
Physical function*	BASFI or Dougados Functional Index
Pain*	VAS/NRS past week in spine, at night, due to AS and VAS/NRS past week, in spine due to AS
Spinal mobility*	Chest expansion and modified Schober and occiput-to-wall distance and lateral spinal flexion
Patient global assessment*	VAS/NRS past week
Morning stiffness*	Duration of morning stiffness in spine past week
Fatigue*	VAS/NRS past week
Peripheral joints and entheses†	Number of swollen joints (44 joint count). Validated enthesitis indexes
Acute phase reactants†	ESR
Spine radiographs‡	Anteroposterior + lateral lumbar and lateral cervical spine and X-ray examination of pelvis to visualise sacroiliac joint and hips)
Hip radiographs‡	As above

*Included in core set for SMARDs/physical therapy.

†Included in core set for SMARDs/physical therapy and clinical record keeping.

‡Included in core set for SMARDs/physical therapy and DC-ART.

AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; BASFI, Bath AS Functional Index; DC-ART, disease-controlling antirheumatic therapy; ESR, erythrocyte sedimentation rate; NRS, numerical rating scale; SMARDs, symptom-modifying antirheumatic drugs; VAS, Visual Analogue Scale.

ASAS has issued recommendations about the use of different assessment tools covering the various domains of disease activity, which are largely determined by the patient's level of treatment (table 3).

Appropriate assessment tools are needed, depending on the clinical pattern of the disease. Table 4 summarises the different clinical patterns in patients with SpA.

Table 4 Evaluation of activity of different clinical patterns of SpA

Axial involvement	Peripheral arthritis	Enthesopathy	Extra-articular features
Night pain	Night pain	Pain	Acute anterior uveitis
Morning stiffness	Morning stiffness	Functional impairment	
CRP	Swollen joint count, CRP		
Pain	Pain	Enthesopathy index	Psoriasis
Functional impairment	Tender joint count Functional impairment		IBD
MRI	US, MRI	US, MRI bone scan	

CRP, C-reactive protein; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; SpA, spondyloarthritis; US, ultrasonography.

In patients with axial involvement, the degree of both night pain and spinal pain during the day is measured using either a Visual Analogue Scale (VAS) or a Numerical Rating Scale (NRS). Morning stiffness in the lumbar spine should be evaluated for both duration and severity. Functional impairment is evaluated using the Bath AS Functional Index (BASFI) (box 10). The score ranges from 0 to 10, where higher values indicate worse

functioning. All the above tools are patient reported and considered subjective. When using the VAS, a value >4 on a scale from 0 to 10 is usually considered as reflecting 'active' disease.

Box 10 Bath Ankylosing Spondylitis Functional Index (BASFI): evaluation of functional impairment

Please indicate your level of ability with each of the following activities during the past week (difficulty is assessed on a VAS/NRS ranging from "easy" to "impossible")

- Putting on your socks or tights without help or aids (e.g., sock aids)
- Bending forward from the waist to pick up a pen from the floor without an aid
- Reaching up to a high shelf without help or aids (e.g., helping hand)
- Getting up out of an armless dining room chair without using your hands or any other help
- Getting up off the floor without help from lying on your back
- Standing unsupported for 10 min without discomfort
- Climbing 12–15 steps without using a handrail or walking aid (one foot each step)
- Looking over your shoulder without turning your body
- Doing physically demanding activities (e.g., physiotherapy exercises, gardening or sports)
- Doing a full day's activities whether it be at home or at work

NRS, numerical rating scale; VAS, visual analogue scale

The main question in daily practice is whether it is mandatory to employ objective methods to evaluate such activity before considering a new treatment, such as an anti-TNF agent. The only current non-subjective instruments reflecting axial disease activity are serum CRP (raised in up to 40% of patients) and the presence of inflammatory lesions on MRI of the spine and/or SI joints.

In peripheral arthritis, disease activity evaluation is similar to that used in rheumatoid arthritis—for example, number of tender joints, number of swollen joints, CRP, etc. Enthesitis assessments may also be used in patients with enthesal involvement. There is no consensus definition of a peripheral 'active' disease. However, the presence of at least three swollen joints is usually considered to reflect active disease, particularly when associated with an increased CRP.

9.1 Composite index to assess disease activity

Besides the different instruments facilitating disease activity assessment of the separate clinical presentations, instruments (e.g., a composite index) have been proposed to allow a general evaluation.

The BASDAI (box 11) is simple to use since it comprises only six questions related to:

The BASDAI score ranges from 0 to 10, higher values indicating more active disease. A score >4 is considered as the threshold above which a disease status can be considered as active. A change of at least 50% in the BASDAI is usually considered as reflecting a clinically relevant improvement.

Box 11 Bath Ankylosing Disease Activity Index: evaluation of disease activity

Patients are asked to answer each of the following relating to the *past week* (measured on VAS/NRS)

- How would you describe the overall level of fatigue/tiredness you have experienced? (assesses fatigue)
- How would you describe the overall level of ankylosing spondylitis neck, back or hip pain you have had? (assesses axial involvement)
- How would you describe the overall level of pain/swelling in joints other than the neck, back or hips you have had? (assesses peripheral joint involvement)
- How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure? (assesses enthesopathy)
- How would you describe the overall level of morning stiffness you have had from the time you wake up? (assesses morning stiffness/inflammation)
- How long does your morning stiffness last from the time you wake up? (assesses morning stiffness/inflammation)
-).

NRS, numerical rating scale; VAS, visual analogue scale

The BASDAI score ranges from 0 to 10, higher values indicating more active disease. A score >4 is considered as the threshold above which a disease status can be considered as active. A change of at least 50% in the BASDAI is usually considered as reflecting a clinically relevant improvement.

9.1.1 AS Disease Activity Score (ASDAS)

More recently, another composite index taking into account some questions from the BASDAI (Q 2 total back pain, Q3 peripheral pain and Q6 morning stiffness), plus the patient global assessment and biological markers of inflammation (either CRP or erythrocyte sedimentation rate) has been proposed (box 12). The ASDAS has been extensively validated. It has been shown to be reliable, discriminative and sensitive. The cut-off points between the disease activity states are: inactive disease ≤ 1.3 , moderate 1.3–2.0, high 2.1–3.5 and very high ≥ 3.5 . The ASDAS cut-off point for clinically important improvement is ≥ 1.1 and the cut-off point for a major improvement is ≥ 2.0 from baseline. However, the ASDAS has still not been evaluated for use in daily practice, whereas the BASDAI is the standard measuring instrument used in clinics for disease activity in axSpA.

Box 12 Evaluation of the activity of the disease – ASDAS-CRP/ESR**ASDAS-CRP***

$0.21 \times \text{Total back pain} + 0.110 \times \text{Patient global} + 0.073 \times \text{Peripheral pain/swelling} + 0.058 \times \text{Duration of morning stiffness} + 0.579 \times \ln(\text{CRP} + 1)$

ASDAS-ESR*

$0.113 \times \text{Patient global} + 0.293 \times \sqrt{\text{ESR}} + 0.086 \times \text{Peripheral pain/swelling} + 0.069 \times \text{Duration of morning stiffness} + 0.079 \times \text{Total back pain}$

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Source: Lukas et al, Ann Rheum Dis 2009;68:18–24.

ASAS has proposed composite indices for monitoring disease activity in clinical trials, although these are designed to be applied in the group setting rather than for individuals, so are of unproven utility in daily

clinical practice. The key responder (ASAS 20 improvement) and remission (ASAS partial remission) criteria used in clinical trials are shown on Box 13 and 14, respectively.

Box 13 ASAS20 improvement criteria

Improvement of at least 20% and absolute improvement of at least 10 on a 0–100 scale in at least three of the following domains:

- Patient global (VAS (0–100))
- Pain (VAS global, past 2 days (0–100))
- Function (BASFI (0–100))
- Inflammation
 - o First choice—two last questions of the BASDAI
 - o Second choice—morning stiffness duration with a maximum of 120 mm on a 0–100 scale

And no deterioration (of at least 20% and absolute deterioration of at least 10 on a 0–100 scale) in the remaining domain.

ASAS, Assessment of SpondyloArthritis international Society; BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Functional Index; VAS, Visual Analogue Scale.

Source: Anderson et al, *Arthritis Rheum* 2001;44:1876–86.

Box 14 ASAS partial remission criteria

A value <20 on a 0–100 scale in each of the four domains:

- Patient global (VAS (0–100))
- Pain (VAS global, past 2 days (0–100))
- Function (BASFI (0–100))
- Inflammation
 - o First choice—two last questions of the BASDAI
 - o Second choice—morning stiffness duration with a maximum of 120 mm on a 0–100 scale

ASAS, Assessment of SpondyloArthritis international Society; BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Functional Index; VAS, Visual Analogue Scale.

Adapted from Anderson et al, *Arthritis Rheum* 2001;44:1876–86.

9.2 What is disease severity?

The term ‘severity’ is often used but not defined for patients with AS. Severity as understood by experts contains all the different aspects of the disease (disease activity, damage, reduced mobility, reduced physical function, reduced social participation). Such ‘severity’ can be assessed using different approaches, such as, functional impairment, limited range of motion, hip involvement, radiological damage, quality of life and even job loss or death. Here, we focus on the four measures that are mainly related to SpA.

9.2.1 Functional impairment

Functional impairment can be related to both the activity and the severity of the disease. Several available instruments (Bath AS Functional Index (BSAFI), Health Assessment Questionnaire (HAQ), Western Ontario and

McMaster Universities osteoarthritis index, etc.) can be used depending on the clinical presentation of SpA (e.g. peripheral versus axial).

9.2.2 Range of motion

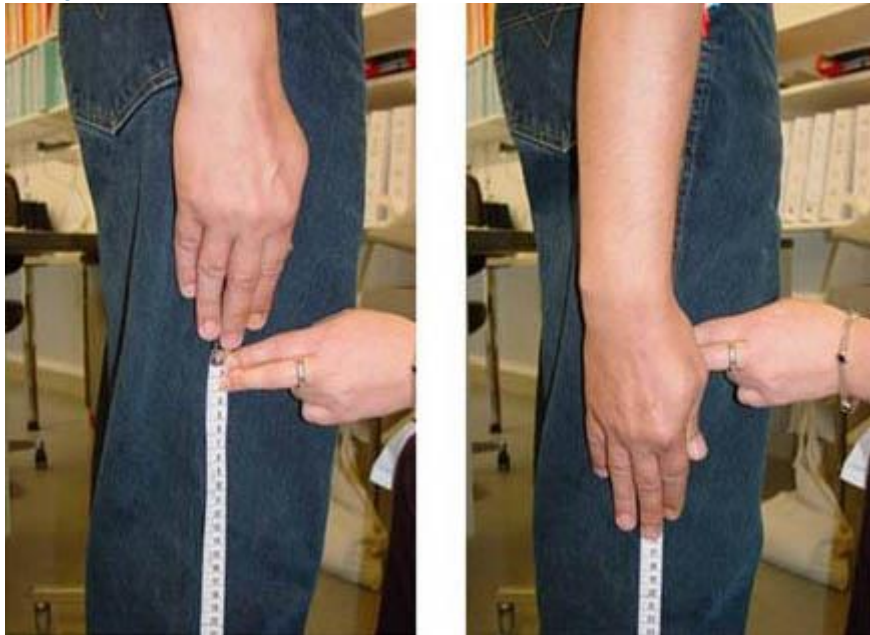
The most commonly used instrument to measure mobility in clinical trials is the Bath AS Metrology Index (BASMI), a composite index combining information from five different assessments: cervical rotation (figure 16), tragus-to-wall distance (figure 17), spinal lateral flexion (figure 18), lumbar flexion (modified Schober's test) (figure 19) and intermalleolar distance (figure 20). Three different definitions have been published: the 2-step definition, the 10-step definition and the linear definition. ASAS recommends the 10-step definition or the linear definition. Table 5 shows details of the BASMI.

Figure 16 Cervical rotation using a goniometer.



Figure 17 Tragus-to-wall distance.



Figure 18 Spinal lateral flexion.**Figure 19 Lumbar flexion (modified Schober's test).****Table 5 Bath Ankylosing Spondylitis Mobility Index (BASMI): evaluation of spinal mobility (Adapted from Jenkinson et al, J Rheumatol 1994;21:1694–8 and van der Heijde et al, Ann Rheum Dis 2008;67:489–93)**

If:	Then score =										
	0	1	2	3	4	5	6	7	8	9	10
Lateral lumbar flexion (cm)	≥20	18–20	15.9– 17.9	13.8– 15.8	11.7– 13.7	9.6– 11.6	7.5– 9.5	5.4– 7.4	3.3– 5.3	1.2– 3.2	≤1.2
Tragus-to-wall distance (cm)	≤10	10– 12.9	13– 15.9	16– 18.9	19– 21.9	22– 24.9	25– 27.9	28– 30.9	31– 33.9	34– 36.9	≥37
Lumbar flexion (modified Schober) (cm)	≥7	6.4– 7.0	5.7– 6.3	5.0– 5.6	4.3– 4.9	3.6– 4.2	2.9– 3.5	2.2– 2.8	1.5– 2.1	0.8– 1.4	≤0.7
Intermalleolar distance (cm)	≥120	110– 119.9	100– 109.9	90– 99.9	80– 89.9	70– 79.9	60– 69.9	50– 59.9	40– 49.9	30– 39.9	≤30
Cervical rotation angle (°)	≥85	76.6– 85	68.1– 76.5	59.6– 68	51.1– 59.5	42.6– 51	34.1– 42.5	25.6– 34	17.1– 25.5	8.6– 17	≤8.5
The BASMI score is the mean of the score of the 5 compartments											

Figure 20 Intermalleolar distance.

9.2.3 Evaluation of range of motion in daily practice

Abnormal postures have to be carefully checked in order to provide the best physical therapy. Once the loss of lumbar lordosis has appeared, thoracic kyphosis and a fixed flexed posture of the cervical spine may follow. The most disabling abnormal posture is the loss of the horizontal view, for which a surgical spinal intervention (*vertebral osteotomy*) may need to be considered (*see also above*).

9.2.4 Hip involvement

Hip involvement is closely related to the severity of spinal ossification and is responsible for significant functional impairment. The prevalence after 10 years of disease is around 10–15% in Western European countries, but up to 40–50% in other parts of the world, such as North Africa. It is typically bilateral. The significance of hip involvement has been shown in a recent multinational study, in which 5% of the patients underwent a total hip arthroplasty. The intermalleolar distance of the BASMI reflects the degree of hip involvement.

9.3 Can we predict the further course of the disease?

The disease course of AS is highly variable and one-third of patients with AS will develop a severe disease, accompanied by structural changes such as syndesmophytes and ankylosis in the spine. Information about the future potential severity of the disease is therefore important. Similar to rheumatoid arthritis, there is a trend towards treating patients efficiently as early as possible and before irreversible structural damage has occurred, although the evidence to support this strategy is currently more limited than in rheumatoid arthritis.

Prognostic assessment is important to guide treatment strategies. Candidate predictors for potentially severe disease are shown in box 15. In general, the negative predictive value is more reliable than the positive predictive value. In other words, the absence of any of the variables listed in box 15 is highly predictive of a good prognosis. Recent data from inception cohorts showed that patients with raised CRP, with extensive inflammation in the SI joints, and patients who smoke are at higher risk of developing structural changes in the SI joints than those patients who do not have these factors.

Box 15 Candidate predictors for potentially severe disease

Presence of the following parameters during the first 2 years:

- Hip involvement
- Erythrocyte sedimentation rate >30 mm/hr
- Reduction in lumbar spine movement
- Dactylitis
- Monoarthritis/oligoarthritis
- Age at onset before 16 years
- Diarrhoea
- Urethritis
- Psoriasis
- Inflammatory bowel disease

Adapted from Amor et al, J Rheumatol 1994;21:1883–7.

10 Management of axSpA

ASAS together with EULAR published in 2006 and updated in 2010 the ASAS/EULAR recommendations for the management of AS (Braun et al, 2011*). Since the evidence on the course and management of axSpA is limited and the literature is mainly based on data about AS, it has been decided to restrict the recommendations to AS, although the experts unanimously agreed that these recommendations can equally be applied to patients with axSpA.

The updated management recommendation includes overarching principles which deal with specific modalities important for each patient with AS. Eleven recommendations address several aspects of the management of patients with AS. It has been stated that management requires a multidisciplinary treatment coordinated by the rheumatologists since AS is a potentially severe disease with diverse manifestations as we have shown in the review above. To prevent deteriorating functioning in patients with AS it is important that the optimal management is based on a combination of non-pharmacological and pharmacological treatment modalities (see chapter 12, Treatment) and that the decision about optimal management is based on a shared decision between patients and rheumatologists. Discrepancies between patients' and physicians' perspectives of the disease and its outcome are well known and should be taken into account in the daily routine for

treating patients with AS. In patients with extra-articular manifestations, close working with specialists in gastroenterology, dermatology and ophthalmology is also required.

10.1 Patient education

Patient education is crucial for the successful management of patients with SpA. Once the diagnosis is made, the patient should be given a clear description of the nature of the disease, including an explanation of the potential clinical symptoms, complications and the possible progression of the target symptom.

To clarify this approach:

- The patient has to be educated clearly about the differences between back pain due to SpA and mechanical back pain. The most common misconceptions are that (a) NSAIDs have a higher toxicity than efficacy and (b) physiotherapy has no effect on the long-term outcome of back pain.
- Information about the possible occurrence of spinal ankylosis and abnormal postures may lead to better compliance with proposed treatments, such as NSAIDs and physiotherapy, and will give the patient a better understanding of the benefits and importance of regular follow-up.
- The patient must be informed about the possibility of the occurrence of other clinical symptoms of SpA. For example, the risk of developing acute anterior uveitis, in which case an early ophthalmic review would be required.

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Summary points

- SpA is a heterogeneous family of disorders characterised by axial inflammatory pain, peripheral arthritis, dactylitis and enthesitis.
- There may be associated extra-articular features such as inflammatory bowel disease, psoriasis, urethritis and anterior uveitis.
- Patients positive for the HLA-B27 tissue antigen have an increased risk of developing SpA.
- Genetic studies suggest also the existence of other predisposing genes, such as the *IL-23R*, *ERAP1*, *IL-1R2*, *ANTXR2*, *TNFSF15*, *2p15* and *21q22* genes.
- Apart from the genetic factors, environmental factors, particularly infections, predispose to the occurrence, or influence the severity, of the disease.
- The IL-23/-17 axis seems to play important role in the pathophysiology of SpA
- The initial symptom of AS is typically inflammatory lower back pain of insidious onset, becoming persistent after a few months. However, a diagnosis of SpA can be made in the absence of inflammatory back pain.
- Arthritis of the peripheral joints is typically oligoarticular, asymmetrical, with involvement of both small and large joints, predominantly of the lower limbs. Dactylitis is key feature of SpA, particularly PsA.
- Acute anterior uveitis is the most common extra-articular manifestation, with 25–40% of patients experiencing one or more episodes. It requires urgent ophthalmological referral since it can lead to permanent visual loss.
- MRI can detect inflammatory lesions long before definite lesions are visible on plain radiographs. A negative MRI does not exclude a diagnosis of SpA.
- The radiographic hallmarks of AS are sacroiliitis, erosions and sclerosis.
- The new ASAS criteria for axSpA have made it possible to diagnose early non-radiographic axSpA as well as established AS.
- Using the new ASAS criteria, diagnosis of axSpA can be based on clinical grounds. This requires the presence of HLA-B27 plus two other SpA features.
- A core set of tools for assessing disease activity and severity in order to facilitate treatment and record keeping has been proposed. This core set consists of patient-reported outcome measures as well as clinical and radiological measurements.
- The domains of pain, patient global assessment of disease activity, morning stiffness, fatigue, spinal mobility and physical function are included in all core sets.
- NSAIDs and exercise are recommended as first-line therapies in patients with axSpA. For those patients who still have an active disease the introduction of tumour necrosis factor α blockers is a major advance in the management of axSpA.

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EULAR on-line course on Rheumatic Diseases

Spondyloarthritis: Pathogenesis, clinical aspects and diagnosis

Stefan Siebert, George Fragoulis, Iain McInnes

A previous version was coauthored by Uta Kiltz, Xenofon Baraliakos, Cecilia Mercieca, Andrew A Borg, Maxime Dougados and Robert Landewé

IN-DEPTH DISCUSSION I

**Classification and diagnosis in early axial
Spondyloarthritis**

Spondyloarthritis (SpA) comprises a group of conditions characterised by sacroiliitis, spondylitis, peripheral arthritis and enthesitis. Over the past years a lot of research has been carried out in this field which has led to major advances and better understanding of the disease pathogenesis. The availability of MRI and the efficacy of TNF- blocking therapies have been the main driving force for these developments. MRI allows for earlier diagnosis while improved biologic therapies may allow for commencement of treatment possibly before structural damage has taken place.

Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial SpA

The validated classification criteria for axial SpA herald a new era in this field making it possible to diagnose both early axial SpA without radiographic changes as well as established SpA (1, 2). This will facilitate the conduct of clinical trials and observational studies as well as the daily management of axial SpA. The term axial SpA encompasses a disease spectrum ranging from inflammatory symptoms and signs but no radiographic changes through to more established disease with obvious structural changes consistent with ankylosing spondylitis (AS).

Although the modified New York criteria for AS (3) perform well in patients with established disease they do not allow diagnosis of SpA until radiographic changes have occurred. Radiographic changes reflect consequences of the inflammation rather than the inflammation itself. MRI has become an invaluable tool in early diagnosis as it can detect active inflammation in the spine and sacroiliac joints (SIJ) that is not visible on plain radiography. Sacroiliitis can be detected by MRI years before it is apparent on a plain radiograph. The previous concept of “pre-radiographic” sacroiliitis implied would develop radiographic changes over time, but recent data suggests that only a proportion will progress, so the preferred terminology now is “non-radiographic”. It is worth noting that the term “non-radiographic” refers to patients with no current imaging evidence of sacroiliitis and those with MRI but not x-ray evidence of sacroiliitis who fulfil the clinical and imaging arms, respectively, of the ASAS classification criteria for axial SpA. Our current stage of knowledge does not allow us to accurately predict which individuals will develop progressive disease, although male gender and the presence of syndesmophytes generally predict progression at a group level. Early diagnosis is important because it has been shown that the burden of early disease is still substantial and comparable to that of later stages (4). In addition anti-TNF agents have been shown to be effective in early disease (5). There is little evidence at present that anti-TNF agents can stop, retard or reverse radiologic progression, but there is gradually accumulating longer term observational data to suggest this may be the case.

Earlier criteria such as the European Spondyloarthropathy Study Group (ESSG) (6) and the Amor criteria (7) were created before MRI was available. Using these criteria patients without sacroiliitis on plain radiography are said to have undifferentiated SpA, without differentiating between axial- and peripheral SpA. This is

relevant when deciding about treatment particularly the use of TNF-blockers in non-radiographic axial SpA. The modified New York criteria focus on AS as a separate disease rather than as part of an entire SpA spectrum. With the ASAS classification criteria for axial SpA there is a recognition of the concept of axial SpA, with AS representing one potential outcome rather than a separate disease. More importantly it has become possible to diagnose non-radiographic axial SpA, a need which was previously unmet.

The ASAS classification criteria for axial SpA were published in 2009. Initially, draft criteria were created based on review of 71 'paper patients' by 20 international experts (1). These criteria were then validated in a large multicentre study (2). The study population consisted of 649 patients with chronic back pain representing the whole spectrum of SpA from the early non-radiographic stage to radiographic sacroiliitis with a mean duration of symptoms of 6.1 years.

The classification criteria comprise a 10-item list of SpA features. Interestingly no spinal mobility measures were included in the new criteria as in early disease these were not found to be useful to differentiate between axial SpA and no SpA. The axial SpA classification criteria have a sensitivity of 82.9% and a specificity of 84.4% with a positive likelihood ratio of 5.3 for axial SpA, increasing the post-test probability of a diagnosis of axial SpA from 60.2% to 89%. When compared to the ESSG and Amor criteria the new ASAS classification criteria were shown to perform better. These criteria are primarily designed as classification criteria and there are currently no diagnostic criteria for axial SpA, so in daily clinical practice one has to adapt a more flexible approach. There are important differences between classification and diagnostic criteria. Most importantly, classification criteria are designed to be applied where the *a priori* diagnosis of axial SpA is suspected in order to create more homogenous cohorts for research purposes. In contrast, diagnostic criteria are applied in clinical settings where the *a priori* diagnosis is unknown, so also require clinical acumen to exclude other potential causes for the patient's symptoms and findings, which is not part of classification criteria. Therefore, while classification criteria can be useful in clinical practice, they cannot simply be applied using a "check box" approach. Given a rheumatology setting with a prevalence of 60% axial SpA as was present in this study these criteria should perform satisfactorily in clinical practice in this setting. Whether they perform as well in populations with a lower prevalence needs to be investigated.

MRI in early axial SpA

The most significant change in the ASAS criteria is the inclusion of MRI as a defining criterion. Axial disease, unlike peripheral disease, is hindered by lack of specific clinical signs or laboratory features. Reliance on clinical symptoms and radiographic changes has resulted in diagnostic delay which may take up to 10 years from onset of symptoms (8). MRI sensitivity for active early inflammation is now well established. MRI has been shown to predict progression to AS as well as response to anti-TNF blocking treatment both in early and

established diseases (5, 9). MRI is now the imaging modality of choice to visualise the SIJs and spine in early disease and is increasingly used clinically and in research (Figure 1).

Figure 1: Florid unilateral sacroiliitis in a patient with a recent diagnosis of Psoriatic arthritis. Erosions (black arrow) of sacroiliac joint and bone oedema (white arrow) are evident. T2- Turbo Inversion Recovery Magnitude (TIRM) sequence.



Indeed, in the validation of the new criteria, MRI findings of the SIJs led to a change in diagnosis in 21% of cases. However, one has to recognise that MRI has limitations in identifying inflammation. In the new ASAS criteria validation cohort, 35% of patients did not have SIJ inflammation on MRI. A negative MRI scan therefore does not exclude a diagnosis of SpA. The new criteria address this issue and allow a diagnosis of axial SpA based on clinical grounds without the need of a positive MRI. In fact a classifying diagnosis of SpA can be made in the presence of HLA-B27 plus 2 other SpA features without MRI or radiographic evidence. This makes HLA-B27 a critical parameter for the diagnosis of SpA in these patients, although it should be noted that the clinical arm had a lower specificity (86%) compared to the imaging arm (97.5%). The authors report that out of the 130 patients with a diagnosis of axial SpA who had undergone an MRI of both SIJs and spine, only 5.4 % had inflammatory lesions solely in the spine without SIJ involvement. In fact the majority had lesions either in SIJs alone or at both sites. Further study needs to be carried out to see whether including spine MRI with SIJ MRI improves sensitivity and specificity of these criteria. T2-weighted fat suppressed fast spin-echo and STIR sequences are recognised as the imaging of choice for bone marrow oedema (BMO) (10). T2-weighted sequences suppress the fat signal allowing visualisation of the bright inflammatory signal in the bone marrow. STIR sequences are generally sufficient to detect inflammation and the use of contrast medium is not recommended in the EULAR recommendations for imaging in the diagnosis and management of SpA (11).

BMO has been shown to correlate with histological inflammation (12). However BMO can also arise from mechanical stress, insufficiency fractures or malignant tumours, so BMO alone does not necessarily imply a diagnosis of axial SpA. As with all imaging, the results need to be interpreted in the context of the clinical presentation and not in isolation. Few studies have addressed the specificity of MRI. Interpretation and the diagnostic value of MRI vary, depending on the facilities and the level of training. This has created an urgent need for a standard definition of active MRI sacroiliitis to be implemented for research purposes and in clinical practice. Recently the ASAS/OMERACT MRI group consisting of two radiologists and eight rheumatologists with a special interest in SpA has put forward a definition for MRI sacroiliitis after reaching a consensus (13). This states that BMO (on STIR) or osteitis (or T1 post Gadolinium) must be clearly present in subchondral or periarticular BMO with sufficient amount of signal. Sufficient signal is defined as more than one BMO lesion on a single slice or if there is only one BMO lesion, this must be present on two consecutive slices. This definition should be applied for the criterion “active sacroiliitis by MRI” in the new ASAS classification criteria for axial SpA. Further prospective validation of this definition with age- and sex-matched controls and radiographic follow up is still required. Inflammatory lesions based on synovitis, enthesitis or capsulitis, but without BMO, were not included in the definition of sacroiliitis on MRI since these very rarely occur in the absence of BMO. The authors also point out that further studies need to look at defining minimum size and variable grades of severity of BMO. Fatty changes seen on T1 MRI sequences indicate chronic changes which may be the consequence of inflammatory or degenerative processes, so are less specific and are not currently included in the ASAS classification criteria, although they may be of value in clinical practice in patients in whom a high clinical suspicion of axial SpA exists (e.g. a 20 year old man with Crohn’s disease).

In a recent paper (14), low severity BMO has been found in individuals with mechanical back pain. On the other hand grade 2 or 3 severity lesions (based on the Leeds scoring system) were more marked in inflammatory back pain (IBP) patients and linked to HLA-B27. Equally important was the fact that a third of patients showed lesions simultaneously in the SIJ and in the lumbar spine, while a small minority had lumbar spine lesions without SIJ lesions.

Until a few years ago, the SIJs were the main site of interest and little attention was given to the spine. Spine inflammation was mainly used to assess disease activity, as a guide to support initiation of anti-TNF treatment and assessment of treatment efficacy. Lately there has been considerable interest in MRI of the spine, both from the diagnostic and prognostic perspectives. It has been shown that in clinically active axial SpA, the SIJs are normal in up to 20% (15) although other studies have reported lower levels. From the prognostic point of view it would be very useful to identify which inflammatory lesions will progress to syndesmophyte formation, since functional outcome is directly related to spinal disease severity but not to SIJ disease (16). There are several MRI scoring systems for assessment of spinal inflammation, including the Ankylosing spondylitis spine

score for activity (ASspiMRI-a), the Berlin method, and the Spondylitis Research Consortium of Canada (SPARCC), although their current use is largely limited to clinical trials (17-18).

Inflammatory back pain

Another important difference in the new ASAS criteria is that IBP is no longer an obligatory criterion. For entry one must have back pain for at least 3 months starting before 45 years of age, while IBP counts as an extra SpA parameter. New clinical criteria have also been proposed for IBP (19), known as the ASAS 'expert' criteria. In this real patient study, experts were blinded to the patients' diagnosis and the criteria scrutinised for their capacity to differentiate between IBP and non-IBP, rather than for diagnosis of AS versus non-AS as previously performed in the Calin's criteria (20). Statistical analysis was then carried out to distinguish which criteria were independently specific to IBP. The new expert criteria should be applied to patients with chronic back pain for > 3 months and the criteria are fulfilled if at least four out of following five parameters are present: age at onset < 40 years, insidious onset, improvement with exercise, no improvement with rest and pain at night (with improvement upon getting up). These criteria were shown to have a sensitivity of 72.4 % and a specificity of 82.2%. These new criteria compare to the previous 2006 Berlin criteria (21) published by the same group. The main difference is the exclusion of early morning stiffness, as well as pain in the second half of the night. The reason given for not including these parameters was that duration and timing were not specifically analysed in this study. Validation in the primary care setting still has to be carried out.

In 2009 ASAS published a handbook guide for assessment of axial SpA (22). This is a compendium of validated classification and outcome measures including clinical and radiological measures.

Conclusion

These are exciting and challenging times in the SpA field. The new ASAS criteria for axial SpA encompassing the whole disease spectrum of axial SpA are a major breakthrough in facilitating future research and earlier treatment in clinical practice. Availability of MRI is another key advancement making it possible to diagnose non-radiographic SpA. However, it is worth remembering that a significant number of patients with features of SpA have normal MRI scans, which implies that a negative MRI of the SIJ does not exclude SpA. In some cases it is still difficult to make a definite diagnosis and the classification criteria are not designed to be rigidly applied in daily clinical practice, so careful clinical assessment and diagnostic work-up remain key.

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6

module

EULAR on-line course on Rheumatic Diseases

Spondyloarthritis: Pathogenesis, clinical aspects and diagnosis

Stefan Siebert, George Fragoulis, Iain McInnes

A previous version was coauthored by Uta Kiltz, Xenofon Baraliakos, Cecilia Mercieca, Andrew A Borg, Maxime Dougados and Robert Landewé

IN-DEPTH DISCUSSION II

HLA and the SPONDYLOARTHROPATHIES

Introduction

The association between spondyloarthropathies and HLA antigens (specifically HLA-B27) has been a major scientific advance because it provides an insight into the complex distribution of genetics, environmental factors and immunology to the pathogenesis of this group of diseases.

HLA-B27 occurs in 6-10% of Caucasians but is present in more than 90% of patients with Ankylosing Spondylitis (AS). Some of the other spondyloarthropathies also show an increased frequency of HLA-B27.

The HLA System

Human leucocyte antigens (HLA)

These are also known as the Major Histocompatibility Complex (MHC) and are cell surface glycoproteins which are present on nucleated cells. Their function is not fully understood but they are the cellular markers of individuality and they play an important role in antigen presentation to T cells and immunological reactivity at the cellular level.

There are two main groups of MHC proteins: the class I antigens (HLA-A,B and C) which are found on most nucleated cells, and the class II antigens (HLA-D/DR) which are only found on cells in the immune system involved in antigen presentation.

The class I antigens have two components: a small fragment identified as β 2 microglobulin, and a larger component (the heavy chain) which carries the antigenic specificity. The base of the antigen is embedded within the cell membrane while the remainder projects above the cell surface with the antigenic portion exposed.

Genetics of the HLA System

Each individual has a limited number of antigens on the cell surface giving each person a biological individuality. The area of chromosome 6 that codes for the HLA antigens is also called the MHC. The MHC also contains the genes coding for complement components C2, C4 and factor B. The HLA antigens are genetically determined and can be divided into groups on the basis of the gene locus which codes for them. These loci have been designated A, B, C, and D/DR.

At each locus, a number of different alleles can be found and these code for the antigens of the A, B, C, D/DR series. To date at least 20 different antigens of the A locus, 30 antigens of the B locus, 8 of the C locus, 10 of the D locus and a similar number of DR antigens have been identified.

Unanswered/Partly answered Questions

The shared genetic background partly explains the inter-relationship between the various spondyloarthropathies. However, several observations remain unresolved including:

1. Not all patients with HLA-B27 develop disease while up to 5% of Caucasian AS sufferers are HLA-B27 negative.

HLA-B27 is the primary disease susceptibility gene for AS, and is thought to contribute about 49% of the population-attributable genetic risk of AS for Caucasians [1-2].

Recent research as part of the genome-wide association study (GWAS) approach using single nucleotide polymorphism (SNP) genotyping techniques have identified several non-MHC genes which confer susceptibility to Crohn's disease and psoriasis such as the gene for the interleukin-23 receptor (IL-23R). IL-23 appears to be a key factor in the regulation of the proinflammatory Th17 cells [1-4]. IL-23 is selectively overexpressed in subclinical intestinal inflammation sites in AS at levels similar to those seen in Crohn's sufferers. The IL-23R gene is thought to contribute roughly 9% of the population-attributable genetic risk for AS in Caucasians [1-3].

Another gene, ERAP1 (also called ERAAP or ARTS1) located on chromosome 5 encodes a transmembrane aminopeptidase with various immunologic functions including trimming of peptides for presentation by MHC class I proteins. Another function of ERAP1 and its genetic variants is the cleavage of cell surface receptors for the pro-inflammatory cytokines IL-1, IL-6 and TNF resulting in down regulation of their signal.

ERAP1 is strongly associated with AS and is thought to contribute roughly 23% of the population-attributable genetic risk for AS in Caucasians [1-2]. Interestingly, the association with ERAP1 is only seen in patients who are HLA-B27 positive, representing a true gene-gene interaction. ERAP1 is also associated with a number of other SpA-related conditions, including Crohn's disease and psoriasis. It is also now recognised that while some ERAP1 variants increase the susceptibility to AS, others are protective.

2. The association between AS and HLA-B27 in blacks [5] (40-50%) and Japanese [6] is not as striking as that in Caucasians.

Nearly 60 subtypes of HLA-B27 have been identified. However, epidemiological studies linking their associations with disease are not present for many of the subtypes [7]. The subtypes from B*2702 through to B*2710, B*2714, B*2715, B*2719 and B*2730 all have proven associations with spondyloarthropathies [8]. The HLA-B*2706 and HLA-B*2709 subtypes were until recently thought to be protective but a few cases of AS have been reported suggesting that they are not absolutely protective but weakly associated with the development of AS [9-11].

These epidemiologic associations between HLA-B27 subtypes and disease are important because they may help elucidate the mechanism of HLA-B27's association with the spondyloarthropathies [12].

3. Relatives of probands with both sacroiliitis and HLA-B27, even when carrying an identical HLA haplotype, frequently remain disease free. HLA-B27 positive relatives of HLA-B27 positive patients are about 20 times more likely to develop AS than are HLA-B27 positive relatives of healthy HLA-B27 positive subjects [13].

The difference in clinical phenotype between HLA-B27 positive and HLA-B27-negative patients has been recognised for over 30 years [14; 15]. HLA-B27 negative AS tends to have a later disease onset, lower incidence of acute anterior uveitis and is significantly more frequently associated with psoriasis, ulcerative colitis and Crohn's disease. Familial aggregation is also uncommon [14; 15].

A recent study from Finland confirmed the observation that individuals who are homozygous for HLA-B27 are more than three times as likely to develop AS as those who are heterozygotes [16; 17]. The authors hypothesized that possible increased cell surface expression of HLA-B27 or potentially increased effects from linked genes may influence the occurrence of the disease process.

4. What is the evidence that HLA-B27 may have a pathogenic role in the Spondyloarthropathies?

At present the precise explanation for the association between HLA-B27 and AS is unknown. The current three major theories (shown in Figure 1) proposed to explain how HLA-B27 contributes to AS are:

1. The arthritogenic peptide theory
2. Homodimerisation theory
3. Endoplasmic reticulum stress and unfolded protein response theory

The "arthritogenic peptide" theory suggests that HLA-B27 has the ability to bind a peptide(s) from a microbial source with the consequent generation of an HLA-B27 restricted CD8+ cytotoxic T cell response [18]. Such a peptide would be bound and presented by all the HLA-B27 disease-associated subtypes but not by other HLA Class I molecules. This hypothesis was dealt a blow by studies in the B27 transgenic mouse model for spondyloarthropathies where it appears that CD8+ T cells do not appear to be involved or required for development on the disease in this model.

Various hypotheses have been put forward on the basis of the complicated structure of HLA-B27 which in addition to having specific antigen-presenting sites, also tends to fold and misfold, forming covalent homodimers that can be expressed on the cell surface. These can then be recognized by leucocyte receptors on immune cells, including Th17 and Natural Killer cells, leading to IL-17 production [18-21]. This theory has

gained some traction recently with the demonstration of differences in KIRD3DL2 receptor binding to HLA-B27 subtypes, independent of the sequence of bound peptide [22].

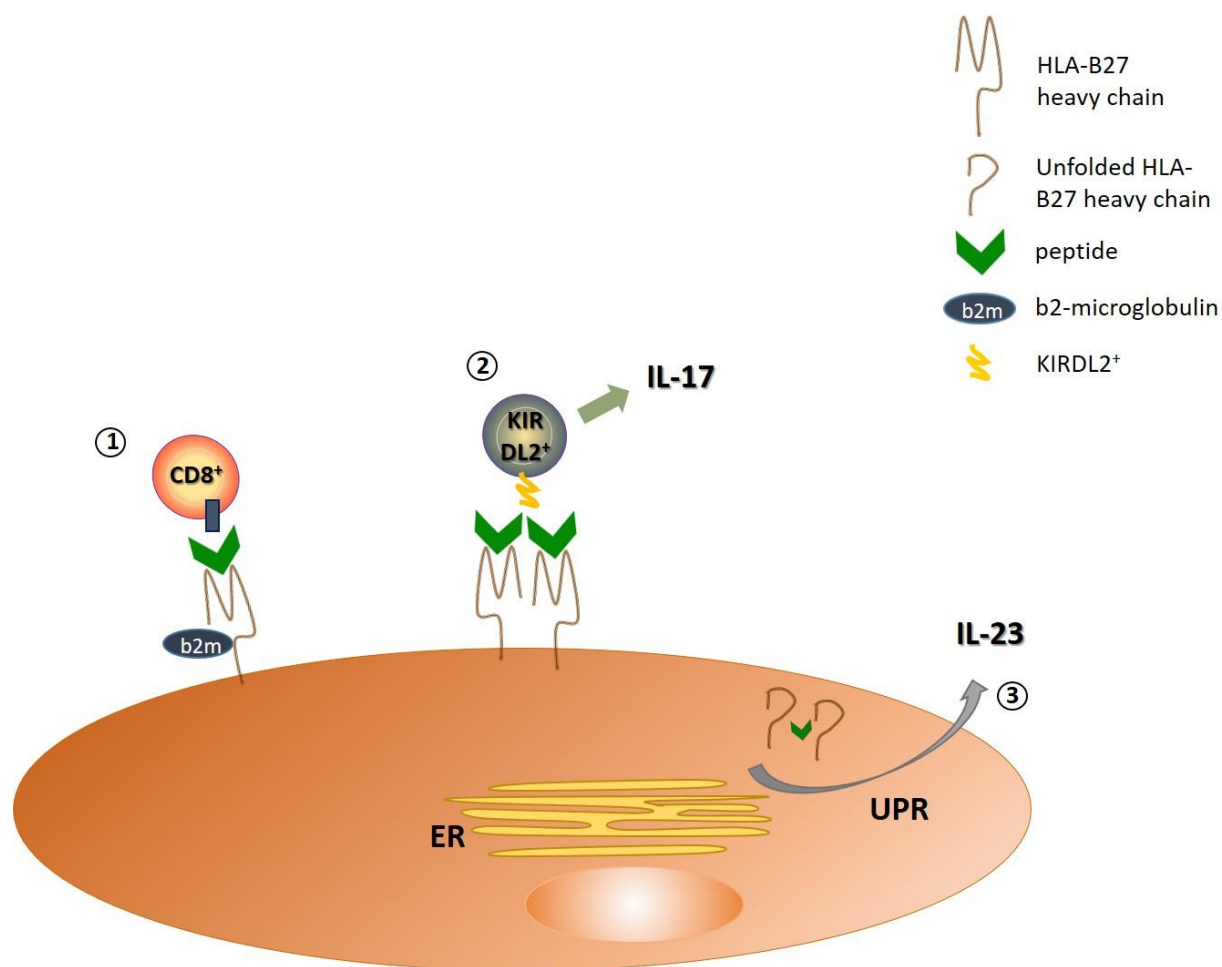
This mechanism however, would not fully explain the differential association of AS with the various subtypes of HLA-B27 described earlier on, with some subtypes appearing to confer a degree of protection (although not complete) to developing the disease.

In addition to forming homodimers, it has been proposed that HLA-B27 may misfold in the endoplasmic reticulum, leading to endoplasmic reticulum stress and the unfolded protein response. Recent data has however failed to demonstrate this in AS and raised doubt about this model.

An older hypothesis proposed molecular mimicry between a viral peptide, such as Epstein-Barr virus, and a self-derived peptide as a potential mechanism. This in turn would trigger a cross-reactive cytotoxic T cell response that activates cell lines that have not been eliminated in the thymus. It is thought that these self-peptide-activated T cells may then contribute to the inflammatory process in later years in AS patients [19-22].

On the balance of the evidence currently available it is unclear whether HLA-B27 predisposes to AS via more than one mechanism or by different mechanisms in different patients. While the exact mechanism of the long recognised association of HLA-B27 with AS remains elusive, the study of HLA-B27 has gained renewed momentum with the identification of other non-HLA susceptibility genes in AS and improved understanding of other components of the immune response in this condition.

Figure 1: HLA-B27 theories. 1. Arthritogenic peptide theory: folded HLA-B27 chain complexed with antigenic peptide and b2 microglobulin activates CD8⁺ T cells. 2. Homodimerisation theory: homodimerized HLA-B27 chains activate KIRDL2⁺ cells to produce IL-17. 3. Unfolded protein response theory: unfolded HLA-B27 chains accumulate in the endoplasmic reticulum, leading to the production of inflammatory cytokines and IL-23. KIR: killer immunoglobulin-like receptor, ER: endoplasmatic reticulum, UPR: unfolded protein response



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Management of spondyloarthritis

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LEARNING OUTCOMES

- ➔ Describe and explain the differences between axial and peripheral spondyloarthritis in the management of spondyloarthritis (SpA)
- ➔ Describe and explain the important role of physical therapy, non-steroidal anti-inflammatory drugs and biologic drugs as well as the limited effect of disease-modifying antirheumatic drugs in the management of SpA
- ➔ Make treatment decisions, taking possible extra-articular manifestations, such as uveitis, psoriasis and inflammatory bowel disease, into account
- ➔ Describe the use of biologic agents, their dose, the indication for treatment and their possible side effects
- ➔ Monitor treatments
- ➔ Describe and explain the role played by allied health professionals in the treatment of rheumatoid arthritis

1 Introduction

The spondyloarthritis (SpA) comprise ankylosing spondylitis (AS), reactive arthritis, arthritis/spondylitis associated with psoriasis and arthritis/spondylitis associated with inflammatory bowel disease (IBD). The main link between them is the association with HLA-B27, the same pattern of peripheral joint involvement with an asymmetrical, pauciarticular, arthritis predominantly of the lower limbs, and the possible occurrence of sacroiliitis, spondylitis, enthesitis, dactylitis and uveitis. The leading clinical symptoms for all subsets of SpA are inflammatory back pain and/or asymmetrical arthritis, predominantly of the lower limbs.

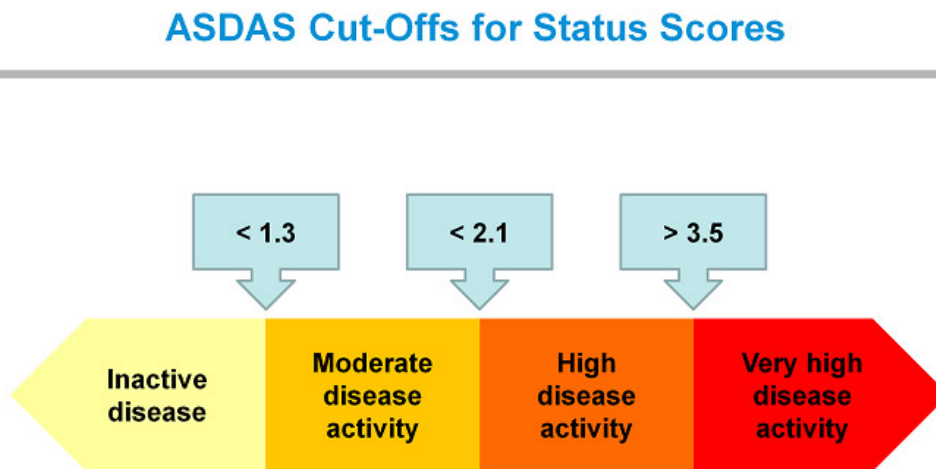
According to the recently published Assessment of SpondyloArthritis international Society (ASAS) classification criteria, SpA can be divided into two subsets: axial and peripheral SpA. The term axial SpA (axSpA) covers both patients with established AS (with radiographic sacroiliitis) and patients without definitive chronic changes visible on X-ray examination, termed non-radiographic axial SpA. When a clinical diagnosis of axSpA has been established, the disease can be classified after the patient has had chronic back pain for longer than 3 months starting at an age <45 years and if there is either sacroiliitis on imaging (which could be chronic changes on X-ray examination or early active inflammatory changes on MRI) plus the presence of one additional typical SpA feature or if the patient is HLA-B27 positive with at least two additional typical SpA features.

Peripheral SpA (pSpA) is characterised by peripheral arthritis, enthesitis or dactylitis. Except in the subgroup of patients with psoriasis, very few studies, and no drug approval, concern pSpA. The term psoriatic arthritis (PsA) comprises different subtypes of inflammatory locomotor manifestations, including arthritis of the fingers or toes joints. There are many drug trials dedicated to this subtype with specific approvals. Therefore, in this article, management for both axSpA and PsA will be covered, and separately. The following discussion of therapeutic options will be split into predominantly axial (including AS) or predominantly peripheral manifestations of SpA (including PsA, IBD arthritis and reactive arthritis).

2 Axial spondyloarthritis

To judge the efficacy of a treatment the Bath AS Disease Activity Index (BASDAI, described in chapter 11) or the ASAS working group response criteria are most often used. Both are based on patients' reported symptoms. More recently, the AS Disease activity Score (ASDAS) was introduced, which encompasses acute phase reactants (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) in addition to patient-reported outcomes from questionnaires (BASDAI: back pain, morning stiffness and patient global assessment of disease activity on a Visual Analogue Scale). Cut-off values for different states of disease activity have been described, with an ASDAS value >2.1 indicative of highly active disease (as described in chapter 11) (figure 1).

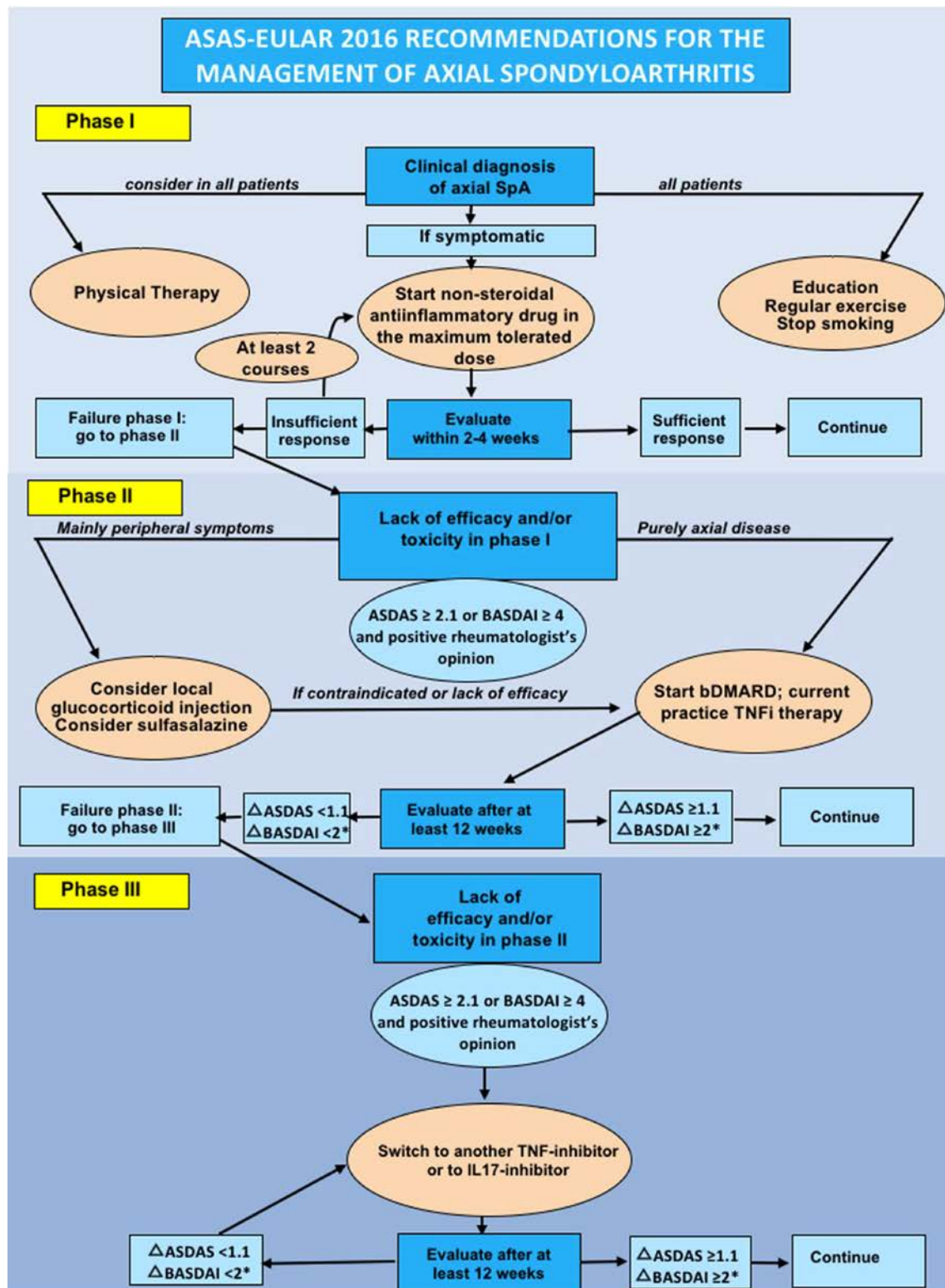
Figure 1 Ankylosing Spondylitis Disease Activity Score (ASDAS). ASDAS cut-off points for status scores.
(Reproduced from Machado et al, Ann Rheum Dis 2011; 70:47–53*.)



Machado P et al. Ann Rheum Dis 2011;70:47-53 (with permission)



Figure 2 Algorithm based on the 2016 update of the ASAS-EULAR recommendations for the management of axial spondyloarthritis. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor; IL17-inhibitor, interleukin-17 inhibitor. *Either BASDAI or ASDAS, but the same outcome per patient. (Reproduced from van der Heijde et al, *Ann Rheum Dis* 2017;76: 978-991.)



Recommendations emerging from the ASAS/EULAR group for the management of the whole group of axSpA have recently been updated in 2016, and are part of the EULAR recommendations. These recommendations are summarised in an algorithm (figure 2) and in 13 bullets (figure 3) and will be discussed in more detail. It can be easily seen from this that non-steroidal anti-inflammatory drugs (NSAIDs) and tumour necrosis factor (TNF) blockers are, up to now, regarded as the most important and almost the only relevant form of medical treatment which has to be combined with non-pharmacological treatments during the entire course of the disease.

Figure 3 2016 Update ASAS-EULAR recommendations for the management of axSpA . (Reproduced from van der Heijde et al, *Ann Rheum Dis* 2017;76: 978-991.)

Table 1 2016 Update of the ASAS-EULAR recommendations for the management of axSpA				
Overarching principles		LoE	GoR	LoA (0–10)
1	axSpA is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary management coordinated by the rheumatologist			9.9 (0.31) 100% ≥8
2	The primary goal of treating the patient with axSpA is to maximise health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation			9.8 (0.47) 100% ≥8
3	The optimal management of patients with axSpA requires a combination of non-pharmacological and pharmacological treatment modalities			9.8 (0.45) 100% ≥8
4	Treatment of axSpA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist			9.5 (0.91) 100% ≥8
5	axSpA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist			9.3 (1.17) 97% ≥8
Recommendations				
1	The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestations) and the patient characteristics including comorbidities and psychosocial factors	5	D	9.7 (0.65) 100% ≥8
2	Disease monitoring of patients with axSpA should include patient-reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and treatment	5	D	9.6 (0.78) 100% ≥8
3	Treatment should be guided according to a predefined treatment target	5	D	8.9 (1.45) 93% ≥8
4	Patients should be educated* about axSpA and encouraged to exercise* on a regular basis and stop smoking‡; physical therapy† should be considered	2* 5‡ 1a†	B* D‡ A†	9.6 (0.78) 100% ≥8
5	Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise	1a	A	9.4 (0.94) 100% ≥8
6	Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated	5	D	8.8 (0.94) 100% ≥8
7	Glucocorticoid injections* directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids‡	2* 5‡	B* D‡	9.4 (0.78) 100% ≥8
8	Patients with purely axial disease should normally not be treated with csDMARDs§; sulfasalazine† may be considered in patients with peripheral arthritis	1a†	A	9.2 (0.78) 100% ≥8
9	bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (figure 1); current practice is to start with TNFi therapy	1a (TNFi); 1b (IL-17i)	A	9.6 (1.09) 93% ≥8
10	If TNFi therapy fails, switching to another TNFi* or IL-17i** therapy should be considered	2* 1b**	B* A**	9.6 (0.95) 97% ≥8
11	If a patient is in sustained remission, tapering of a bDMARD can be considered	2	B	9.1 (1.57) 97% ≥8
12	Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity	4	C	9.4 (0.82) 100% ≥8
13	If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed	5	D	9.9 (0.31) 97% ≥8

§1a (sulfasalazine; methotrexate); 1b (leflunomide); 4 other csDMARDs.

axSpA, axial spondyloarthritis; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GoR, grade of recommendation; IL-17i, interleukin-17 inhibitor; LoA, level of agreement; LoE, level of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.

For the management of axSpA, an early diagnosis is important for several reasons: (i) an early correct diagnosis avoids unnecessary diagnostic procedures and wrong treatments; (ii) emphasises the importance of starting

physical treatment early; (iii) enables treatment with NSAIDs to be started and continued in symptomatic patients once the diagnosis is made; (iv) enables early use of TNF blockers in patients with axSpA refractory to conventional treatment in the presence of an active disease and radiographic sacroiliitis and/or inflammation of the sacroiliac joints and/or elevated C-reactive protein (CRP) level; (v) enables the use of another biologic drug, an anti-IL17 one, secukinumab, in case of TNF blockers failure and in presence of radiographic sacroiliitis. A major obstacle in axSpA to any earlier treatment is the long delay of 5–10 years between the first (chronic) symptoms of the disease and the final diagnosis. Thus, starting treatment of axSpA earlier is closely related to the strategies for early diagnosis of axSpA.

2.1 Physical therapy and stop smoking

Physical therapy is the most important non-pharmacological aspect of axSpA management. Its primary aims are to prevent and/or retard restriction of spinal mobility and the development of disability, and to improve the symptoms of pain and stiffness. The effectiveness of these treatments is described in several studies (Van Tubergen et al, 2001) and highlighted in a recent systematic review (van den Berg R, et al 2012) Once the diagnosis is made the patient should be referred to a physical therapist, who will teach the patient the exercises that should be performed regularly.

Because the main long-term outcome, which should be prevented is a flexion deformity of the spine, exercises concentrate on extension and rotation of the spine. Moreover, physical exercises improve muscle strength and decrease the risk of cardiovascular disease.

The patients should be advised to exercise daily at home and to attend weekly group physical therapy. The patient's own efforts are the key to future success and the patient with AS has to be convinced that a daily exercise programme should be a normal part of the day. If patients are symptomatic and complain about pain or stiffness they should be treated, in addition, with NSAIDs or other effective drugs to permit full mobilisation during the exercises.

These exercises should be continued regularly throughout life, particularly in the forms with radiographic signs of ossification or persistent disease activity. Furthermore, patients should be encouraged to participate in activities such as swimming and cycling.

In addition to stimulate physical activity, more evidence has been raised about the negative effects of smoking. Smoking is associated with a more rapid radiographic progression and increases the cardiovascular risk. Therefore, rheumatologists should encourage the Ax Spa patients to stop smoking (bullet 4).

2.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are regarded as the cornerstone of pharmacological intervention for axSpA, reducing pain and stiffness rapidly after 48–72 h. One of the first NSAIDs used for the treatment of axSpA was phenylbutazone, but this drug is seldom used nowadays because of its potential side effects, such as bone marrow depression. Many other NSAIDs have been shown to be effective.

Several placebo-controlled trials investigating different NSAIDs, including cyclo-oxygenase-2 (Cox-2)-selective inhibitors, convincingly showed good efficacy compared with placebo treatment. The advantage of selective Cox-2 inhibitors (celecoxib, etoricoxib) is the lower risk of gastrointestinal side effects such as the onset of peptic ulcers.

A selection of NSAIDs with the maximal recommended daily dose, is shown in table 1. Most importantly, when patients with axSpA are asked about the level of efficacy of NSAIDs, 70–80% report a good or very good improvement of their symptoms. In contrast, this level of response is only reported by about 15% of patients with chronic low back pain of non-inflammatory causes. Furthermore, a good response to NSAID treatment is also used in diagnosis to differentiate chronic back pain in patients with axSpA from pain with other causes (figure 4).

Table 1 Doses of non-steroidal anti-inflammatory drugs used/tested in ankylosing spondylitis

Drug	Half-life (h)	Approved maximal daily dose for arthritis (mg)
Aceclofenac	4–4.3	200
Celecoxib	8–12	400
Etoricoxib	About 22	90
Ibuprofen	1.8–3.5	2400
Indometacin*	2	150
Diclofenac*	About 2	150
Ketoprofen	1.5–2.5	200
Naproxen	10–18	1000
Meloxicam	About 20	15
Piroxicam	30–60	20
Phenylbutazone	50–100	600
Flurbiprofen*	2.8 -12 hours	50, 100 and 200 mg

*Retard formula available.

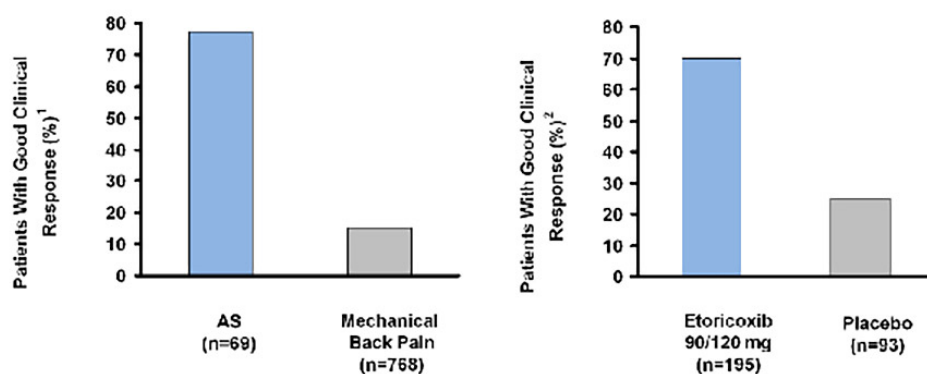
Normally an optimal effect of an NSAID is reached in about 2 weeks, but sometimes longer is needed to determine the optimal drug and dose. In many patients a full dose is necessary to cover the entire day (table 1). If morning stiffness and pain at night are the predominant symptoms a long-acting night-time dose might be effective.

The high efficacy of NSAIDs for the treatment of axSpA is especially interesting because other anti-inflammatory treatments, such as glucocorticoids or disease-modifying antirheumatic drugs (DMARDs), are

much less effective (see below) than NSAIDs, in contrast, for example, to their good efficacy in the treatment of rheumatoid arthritis (RA).

Figure 4 Efficacy of non-steroidal anti-inflammatory drugs for treatment of ankylosing spondylitis (AS).
(Adapted from 1 Amor et al, *Rev Rheum Engl Ed* 1995;62:10–5; 2 van der Heijde et al, *Arthritis Rheum* 2005a;52:1205–15*.)

Efficacy of NSAIDs for the Treatment of Patients with Ankylosing Spondylitis



1. Amor B et al, *Rev Rheum Engl Ed* 1995;62:10–5

2. van der Heijde D et al *Arthritis Rheum* 2005;52:1205–15

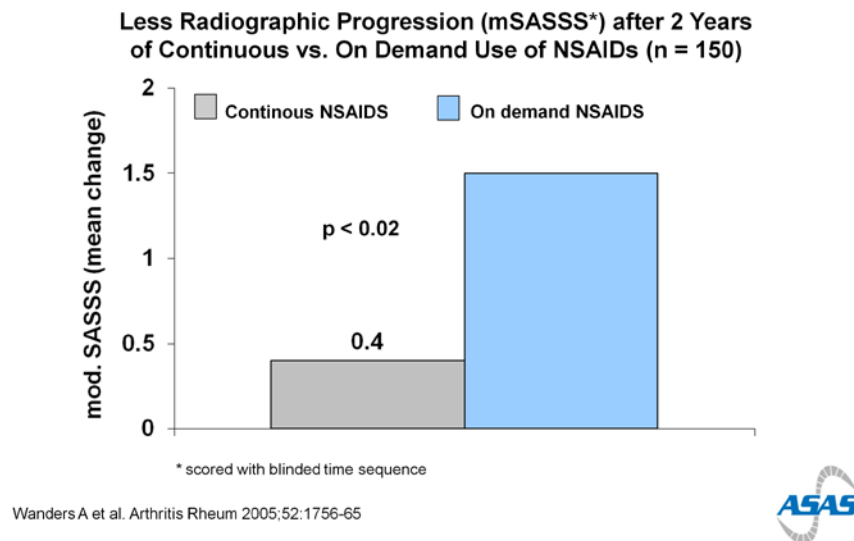


A few studies (figure 5) suggest that NSAIDs might have disease-modifying properties because radiological progression of the spine is retarded when the drugs are given continuously as a daily dose over 2 years compared with an on-demand treatment schedule in radiographic forms of axSpA (i.e. AS). Recently, these data were reanalysed, showing that, in particular, patients with a high inflammatory burden (as measured by time-averaged CRP) benefit from the use of continuous NSAIDs, potentially identifying a subgroup of patients with AS with a favourable risk–benefit ratio. Data from the German Spondyloarthritis Inception cohort (GESPIC) confirmed these findings, showing a slower rate of radiographic progression over 2 years in patients taking high-dose NSAIDs, especially when CRP levels and baseline syndesmophytes are high. Data were based on the ASAS-NSAID intake score (which includes dose and duration of intake). An ASAS-NSAID intake score >50 was associated with a significantly lower radiographic progression based on the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) compared with a low NSAID intake (NSAID index <50) (Poddubnyy et al, 2012). However, a recent randomized study comparing continuous use of diclofenac versus on-demand use over 2 years, did not show any favourable spinal structural effect of the continuous regimen, arguing against a

protective structural effect of NSAIDs (or at least diclofenac). Thus it can be considered that the on-demand NSAIDs use, strictly adapted to the symptoms, remains the rule.

Figure 5 Less radiographic progression (mSASSS) after 2 years of continuous versus on-demand use of non-steroidal anti-inflammatory drugs (NSAIDs) (scored with known sequence). mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score. (Adapted from Wanders et al, Arthritis Rheum 2005;52:1756–65*.)

NSAID Therapy in Ankylosing Spondylitis: Radiographic Progression



Thus, the primary aim for the use of NSAIDs, based on their good efficacy for the treatment of signs and symptoms, their ability to facilitate regular physical therapy and their possible influence on radiological progression, is to obtain a patient free of symptoms. Obviously, the side effects of NSAIDs have to be taken into account using such a treatment strategy. The side effects of the non-selective and the Cox-2 selective NSAIDs are now known better than previously. Gastrointestinal side effects, such as peptic ulcers, can be prevented by concomitant use of proton pump inhibitors (such as omeprazole) and the intake of NSAIDs during meals. Selective Cox-2 inhibitors can further reduce the risk of gastrointestinal side effects compared with conventional NSAIDs. An increased risk of cardiovascular event has been reported in studies. A metaanalysis on this issue has shown that COX-2–selective inhibitors were associated with a significantly increased relative risk (1.42 (95% confidence interval [95% CI] 1.13–1.78) ($P = 0.003$) for serious cardiovascular events in comparison with placebo. Ibuprofen and diclofenac showed similar relative risks; however, naproxen was the only NSAID with no increased relative risk that can probably be explained by the capacity of naproxen to inhibit platelet aggregation. Therefore, all NSAIDs, with the probable exception of naproxen, are associated with a slightly increased risk of cardiovascular disease. Patients who still have active disease despite treatment with NSAIDs or who do not tolerate such a treatment should be considered as candidates for other treatments (see below).

A similar efficacy can be expected in the treatment of non-radiographic axial SpA, although there are no studies in this area.

2.3 Analgesics

Simple analgesics have a limited role in the treatment of axSpA. Although there are no formal studies proving their efficacy, analgesics, such as paracetamol and opioids, might be considered for pain control in patients with axSpA in whom NSAIDs are insufficient, contraindicated and/or poorly tolerated (figure 3). Up to one-third of patients take these types of analgesics, often as over-the-counter drugs rather than as prescribed drugs.

2.4 Glucocorticoids

2.4.1 Systemic glucocorticoids

In contrast to their use for the treatment of other inflammatory rheumatic diseases such as RA or systemic lupus erythematosus, systemic glucocorticoids do not play a major part in the treatment of axSpA. This conclusion is based on clinical experience and on one recent clinical trial. While peripheral arthritis often improves if patients are treated with a moderate dose of prednisolone (20–30 mg/day), axial manifestations improve only slightly, if at all, even if a relatively high dose of ≥ 50 mg/day of prednisolone is given.

A few small studies describe good short-term efficacy of intravenous pulse methylprednisolone (1000 mg/day for 3 days) in patients with treatment-refractory AS. However, there is no evidence for a long-term effect of such treatment.

2.4.2 Intra-articular glucocorticoids

Local glucocorticoid injections are recommended for peripheral joint manifestations and are sometimes used for the treatment of enthesitis.

Results for the efficacy of intra-articular injections of glucocorticoids into the sacroiliac joints are contradictory. Usually, 40 mg of triamcinolone is injected. The response rate is probably higher if the intra-articular position of the needle is guided by ultrasound, CT, or—if available—by an open low-field MR scanner. An improvement of symptoms and a reduction of inflammation as detected by MRI have been demonstrated up to 6 months and sometimes even longer. Non-CT- or non-MRI-guided local injections of the sacroiliac joint (most of them probably periarticular) have also been reported to be occasionally effective, although no formal study is available.

2.5 Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)

In general, csDMARDs, which play such a dominant role in the treatment of RA, have no proven efficacy for the axial manifestations of axSpA.

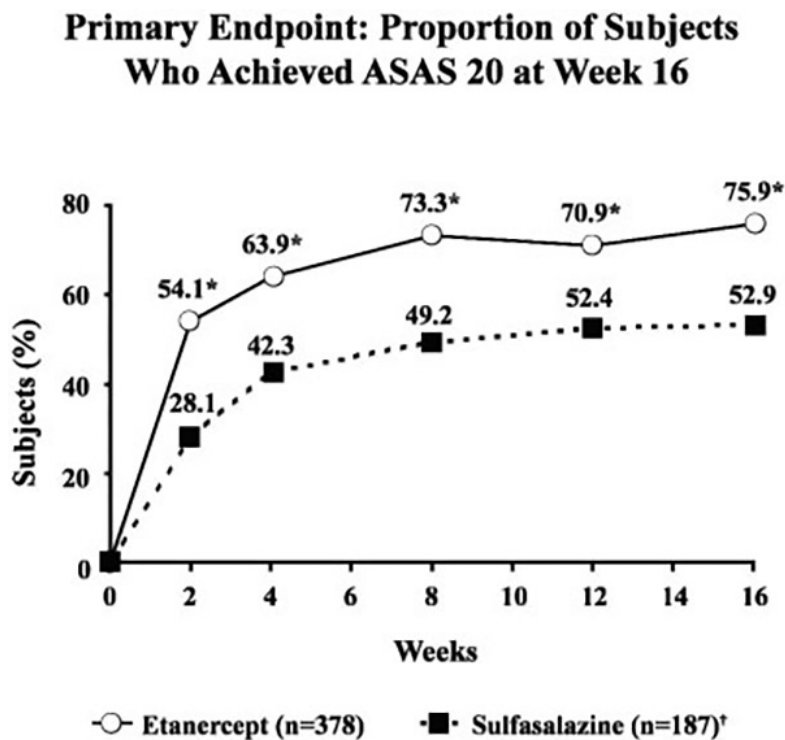
Sulfasalazine (SSZ) is the best investigated csDMARD for the treatment of axSpA. A Cochrane review article analysed the studies in AS (Chen and Liu, 2005). Eleven studies were included in the data analysis. The pooled analysis showed that the difference between intervention groups was significant, favouring sulfasalazine over placebo, but only when the erythrocyte sedimentation rate and morning stiffness were increased, and not for any other variables. Only one trial investigating patients with a relatively short disease duration (<6 years) showed a benefit in primary outcome parameters, including back pain, spinal mobility and a patient's well-being.

However, several trials showed a higher efficacy of SSZ compared with placebo in the presence of peripheral arthritis. Normally, treatment with a dose of 2×1000 mg/day, which can be increased to 3×1000 mg/day, for a duration of up to 4 months is necessary before a treatment failure can be stated.

SSZ is the only csDMARD that has been tested in a placebo-controlled study in patients with inflammatory back pain as part of a diagnosis of axSpA (without, however, evidence of spinal ankylosis); all 230 patients had a disease duration of <5 years. SSZ was effective for axial symptoms in the subgroup of patients without peripheral arthritis (Amor et al, 1984). However, in the total group, treatment with SSZ (2 g/ day) for 24 weeks was no better than placebo for its effect on signs and symptoms as measured by the BASDAI. In a double-blind, head-to-head comparison of SSZ and etanercept, SSZ effectively reduced peripheral arthritis, but also decreased axial symptoms, as illustrated by a decrease of the ASAS 20 (Braun et al, 2011) but with a smaller treatment effect, compared to etanercept (figure 6).

In view of all these results, SSZ is not recommended for the treatment of axial manifestations of axSpA but can be used in cases of peripheral arthritis in patients with axSpA (figure 3).

Figure 6 Double-blind, head-to-head comparison of sulfasalazine and etanercept. ASAS, Assessment in Ankylosing Spondylitis. (Reproduced with permission from Braun et al, *Arthritis Rheum* 2011;63:1543–51*.)

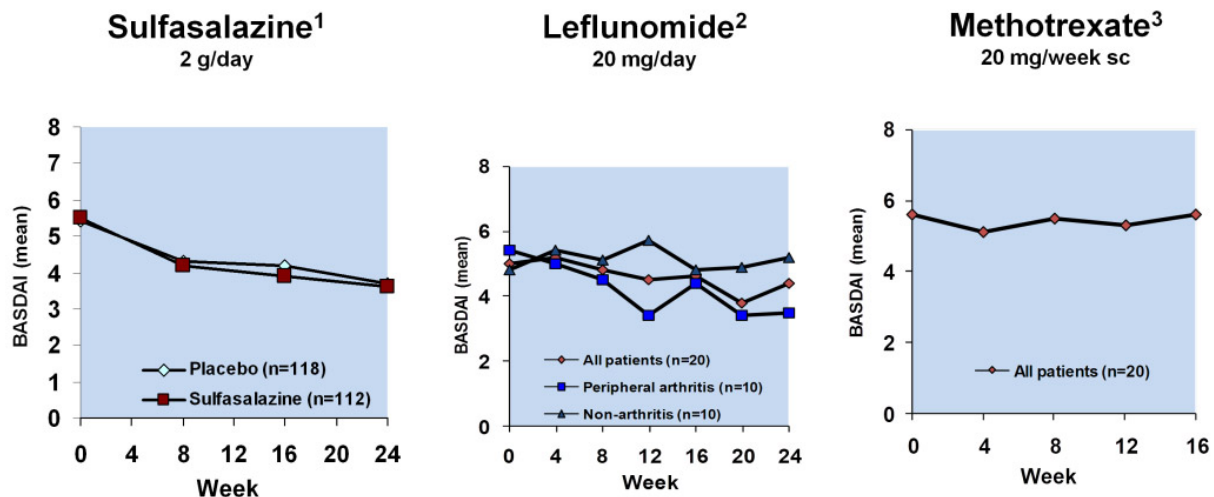


Given the good efficacy of methotrexate for the treatment of RA, the lack of good studies in axSpA is surprising. A recent Cochrane review of the use of methotrexate in AS identified three randomised controlled trials which included 116 participants (Chen et al, 2013). The authors concluded that there is insufficient evidence to support any benefit of methotrexate in the treatment of AS. A 16-week open-label trial of methotrexate, 20 mg subcutaneously a week, showed no effect on axial symptoms and only some improvement in peripheral symptoms. Therefore, methotrexate is not recommended for treatment of the axial manifestations of AS, though in some patients with predominantly peripheral arthritis a trial might be justified.

There is no evidence that any of the other csDMARDs often used for the treatment of RA have a role in the treatment of patients with axSpA (figure 7).

Figure 7 Conventional disease-modifying antirheumatic drugs (CSDMARDs) are largely not effective for the treatment of ankylosing spondylitis. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. (Adapted from 1Braun et al, Ann Rheum Dis 2006b;65:1147–53; 2Haibel et al, Ann Rheum Dis 2005a;64:124–6; 3Haibel et al, Ann Rheum Dis 2007;66:419–21.)

Conventional DMARDs Are Largely Not Effective for the Treatment of Patients with AS



1. Braun J et al. Ann Rheum Dis 2006;65:1147-53
2. Haibel H et al. Ann Rheum Dis 2005;64:124-6.
3. Haibel H et al. Ann Rheum Dis. 2007;66:419-21.



Leflunomide was tested in AS in an open-label study, which showed efficacy for the peripheral arthritis but not for the axial symptoms. This observation was confirmed by a randomised placebo-controlled trial, which showed no beneficial effects of leflunomide on the axial component of AS (van Denderen et al, 2005*).

There is also no evidence that drugs such as methotrexate, leflunomide or ciclosporin are effective in non-radiographic axSpA.

Thalidomide has also been tested for the treatment of patients with AS in open uncontrolled trials with some success, but is regarded as too toxic for widespread use. It was shown to reduce recurrence of symptoms in patients with AS after discontinuation of etanercept (Brebant et al, 1999; Deng et al, 2013).

Bisphosphonates, have been tested in rheumatic diseases because of their possible anti-inflammatory action and inhibiting effect on osteoclasts. In a 6-month randomised controlled trial 60 mg of pamidronate given intravenously once a month was better than a small placebo-like dose of 10 mg pamidronate, leading to a significant improvement of function and pain. Such an effect only became evident after 3 months of

treatment. A positive effect was not found in other open trials treating patients with AS with the same dosage over 3 months. Therefore, further studies are needed before this treatment can be recommended.

2.6 Biologic disease-modifying antirheumatic drugs (bDMARDs)

Until very recently, TNF blockers were the only available bDMARDs for patients with active axSpA, and were a major breakthrough in the treatment of this disease. Very recently other bDMARDs (i.e., IL-17 inhibitors) have been approved for the use in AS, and have proven a good to very good efficacy in these patients.

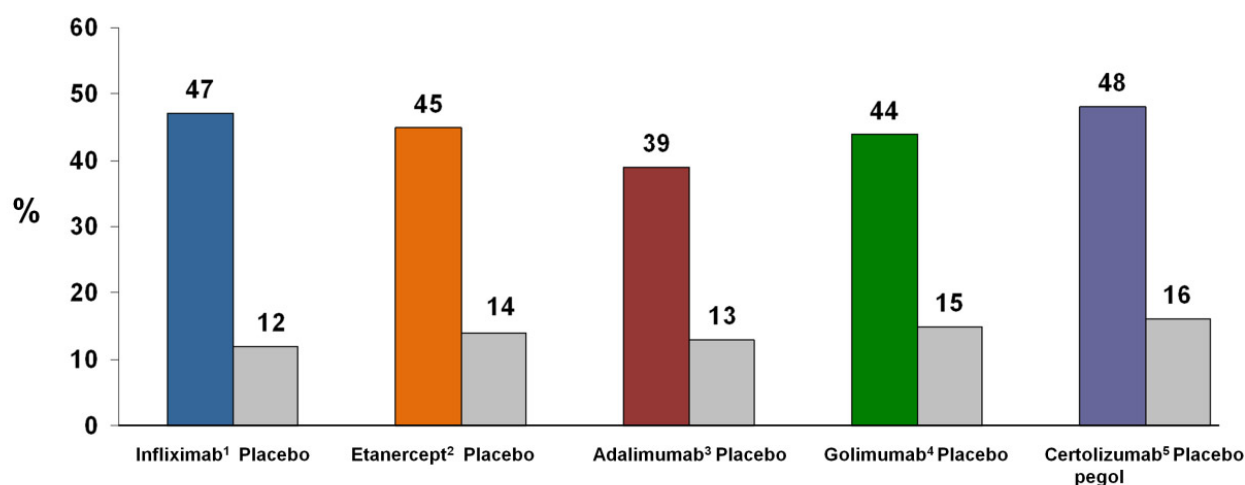
2.6.1 TNF α blocking agents

As a consequence of the limited treatment options for patients with AS discussed above, the demonstration of the good or very good efficacy of TNF blockers for patients with active axSpA can be regarded as a major breakthrough in the treatment of this disease. These drugs improve signs and symptoms rapidly and in a high percentage of patients both in patients with AS (figure 8) and nr-axSpA (figure 9), and also reduce acute inflammation in sacroiliac joints and the spine as shown by MRI. However, it should be emphasized that the beneficial effect in nr-axSpA appeared mainly in patients with objective signs of inflammation (elevated CRP and/or active sacroiliitis on MRI, figure 9)). There are some data that support the claim that these treatments also have structure-modifying effects in patients with axSpA, especially if started relatively early in the disease (< 10 years of symptom duration) and after continuation of 4 years or longer (figure 10, Haroon et al, 2013; Machado, 2013; Baraliakos et al, 2014)..

Figure 8 Assessment in Ankylosing Spondylitis (ASAS) 40 response after 24 weeks of treatment of patients with ankylosing spondylitis (AS) with tumour necrosis factor α (TNF α) blocking agents. These are five different studies with no head-to-head comparison. (Adapted from 1van der Heijde et al, Arthritis Rheum 2005b;52:582–91; 2Davis et al, Ann Rheum Dis 2005;64:1557–62; 3van der Heijde et al, Arthritis Rheum 2006;54:2136–46; 4Inman et al, Arthritis Rheum 2008;58:3402–12; 5Landeweet al, Ann Rheum Dis 2014;73:394–7*.)

ASAS 40 Response after 24 Weeks of Treatment of AS Patients with TNF α Blocking Agents*

*Different studies, no head to head comparison

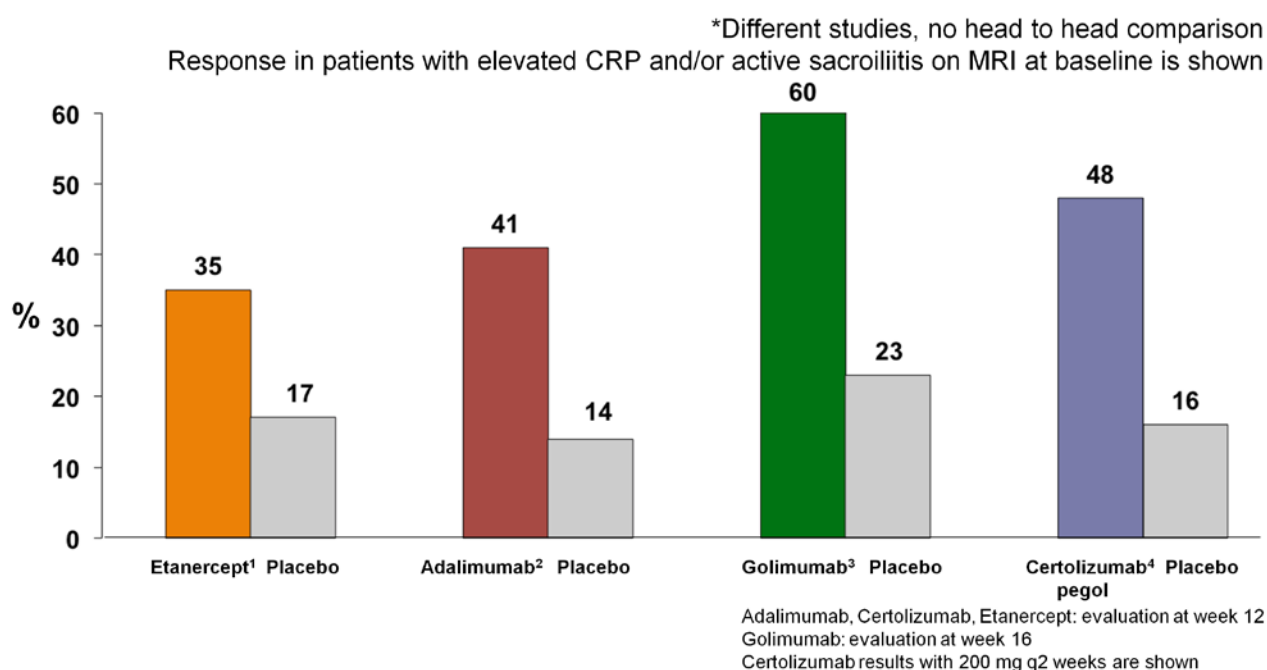


1. van der Heijde D et al. Arthritis Rheum 2005;52:582-91
2. Davis JC et al Ann Rheum Dis 2005;64:1557-62
3. van der Heijde D et al. Arthritis Rheum 2006;54:2136-46
4. Inman RD et al. Arthritis Rheum 2008;58:3402-12
5. Landewé et al. Ann Rheum Dis 2014;73:39-47



Figure 9 Assessment in Ankylosing Spondylitis (ASAS) 40 response after 24 weeks of treatment of patients with non-radiographic axial spondyloarthritis (nr-axSpA) AND elevated CRP and/or active sacroiliitis on MRI at baseline with tumour necrosis factor α (TNF α) blocking agents. These are four different studies with no head-to-head comparison. (Adapted from 1Dougados et al, Arthritis Rheumatol 2014;66:2091-102; 2 Sieper et al, Ann Rheum Dis 2013;72:815-22; 3Sieper et al, Arthritis Rheumatol 2015; 67:2702-12; 4 Landewé et al, Ann Rheum Dis 2014;73:39-47*)

ASAS 40 Response after 12 (16) Weeks of Treatment of Nr-axSpA Patients with TNF α Blocking Agents*

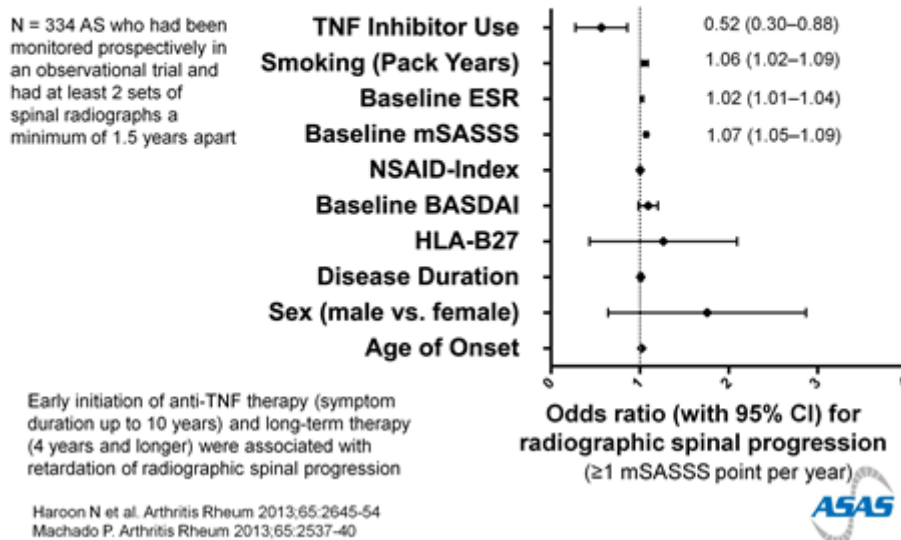


1. Dougados M et al. Arthritis Rheumatol 2014;66:2091-102; Pfizer, data on file
2. Sieper J et al. Ann Rheum Dis 2013;72:815-22
3. Sieper J et al. Arthritis Rheumatol 2015
4. Landewé et al. Ann Rheum Dis 2014;73:39-47



Figure 10 Early Initiation of Anti-TNF α therapy does delay radiographic progression in AS on the long term. AS, ankylosing spondylitis; ASAS, Assessment in Ankylosing Spondylitis; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score;. (Adapted from 1 Haroon et al I, *Arthritis Rheum* 2013;65:2645-54; 2 Machado P et al, *Arthritis Rheum* 2013;65:2537-40.)

Anti-TNF Therapy Might Slow Radiographic Progression in AS: Data from an Observational Study



Five biological agents targeting TNF are now available, which have been shown to be effective for the treatment of AS and nr-axSpA. These are the chimeric (one-quarter murine and three-quarters human) monoclonal IgG1 antibody, infliximab; the recombinant 75 kDa TNF receptor IgG1 fusion protein, etanercept, two fully human monoclonal antibodies, adalimumab and golimumab and the Fab' fragment of a human monoclonal antibody, certolizumab. All of them have all been approved for AS both in the European Community and the USA. They (except infliximab) have also been approved more recently for patients with nr-axSpA, but only when objective signs of inflammation (elevated CRP and/or MRI sacroiliitis) are present.

Infliximab is given as an intravenous infusion over 2 h in a dose of 5 mg/kg every 6 weeks, etanercept is given subcutaneously at a dose of 50 mg once a week, adalimumab at a dose of 40 mg subcutaneously every other week, golimumab at a monthly dose of 50 mg subcutaneously, and certolizumab at a loading dose of 400mg subcutaneously every other week for one month and then 200mg every other week. (Braun et al, 2012).

In nearly all AS studies infliximab was given intravenously at a dose of 5 mg/kg body weight at weeks 0, 2, 6 and thereafter every 6–8 weeks. In several open-label studies an often dramatic improvement in signs and symptoms was seen beginning on the same day or in the days after the first infusion, which could subsequently be confirmed in placebo-controlled randomised controlled trials (figure 8). In all these studies infliximab was given as monotherapy to patients whose disease was active despite previous treatment with

NSAIDs. Normally, continuation of NSAID treatment was permitted. The crucial end point in all these studies was a 50% improvement in disease activity (BASDAI) or in a composite clinical score (ASAS percentage improvement). This end point was reached uniformly by about 50% of patients in the placebo-controlled trials with about $\leq 10\%$ of the placebo group reaching this level of response, and in up to 60–70% in the open-label studies. Interestingly, between 20% and 25% of these patients with active AS even fulfilled the criteria for partial remission. Also the number of enthesitic sites, the number of affected peripheral joints, function and spinal mobility improved, sometimes significantly, during the placebo-controlled phase. Long-term follow-up results from these studies have been published for up to 8 years, showing a good long-term efficacy, if treatment is continued. After 3 years about 70% of the first patients are still being treated with this drug.

However, when infliximab was stopped after 3 years of treatment, patients relapsed between weeks 7 and 45, and by week 52 all except one patient out of 41 (97.6%) had experienced a flare. When treatment with infliximab was restarted all patients except one improved, similarly to the initial response, and the drug was well tolerated. Thus, for this group of patients with active longstanding disease (mean disease duration >10 years) infliximab has to be given long term. It is not known whether remission or significant improvement can be achieved even after discontinuation of infliximab treatment if patients are treated early in the course of their disease (see also below).

Infliximab has been tested in all placebo-controlled trials in a dose of 5 mg/kg body weight given at weeks 0, 2, 6 and afterwards every 6 or 8 weeks. No study comparing the two intervals has been performed. For some patients the 8-week interval will be sufficient but others need a shorter interval. In general, the interval can be determined according to the patient's symptoms and some patients tolerate even longer intervals. Some data indicate that 3 mg/kg body weight might also be effective in some patients with axSpA.

Over recent years, MRI has proved useful for the detection of acute inflammation in the sacroiliac joints and spine. Serial MRI studies performed in patients in 18 randomized controlled trials showed a significant regression after 3–6 months of treatment of active inflammatory lesions in the spine but not in the placebo-treated group (figures 12).

Several double-blind placebo-controlled trials with etanercept in AS showed a similar efficacy profile to that shown with infliximab, for all the variables discussed above (figure 9): short-term and long-term efficacy (figure 10) and reduction of acute inflammation as shown by MRI (figure 13). In the first studies, etanercept was given in a dose of 25 mg subcutaneously twice a week, but more recent studies showed that 50 mg subcutaneously given once a week has similar efficacy.

Figure 11 ASSERT: improvement from baseline in MRI activity score (STIR) at week 24. (Reproduced with permission from Braun et al, Arthritis Rheum 2006a;54:1646–52*.)

Improvement from Baseline in MRI Activity Score (STIR) at Week 24

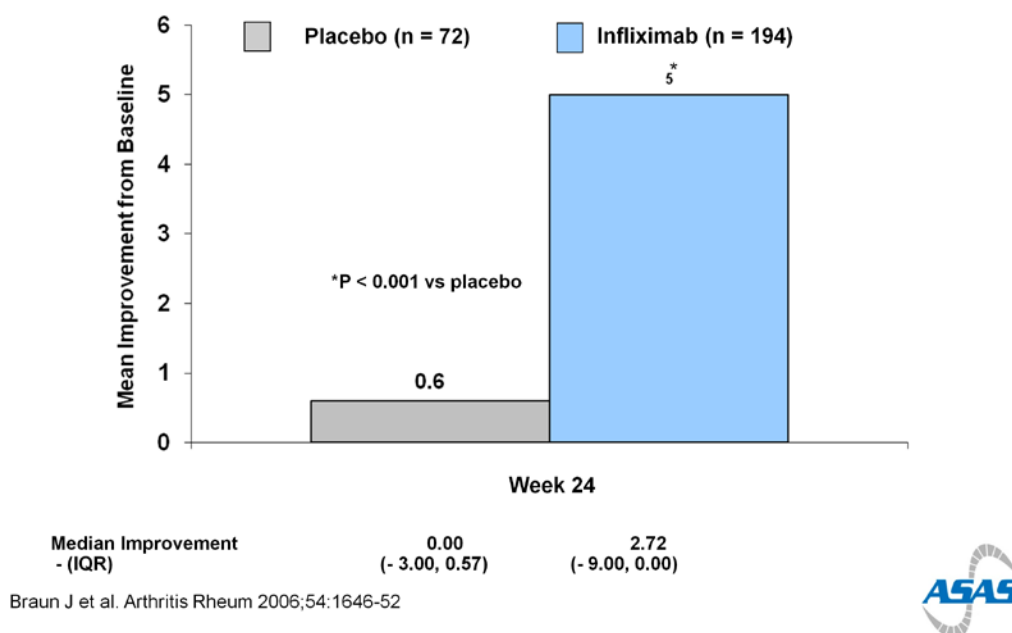
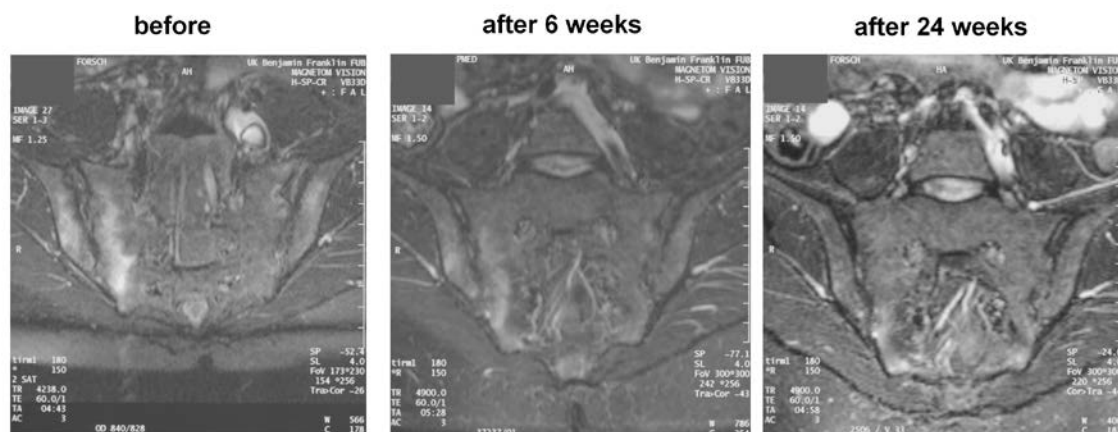


Figure 12 MRI of sacroiliac joints before and after etanercept treatment. (Reproduced from Rudwaleit et al, Ann Rheum Dis 2005;64:1305–10.)

MRI of the Sacroiliac Joints Before and After Etanercept Treatment (STIR)



Rudwaleit M et al. Ann Rheum Dis 2005;64:1305-1310 (with permission)



As with infliximab, a relapse occurred at a mean of 6.2 ± 3 weeks, and at 35 weeks all 30 patients had relapsed, when treatment with etanercept was stopped. Again, a comparable clinical response was seen when the drug was restarted.

Adalimumab is another TNF-blocking agent, which has been shown to be effective for the treatment of AS in 2 large randomized placebo-controlled studies (figures 9 and 10). In contrast to other TNF-blocker studies, inclusion of patients with total spinal ankylosis, according to the treating doctor, was permitted. From this small group, three of the six (50%) adalimumab-treated patients achieved an ASAS 20 response at week 12, compared with 0% (none of five) of the placebo-treated patients, indicating that even in longstanding disease there can still be ongoing inflammation and that a proportion of these patients show a good clinical response if treated with TNF blockers.

Golimumab and Certolizumab are the latest TNF-blocking agents to be approved for treatment of AS. It has shown similar efficacy to the other three TNF blockers (Inman et al, 2008; Landewé et al, 2014).

Table 2 Dose and treatment interval for the four TNF-blocking agents used in Spondyloarthritis

Drug	Dosage AS	Dosage PsA	Dosage IBD	Application
Infliximab	5 mg/kg	5 mg/kg	5 mg/kg	IV at weeks 0, 2, 6, q6/q8*
Etanercept	25 mg	25 mg	Not used	SC twice weekly
	50 mg	50 mg		SC once weekly
Adalimumab	40 mg	40 mg	40 mg	SC every 2 weeks†
Golimumab	50 mg	50 mg		SC once monthly
Certolizumab pegol	400mg as load dose and 200mg thereafter	400mg as load dose and 200mg thereafter	400mg	SC every 2 weeks§

*Psoriatic arthritis and IBD; dose escalation to 7.5 mg/kg is possible. †For IBD and plaque psoriasis: initially higher dose. § For IBD 400mg is every 4 weeks

AS, ankylosing spondylitis; IBD, inflammatory bowel disease; IV, intravenously; PsA, psoriatic arthritis; SC, subcutaneously; TNF, tumour necrosis factor.

As in AS, TNF blockers efficacy in nr-axSpA has been confirmed in several randomized clinical trials (figure 9). The first of them concerned adalimumab (Sieper et al, 2013): a trial in which 185 patients fulfilling the ASAS criteria for axSpa but not the mNY criteria for AS were treated either with placebo or 40 mg adalimumab given every second week subcutaneously over 12 weeks. Significantly more patients in the adalimumab group achieved ASAS40 at week 12 compared with patients in the placebo group (36% vs 15%, $p < 0.001$). Shorter disease duration, younger age, elevated baseline C-reactive protein or higher SPARCC MRI sacroiliac joint scores were associated with better week 12 responses to adalimumab.

For inclusion in the infliximab trial, patients with axial SpA with a symptom duration of ≤ 3 years had to be HLA-B27 positive and had to have a positive MRI showing active inflammation in the sacroiliac joint. In this trial with mainly nr-axSpA patients, but also some AS patients, ASAS 40 and ASAS partial remission was reached after 16 weeks of infliximab treatment in 61% and 55% of patients, respectively, compared with a placebo response of 19% and 10%, respectively. Active inflammation of the sacroiliac joints and the spine as shown by MRI improved also significantly more in the infliximab group than in the placebo group.

In the etanercept trial, 215 patients fulfilling the ASAS criteria for axSpA but not the modified New York radiographic criteria for ankylosing spondylitis (as assessed by a radiologist at the central trial site) and with a symptom duration of >3 months but <5 years and an active (score of ≥ 4 on the BASDAI) and refractory disease (unsuccessfully treated with ≥ 2 NSAIDs) were included to receive either etanercept 50 mg/week or placebo and continued background NSAID treatment for 12 weeks. Among them, 174 (81%) had MRI-confirmed sacroiliitis. At 12 weeks, the proportion of patients with improvement according to the ASAS40 was significantly higher in the etanercept group than in the placebo group (32% vs. 16%) and the reduction in MRI-based scores for sacroiliac joint inflammation and spinal inflammation was greater in the etanercept group. Furthermore, post hoc analyses suggested a possible association between higher baseline C-reactive protein levels or MRI sacroiliac joint inflammation scores and higher rates of ASAS40 response to etanercept.

The certolizumab trial included 325 axSpA patients (including both AS and nr-axSpA) who were randomized 1:1:1 to placebo, CZP 200 mg every 2 weeks or CZP 400 mg every 4 weeks (Q4W). Similar improvements were reported with CZP versus placebo in both AS and nr-axSpA subpopulations, with an ASAS 40 response of 56% (Figure 9).

Finally, in the golimumab trial, 198 patients with nr-axSpA according to the ASAS criteria and <5 years of disease were randomized to receive either golimumab or placebo. An ASAS40 response was also achieved by significantly more patients in the golimumab group compared with the placebo group (57% versus 23%).

Taken together, these data indicate that patients with radiographic-axSpA who do not respond to NSAIDs and physical therapy, and with an elevated CRP and/or inflammatory signs of the sacroiliac joints at MRI, respond well to TNF blockers.

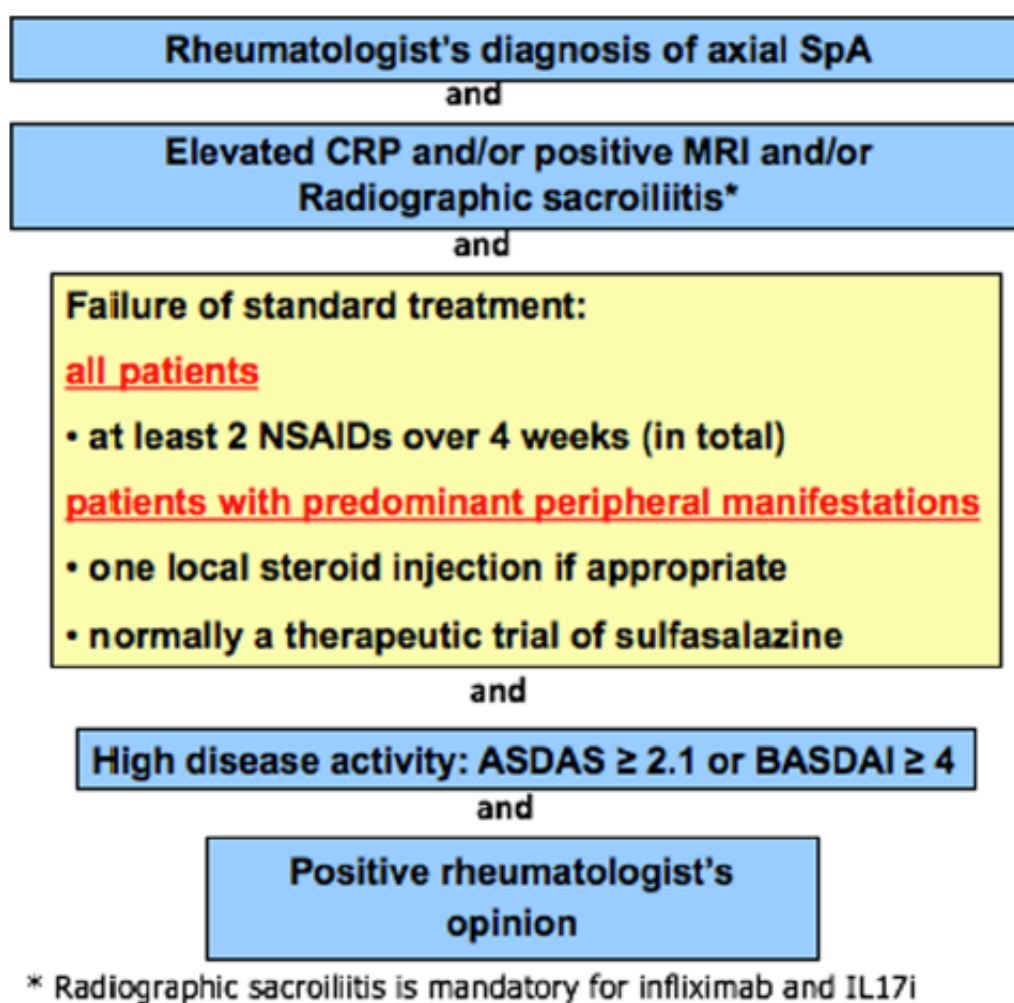
2.6.1.b Anti-TNF therapy in the treatment of juvenile SpA

The first symptoms of AS occur before the age of 20 years in 15–20% of cases, and juvenile and adult SpA should be seen as one disease with a continuum. While the juvenile forms normally present first with a predominance of peripheral manifestations (enthesitis and peripheral arthritis), later on many of them develop typical AS. In two small open-label studies both infliximab and etanercept showed a good efficacy in patients with juvenile SpA or enthesitis-related arthritis (Homeff and Burgos-Vargas, 2002).

2.6.1.c Which patients with axSpA should be treated with TNF blockers?

Recommendations for which patients with axSpA should be treated with TNF blockers are desirable, especially in view of possible side effects and the relatively high costs of these drugs. Thus, patients with the best risk/benefit ratio should be treated preferentially. An international ASAS-EULAR consensus statement for the use of anti-TNF agents in patients with axSpA was recently updated in 2016 (figure 13)..

Figure 13 ASAS-EULAR recommendations for the treatment of patients with axSpA with bDMARDs. CRP, C-reactive protein; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; IL17i, interleukin-17 inhibitor. (Reproduced from van der Heijde et al, *Ann Rheum Dis* 2011;70:905–8.)



These recommendations were developed on the basis of a review of published reports and consensus meetings of international experts from the ASAS working group. According to these recommendations, for the initiation of bDMARD therapy the criteria shown in figure 13 should be fulfilled.

In the initial recommendations a diagnosis of definitive AS, normally fulfilling the modified New York criteria, was required. However, it should be kept in mind that these criteria were developed as classification criteria

and that patients might not show radiological sacroiliitis but might show, acute sacroiliitis reflected by bone marrow oedema visible on MRI. More recently, ASAS has used the new classification criteria for axial SpA in an update of the ASAS recommendations for the treatment of axSpA with TNF blockers. The presence of active disease for at least 4 weeks as defined by both a sustained BASDAI of at least 4 (on a scale between 0 and 10) or an ASDAS of at least 2.1 and an expert opinion based on clinical features, acute phase reactants and sacroiliitis on imaging modalities is required.

TNF blockers (except infliximab) are now registered in some European countries for the treatment of nr-axSpA but only in cases where CRP is raised and/or sacroiliitis is visible on MRI. The expert will normally be a rheumatologist who will judge, in addition to the patient's symptoms, the objective parameters of activity/inflammation. An additional criterion is the presence of refractory disease defined by the failure of at least two NSAIDs during a 3-month period (this was changed to a 1-month period in the updated version), failure of intra-articular steroids if indicated and failure of SSZ (or methotrexate, according to the updated versions) in patients with peripheral arthritis. These recommendations are also in accordance with the ASAS/EULAR recommendations for the management of AS, which do not suggest a role for CSDMARD treatment for predominantly axial manifestations of AS.

There is also growing evidence that patients with axSpA, particularly those early in the course of their disease and with a raised CRP, respond better to treatment with TNF blockers, probably indicating that symptoms at the start are mostly caused by inflammation whereas later on pain and other symptoms might be present for different reasons.

2.6.1.d Administration of TNF-blocking agents

- Screening before starting anti-TNF therapy

The usual precautions and contraindications for biological treatment should be followed. In short: screening for latent tuberculosis infection should be performed according to local guidelines (a tuberculin skin test (Mantoux test) and/or an interferon-gamma release assay) and chest X-ray examination. In high-risk groups or in those vaccinated against tuberculosis (Bacille Calmette–Guérin (BCG) vaccination), the interferon-gamma release assay should be considered. When a positive reaction occurs, appropriate prophylaxis should be given, such as treatment with isoniazid, before the start of biological agents, according to local guidelines.

Screening for hepatitis B should be considered in populations at risk.

Patients who have congestive cardiac failure (New York Heart Association class III–IV) and patients who were recently diagnosed with cancer should not start anti-TNF therapy.

Furthermore, it is important to inform patients that they cannot receive immunisation with attenuated, live-virus preparation (such as yellow fever) during treatment with anti-TNF agents.

In patients who want to become pregnant treatment with anti-TNF can be continued until conception. Continuation throughout the pregnancy will be discussed depending on the disease activity/severity.

2.6.1.e Adverse events of anti-TNF therapy for SpA

Adverse events in patients with axSpA and other SpA treated with TNF blockers do not differ from those seen in other diseases, such as RA and Crohn's disease (CD). However, patients with axSpA are normally younger and have been less frequently treated with glucocorticoids or immunosuppressive drugs than patients with the other two diseases. Thus, the number and severity of side effects can be expected to be at least no higher than with other chronic inflammatory diseases, and might even be lower; comparative data on this are not available. Infections including opportunistic infections may occur in a small percentage of patients. The occurrence of demyelination and deterioration of congestive heart failure has been reported occasionally.

An approximately twofold risk of development of non-melanoma skin cancer has been reported.

In patients with axSpA, the clinical inefficacy of infliximab or adalimumab correlates with the presence of low serum trough infliximab or adalimumab levels and the presence of antibodies against infliximab or adalimumab (de Vries et al, 2007; de Vries et al, 2009). Moreover, development of anti-infliximab antibodies can precede an infusion reaction. The mechanism of the decrease in efficacy can be explained by lower serum trough infliximab or adalimumab levels, caused by neutralising antibodies against the idiotypic of infliximab and adalimumab, and enhanced clearance due to immune complex formation of antibodies against biological agents. Another TNF blocking agent, etanercept, does not seem to have high immunogenic properties, although response rates are similar among the four TNF blockers (de Vries et al, 2009).

Reports of the treatment of RA and of CD suggest that combining infliximab with another immunosuppressive agent such as azathioprine, methotrexate or glucocorticoids, might reduce side effects, such as allergic reactions. These immunosuppressive agents might even prevent intolerance to infliximab treatment, most probably owing to the inhibition of anti-infliximab antibodies. A recent study indicated that a combination of infliximab with methotrexate in AS was not more effective and did not reduce side effects compared with infliximab alone. It has also to be kept in mind that these drugs are added to infliximab to avoid side effects (production of antibodies) but do not have efficacy on disease activity itself in AS, which differs from their use in RA and CD.

Contradictory results have been reported with regard to the influence of csDMARDs in the anti-TNF alpha drug retention rate: Lie et al reported a decreased risk of 12 to 29% in the drug discontinuation over time in

patients with comedication with csDMARDs, while Sepriano et al did not find any significant effect on such drug survival.

Therefore, for now, there is not sufficient evidence to combine TNF-blocking agents with immunosuppressive drugs in SpA.

2.6.2 IL-17 blocking agents

The recent published data on IL-17 inhibitors has been a major breakthrough in the treatment of this disease. Secukinumab, a monoclonal antibody directed against IL17A, has proven to improve signs and symptoms rapidly and in a high percentage of patients in patients with AS (nr-axSpA studies are ongoing), both in biologic-naïve patients and in patients refractory to TNF alpha blockers. Identically to TNF alpha blockers, there are no data yet to support the claim that this treatment also have structure-modifying effects in patients with AS (Baeten et al, 2015; Sieper et al, 2016). Secukinumab has been approved in Europe for AS, at the dosage of 150 mg subcutaneously administered, at a frequency of once a month after five weekly injections.

2.6.3 Other biological agents.

The cytokine interleukin 1 has also been a target in the development of new drugs. So far the interleukin 1 receptor antagonist, anakinra, has been shown to be effective in the treatment of patients with RA. Only two open studies have examined the efficacy of anakinra in AS, with conflicting results (Haibel et al, 2005b). At present, anakinra does not seem to have a role in the treatment of AS.

Abatacept and rituximab were evaluated in small open-label studies. No relevant clinical responses were seen, particularly as these trials were not placebo-controlled. Moreover, the results were certainly disappointing for the subgroup of patients for whom previous TNF blockade had failed.

Treatments targeting the interleukin 6 pathway (tocilizumab) were tested in formal randomised placebo-controlled studies, but failed to show a significant improvement over placebo (Sieper et al, 2014).

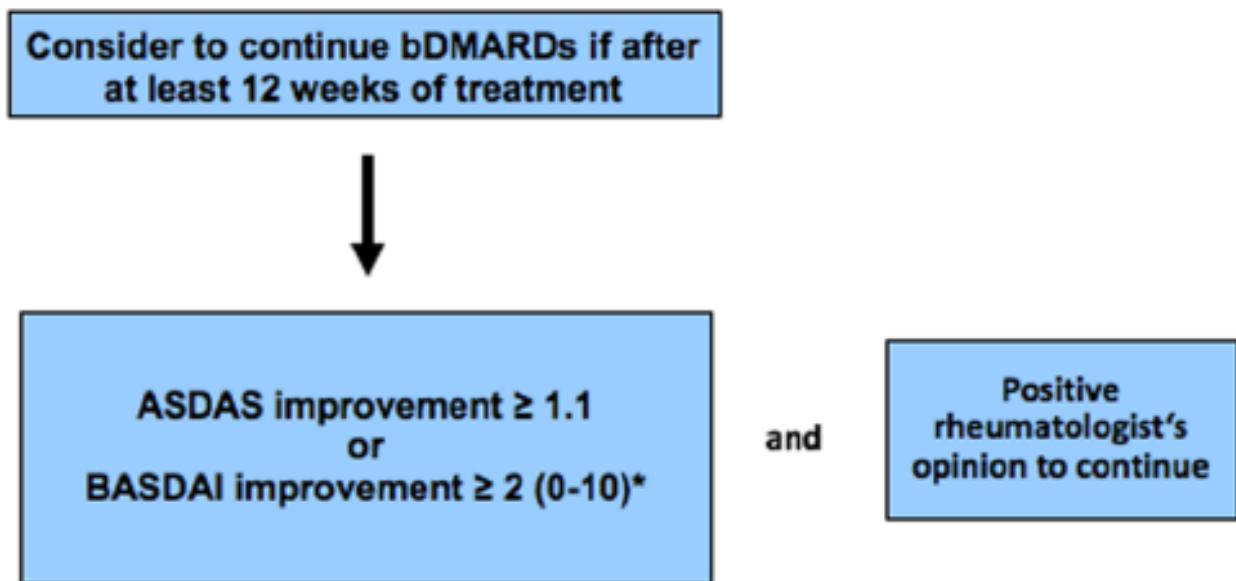
2.6.4 Monitoring bDMARDs in axSpA

For the monitoring of bDMARDs in axSpA, both the BASDAI and the ASAS core set (in the domains of patient global assessment, pain, function and spinal mobility) for clinical practice should be used regularly. ASDAS may have better discriminative characteristics than patient-reported outcomes.

Discontinuation of anti-TNF therapy should be strongly considered in non-responders after 12 weeks' treatment (figure 15). Response is defined as improvement of (a) at least 50% or 2 units (on a 0–10 scale) of the BASDAI, (b) in addition to an expert opinion that treatment should be continued, again relying not only on the patients' subjective symptoms. The same attitude may be considered with the IL17 blocker.

A decrease of ASDAS of ≥ 1.1 (figure 1) is defined as clinically important improvement and ≥ 2.0 as a major improvement. Similar recommendations or guidelines have been published by national societies such as the Canadian Rheumatology Association and the British Society of Rheumatology or in the USA (www.spondylitis.org/physician_resources/guidelines.aspx) following the reasoning of the ASAS recommendations, only with slight modifications.

Figure 14 ASAS-EULAR recommendations for the continuation of bDMARDs. ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease modifying anti-rheumatic drug. (Adapted from van der Heijde et al, *Ann Rheum Dis* 2017;76:978-991.)



* Either ASDAS or BASDAI can be used, but the same measure per patient

2.7 Other non-biological agents.

A small molecule, or “targeted DMARD”, is under development in AS. This molecule, Apremilast, works as an inhibitor of the phosphodiesterase 4, and is orally administered. Only results of a proof of concept study are yet available.

Recently, preliminary results obtained with tofacitinib, an orally administered JAK inhibitor, have been reported.

3 Management of extraspinal manifestations in axSpA

The extraspinal or extra-articular manifestations (EAMs) of axSpA can be divided into so-called SpA concept-related EAMs and non-concept-related diseases (figure 16).

Figure 16 Extra-articular manifestations in spondyloarthritis. SpA, spondyloarthritis; TNF, tumour necrosis factor.

Extra-Articular Manifestations in Spondyloarthritis

Concept related

Eye-skin-gut-urogenital

- Frequent (20-60%)
- Clinical inflammation
 - At any moment of the disease evolution
- Sometimes related to axial or joint inflammation
- Effect of classical SpA drugs

=> Effect of TNF-blockers proven

Not concept related

Lung-kidney-heart-nerve

- Very rare (1%)
- Mostly subclinical
 - Long standing disease
- Not related to locomotor disease
- No effect of classical SpA drugs

=> Effect of TNF-blockers unknown



The concept-related EAMs, such as uveitis, psoriasis and IBD, are usually also a manifestation of chronic immune-mediated inflammation occurring at another (related) body system (eye, skin, gut). Their management is closely related to the treatment of the rheumatological component of the disease; this will be discussed in the next part of this chapter, as well as in the online 'in-depth-discussions'. The non-related manifestations, such as aortic insufficiency, pulmonary fibrosis and renal amyloidosis, may occur in a small percentage of patients with axSpA, mostly in longstanding disease. Conventional SpA treatments do not seem to affect these rare conditions and it remains to be seen whether these complications can be avoided by earlier treatment with bDMARDs. It would, however, seem logical that efficient abrogation of longstanding inflammation might prevent consequences such as amyloidosis. When these manifestations are present, they should be treated similarly to those caused by other underlying diseases.

4 Management of osteoporosis in axSpA

Osteoporosis is a common manifestation in axSpA, not only as a consequence of limited mobility, but also because of local and general inflammation. Vertebral fractures often occur in this relatively young and male population. The role of treatment such as bisphosphonates is not yet elucidated. No studies have been performed in patients with axSpA to determine the efficacy of bisphosphonates on bone mineral density, or the influence of these drugs on progressive ankylosis of the spine and syndesmophyte formation.

More recently, it has been shown that treatment of active axSpA with TNF blockers induces a rapid improvement of bone mineral density after just 6 months of treatment with infliximab or etanercept, but not with placebo.

5 Cardiovascular comorbidity in axSpA

Cardiovascular comorbidity in axSpA causes increased mortality, as described in detail in chapter 17. The risk of atherosclerosis is doubled in this disease, which results in a higher risk of myocardial infarction. Additionally, conduction disturbances of the atrioventricular node related to HLA-B27 are increased in AS, as well as the risk of aortic insufficiency due to cardiac inflammation in longstanding disease. Therefore, the EULAR recommendations for cardiovascular risk management also apply to axSpA (chapter 17).

6 Surgical intervention in axSpA

Hip arthritis occurs in up to one-third of patients with AS most often early in the disease (first 10 years) and is more common if the disease starts early in life. A total hip replacement is necessary in about 5% of all patients with AS and is associated with good long-term results. Although patients with axSpA are normally younger than others undergoing hip replacement, the revision rate is no higher. There is no major difference in durability or complications between cemented and non-cemented hip prostheses, but non-cemented total hip replacement is preferable in younger patients because revision is technically easier.

The ankylosis of the spine results in obvious limitation of movement and elasticity. The reduced flexibility in combination with osteoporosis of the spine, as a consequence of lack of movement and of local and systemic inflammation, renders the spine susceptible to a variety of complications, including fracture and dislocation, sometimes even after a minor trauma (Gelman and Umber, 1978).

Spinal instability can also occur as a consequence of a severe Anderson lesion (disco vertebral erosions and destruction). Pain and/or neurological involvement are indications for fusion operations. Severe complications, such as neurological problems, occur in about 2–4% of patients (Fox et al, 1993). Atlantoaxial and atlanto-occipital subluxation and spinal stenosis can be other reasons for surgical interventions. In cases of severe and invalidating thoracolumbar kyphosis a correction can be performed by lumbar osteotomy in specialised centres (Van Royen et al, 1999).

7 Axial manifestations in patients with psoriasis or IBD

If axSpA occurs in association with psoriasis or IBD, the treatment algorithm is similar to that for patients with primary axSpA. NSAIDs should be used with caution in patients with IBD (see section 14.2).

8 Predominant peripheral SpA

Peripheral arthritis and enthesitis occur in about 30–40% of patients with axSpA (usually in a transient and/or relapsing form), but are in general characteristic for the whole group of SpA, where they occur in a typical pattern involving predominantly the lower limbs asymmetrically. Part of the rationale for dividing SpA into predominantly axial or peripheral SpA lies in the differences of the treatment options for these two major disease manifestations (see also ASAS/EULAR Recommendations for the treatment of axSpA). Contrary to axial disease (where csDMARDs are not efficacious and NSAIDs are the only conventional medical treatments), drugs like sulfasalazine, methotrexate and leflunomide seem to play a role in the treatment of the peripheral manifestations of SpA. Apart from these oral drugs, local steroid injections are successfully used in daily practice to treat peripheral arthritis, dactylitis and some forms of enthesitis, especially in cases of localised, monoarticular or pauciarticular joint involvement. When these conventional treatment options fail, bDMARDs may be indicated. In the following discussion each drug class will be presented separately for the SpA subgroups with predominant peripheral involvement: we will discuss psoriatic disease, arthritis associated with IBD and reactive arthritis.

8.1 Psoriatic arthritis

Psoriatic arthritis (PsA) is associated with various patterns of rheumatological manifestations, which is reflected by the currently most used CASPAR classification criteria (figure 17). In the initial description by Moll and Wright, five different rheumatological patterns were described: polyarticular (RA-like) and oligoarticular (SpA-like) peripheral joint involvement, distal interphalangeal joint involvement, axial disease and arthritis mutilans. Lately, the relevance of this sub classification has been challenged as patients may change from one pattern to the other spontaneously or as a consequence of treatment. Instead of classifying patients within a specific subgroup, different domains are now recognised within the full spectrum of psoriatic disease, and treatment is tailored to the importance of specific domains, such as peripheral arthritis, enthesitis, dactylitis, spondylitis, skin and nail disease. Ideally, treatment should always be aimed at improving all manifestations of the disease. In daily practice this can be achieved by treating patients with multiple drugs with different actions that can be safely combined together, or by the use of a single agent, that can deal with both skin and joint manifestations.

Figure 15 Classification criteria for psoriatic arthritis (CASPAR). PsA, psoriatic arthritis. (Adapted from Taylor et al, Arthritis Rheum 2006;54:2665–73.)

Classification of Psoriatic-Arthritis: CASPAR Criteria

To meet the CASPAR criteria for PsA, a patient must have inflammatory articular disease (joint, spine, or enthesal) and score ≥ 3 points based on these categories.	
	POINTS
1. Evidence of psoriasis Current psoriasis Personal history of psoriasis Family history of psoriasis	2 or 1 or 1
2. Psoriatic nail dystrophy Pitting, onycholysis, hyperkeratosis	1
3. Negative test result for rheumatoid factor	1
4. Dactylitis Current swelling of an entire digit History of dactylitis	1 or 1
5. Radiologic evidence of juxta-articular new bone formation Ill-defined ossification near joint margins on plain x-rays of hand/foot	1

CASPAR, Classification criteria for Psoriatic Arthritis
Taylor W et al. Arthritis Rheum 2006;54:2665-2673



About 8–40% of patients with psoriasis will develop arthritis; the prevalence of PsA is estimated at 0.3% of the population, the incidence at 6–8/100 000. In about 63% of cases, psoriasis is already present before the arthritis occurs; in 19%, both manifestations occur simultaneously, but in up to 18% of patients, a typical arthritis develops before any sign of classic psoriasis. In these last cases, diagnosis may be difficult and physicians should pay particular attention to discrete skin and/or nail lesions. For peripheral joint manifestations, the pattern of involvement is often asymmetrical; this is of course evident in cases of SpA-like, oligoarticular, lower limb involvement, but even in polyarticular disease (which has recently been considered to be the most prevalent manifestation), the symmetry is usually not as pronounced as in typical RA. Distal interphalangeal joint joints of the hands and feet may be involved in all classic subtypes. Dactylitis and enthesitis, manifestations typical for the whole group of SpA, are also often found in patients with PsA.

No good correlation is found between the severity of skin involvement and arthritis.

Whereas there are only limited—good quality—data on the treatment of PsA with csDMARDs, the previous decade has witnessed a wealth of clinical trial data with multiple biological agents, mainly belonging to the

class of TNF α blockers. Treatment guidelines for PsA have been published by the international group GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) (figure 18) and by EULAR (figure 19).

Figure 16 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2015 Treatment Recommendations for Psoriatic Arthritis.. CsA, ciclosporin A; DMARD, disease-modifying antirheumatic drug; IA, intra-articular; LEF, leflunomide; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PUVA, psoralen and ultraviolet A treatment; SSZ, sulfasalazine; TNF, tumour necrosis factor; UVB, ultraviolet B. (Reproduced from Coates and Ritchlin, *Arthritis Rheumatol.* 2016;68:1060-71).

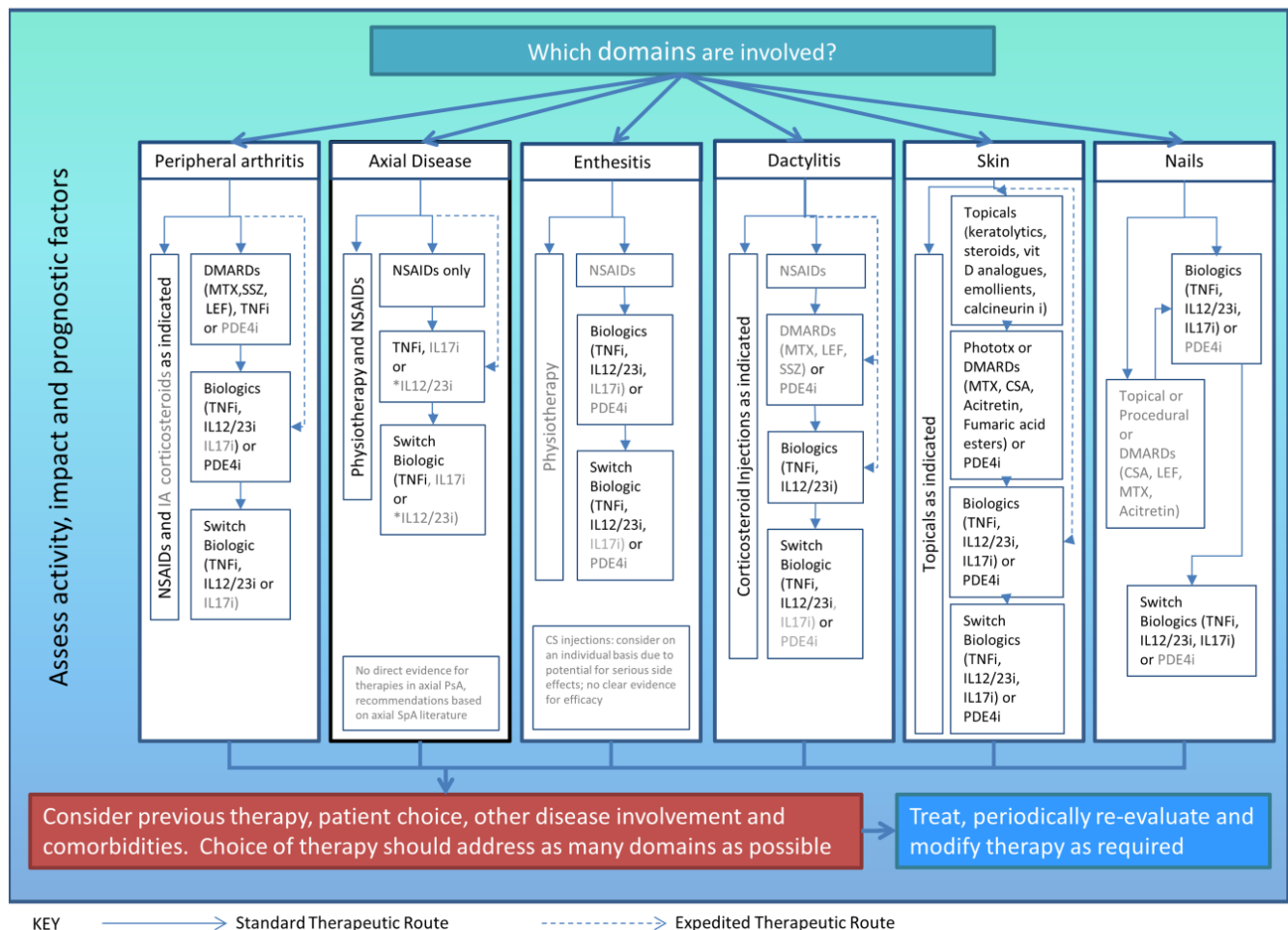
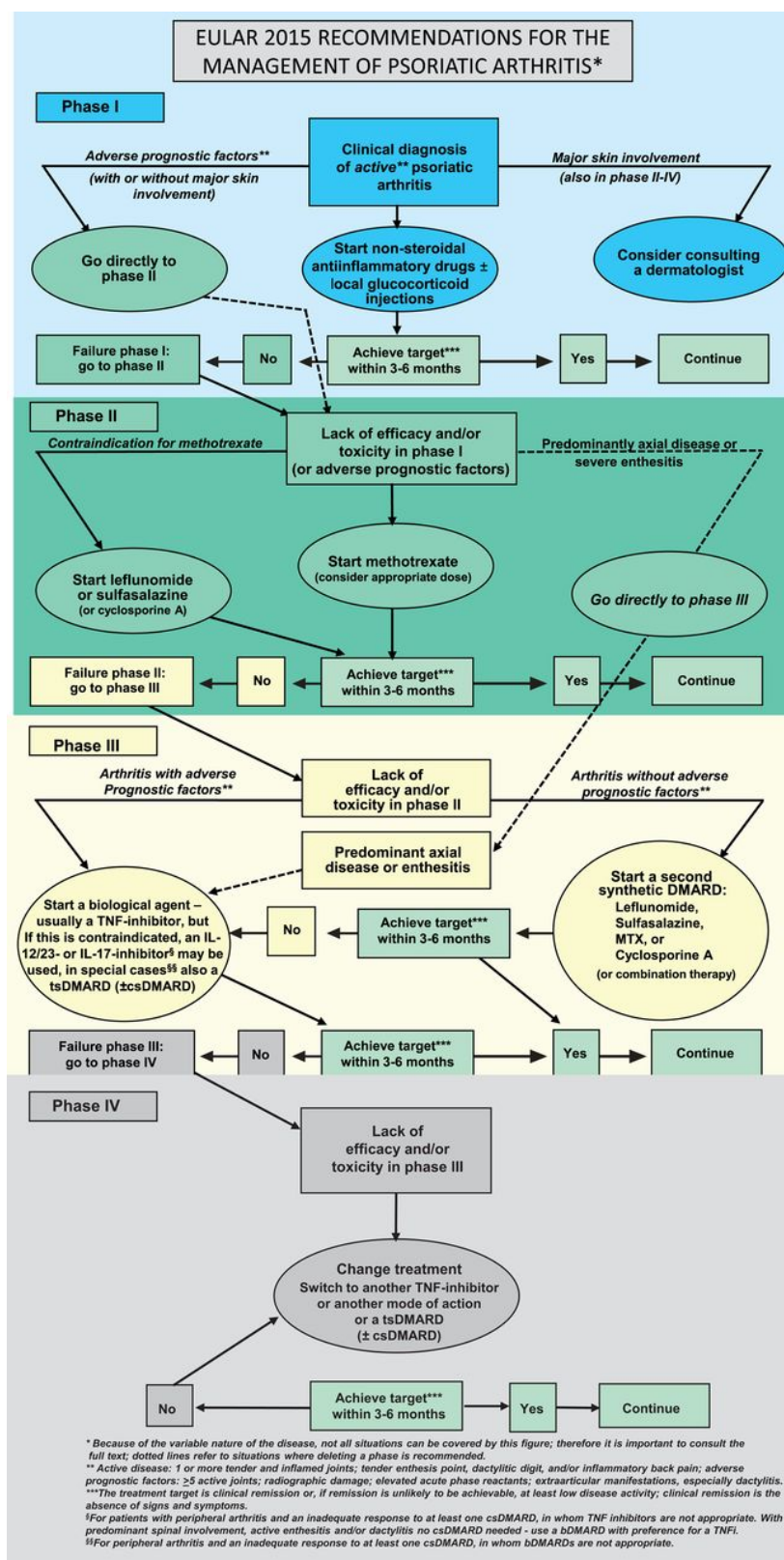


Figure 17 European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. (Reproduced from Gossec et al, Ann Rheum Dis. 2016;75:499-510).



8.1.1 NSAIDs

NSAIDs are widely used in daily clinical practice for the initial treatment of any type of arthritis, and are also the first level of treatment in the GRAPPA and EULAR PsA treatment algorithm. Some studies show that conventional NSAIDs have good efficacy in the treatment in PsA; no randomised controlled trial has been performed with Cox-2- specific NSAIDs. Improvement of the skin was not seen in these studies, and there are even reports of an exacerbation of the skin manifestations in patients treated with NSAIDs.

8.1.2 Glucocorticoids

Efficacy and side effects of oral or parenteral glucocorticoids have not been studied systematically in PsA. Nevertheless, registry data suggest that (low-dose) systemic steroid therapy is quite frequently used in daily practice. Because dose reduction or withdrawal of glucocorticoids can induce a flare of psoriasis, these drugs should be used with caution in patients with PsA and, if necessary, at a low dose and only for a limited time. Intra-articular injections of glucocorticoids are often used in clinical practice, especially for monoarthritis and oligoarthritis. An injection through affected skin should be avoided.

8.1.3 csDisease-modifying antirheumatic drugs

The use of csDMARDs for PsA has historically followed the treatment schedules used in RA for patients with peripheral arthritis and psoriasis. As discussed above, csDMARDs do not play a role in the treatment of axial SpA manifestations, but they have some proven efficacy in pSpA, with data available for sulfasalazine, leflunomide, methotrexate and ciclosporin. However, clinical trials with csDMARDs in PsA were often non-controlled, used different classification and improvement criteria (making comparison between trials difficult) and included only small number of patients with PsA, in an attempt to demonstrate roughly similar efficacy to RA. Interestingly, leflunomide was the only drug with proven efficacy in a double-blind, placebo-controlled study (Kaltwasser et al). In the recently published placebo-controlled, MIPA study (Methotrexate In Psoriatic Arthritis), methotrexate failed to show significant effects on arthritis (Kingsley et al), which is counterintuitive as most rheumatologists in daily practice would use methotrexate as the first line of csDMARD treatment in PsA (which is also incorporated in the EULAR treatment algorithm). In the RESPOND trial (Baranauskaite et al, 2012), comparing methotrexate monotherapy with a combination of methotrexate and infliximab in patients with relatively early PsA (2.8–3.7 years), an ACR 20 response in 66.7%, an ACR 50 response in 39.6% and an ACR 70 response in 18.8% of patients receiving monotherapy was seen. Data from the NOR-DMARD register concluded that the 6-month efficacy of sulfasalazine, leflunomide and methotrexate was similar.

Data indicating that combination treatment of methotrexate and ciclosporin is quite effective for arthritis and psoriasis are limited; combination treatment with leflunomide and methotrexate showed a significantly better effect on arthritis than monotherapy, without increasing the risk of adverse reactions. Available data are

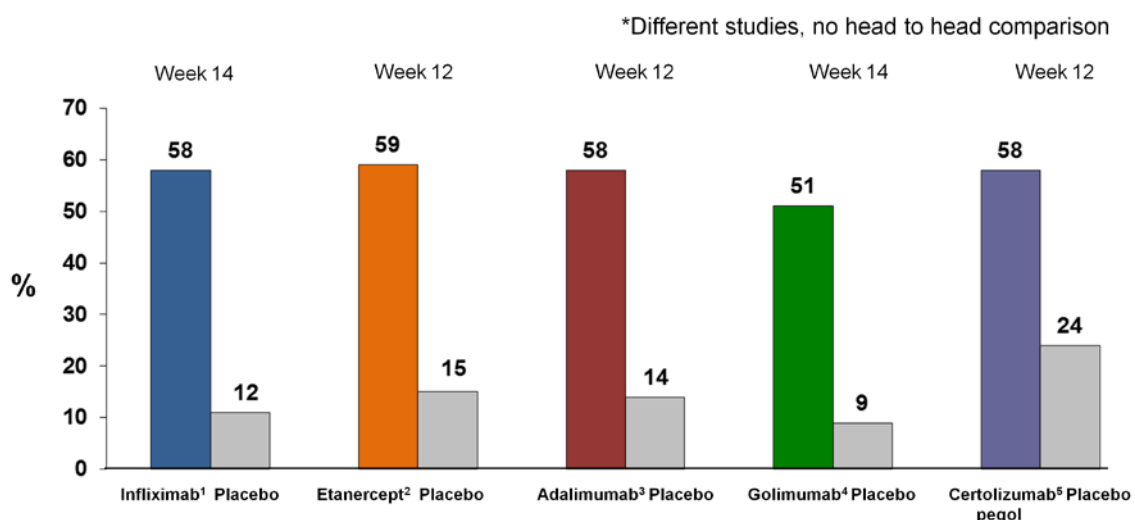
conflicting as to whether these drugs have an influence on radiological progression. In an Italian study on 174 patients with PsA, intake of methotrexate resulted in a good long-term effect on peripheral arthritis, but radiological joint damage scores deteriorated by 83%. However, when historic patient cohorts treated with methotrexate were compared, a more recent patient group demonstrated better efficacy both on signs and symptoms as well as on the retardation of structural damage. Although this cannot be formally proved, these observed effects are probably the consequence of a higher weekly dose of methotrexate and an earlier start of csDMARD treatment (Chandran et al, 2008). For all these drugs some improvement of psoriasis has also been reported, with ciclosporin and methotrexate probably being the most effective. Antimalarial agents and oral or injectable gold have no role in the treatment of PsA.

8.1.4 TNF-blocking agents

All five TNF-blocking agents approved for the treatment of patients with active AS, have also demonstrated remarkable effectiveness in the treatment of patients with active PsA, (figure 20), leading to an approved indication for use in PsA in the EU and the USA.

Figure 18 American College of Rheumatology (ACR) 20 response in patients with psoriatic arthritis treated with tumour necrosis factor α (TNF α) blockers. Five different studies with no head-to-head comparison. (Adapted from 1Antoni et al, *Ann Rheum Dis* 2005;64:1150–7; 2Mease et al, *Arthritis Rheum* 2004;50:2264–72; 3Mease et al, *Arthritis Rheum* 2005;52:3279–89; 4Kavanaugh et al, *Arthritis Rheum* 2009;60:976–86; Mease P et al, *Ann Rheum Dis* 2014;73:48–55. Slide reproduced from the ASAS slide kit.)

ACR 20-Response in Patients with Psoriatic Arthritis Treated with TNF α -Blockers*



1. Antoni C et al. *Ann Rheum Dis* 2005;64:1150–57
2. Mease P et al. *Arthritis Rheum* 2004;50:2264–72
3. Mease P et al. *Arthritis Rheum* 2005;52:3279–89
4. Kavanaugh A et al. *Arthritis Rheum* 2009;60:976–86
5. Mease P et al. *Ann Rheum Dis* 2014;73:48–55



In all studies continuation of previous csDMARD treatment (usually methotrexate) was permitted, but not necessary for inclusion. Interestingly, the level of response was similar in patients receiving anti-TNF monotherapy, compared with those receiving a TNF blocker in combination with a csDMARD. However, these data do not allow us to conclude if—for a patient with newly diagnosed PsA—there would be an advantage for combination therapy with csDMARD plus an anti-TNF biological agent over monotherapy with either the csDMARD or the TNF blocker alone. For the approved TNF-blocking agents, there is no difference in the dose and administration schedule compared with treatment of patients with AS.

Contrary to the data with csDMARDs, there is convincing evidence that TNF-blocking agents can halt structural damage in pSpA, as shown by stable erosion and joint narrowing scores of the radiographs of hands and feet in patients treated with a TNF blocker, compared with further progression in the placebo group.

Few studies are available on the treatment of enthesitis. Evidence suggests, that NSAIDs, glucocorticoid injections and physiotherapy improve the symptoms caused by enthesitis. There is no proof that csDMARDs have any efficacy on this type of lesion, which is why these drugs are not incorporated in the GRAPPA treatment guidelines. Although different instruments (enthesitis indices) were used in the pivotal studies on anti-TNF agents in PsA (which makes comparison difficult), there is clinical consensus that all these biological agents can treat refractory inflammation at the site of the enthesis when a standard dosing schedule is used. Interestingly, in the PRESTA (Psoriasis Randomized Etanercept Study in subjects with psoriatic Arthritis) trial, 50 mg etanercept given twice weekly had no greater effect on the rheumatic manifestations (with—in addition to the known efficacy on peripheral arthritis—a clear improvement of enthesal manifestations and dactylitis) than the standard rheumatological dose of 50 mg weekly.

Similarly, there are few studies on the treatment of dactylitis. Methotrexate, sulfasalazine, ciclosporin and leflunomide may all have some efficacy. Mostly based on expert opinion, systemic glucocorticoids and intra-articular glucocorticoid injections seem to have some role in the treatment of dactylitis. Finally, it has been shown that all four TNF blockers improve the signs and symptoms of active dactylitis.

Remarkable efficacy is also seen in the skin and nail manifestations of PsA. With monoclonal antibodies (infliximab, adalimumab and golimumab) given at the standard 'rheumatological' dose, Psoriasis Area and Severity Index (PASI) 75 skin responses are usually found in up to 60% of patients. With etanercept 50 mg weekly, clinical trials both in PsA and in psoriasis showed lower PASI 75 responses; in psoriasis studies a higher dose of 50 mg twice weekly yielded a better skin response (this 'skin dose-response' was also seen in the above-mentioned PRESTA trial). For comparison, in the placebo-controlled PsA study with leflunomide, the active drug achieved only an ACR 20 and a PASI 75 response at week 24 in 36% and 17% of patients, respectively.

8.1.5 New biological agents, and other agents, in PsA

Interleukin (IL)-12 and IL-23 have important roles in the pathophysiology of psoriasis. Ustekinumab is a human monoclonal antibody with high affinity for the p40 subunit of IL-12 and IL-23. Based upon two large, double-blind, placebo-controlled, phase III studies, the drug was approved for the treatment of psoriasis. The compound was also investigated in PsA. McInnes et al, (2013) reported the 1-year results of a phase III study in patients naïve for TNF blockers comparing ustekinumab at two different doses (45 and 90 mg) with placebo, administered subcutaneously at week 0, week 4 and every 12 weeks thereafter. At week 24, an ACR 20 response was seen in 22.8%, 42.4% and 49.5% of patients treated with placebo, ustekinumab 45 mg or 90 mg, respectively. When the two ustekinumab groups were combined, an ACR 20 response was seen in 46.0%, whereas more stringent improvement criteria, such as ACR 50 and ACR 70 response, were seen in 26.4% and 13.2%, respectively. The known efficacy on skin disease was confirmed, with 59.9% of patients in the combined ustekinumab group achieving a PASI 75 skin response (compared with only 11.0% in the placebo group). Another RCT, (Ritchlin et al, 2014) included 312 adults with active PsA who were randomised to ustekinumab 45 mg or 90 mg at week 0, week 4, q12 weeks or placebo at week 0, week 4, week 16 and crossover to ustekinumab 45 mg at week 24, week 28 and week 40. Efficacy was assessed in all patients, anti-TNF-naïve (n=132) patients and anti-TNF-experienced (n=180) patients. More ustekinumab-treated (43.8% combined) than placebo-treated (20.2%) patients achieved ACR20 at week 24 ($p<0.001$). Among patients previously treated with ≥ 1 TNF inhibitor, sustained ustekinumab efficacy was also observed (week 24 combined vs placebo: ACR20 35.6% vs 14.5%). Interestingly, post-hoc data recently published also suggested a beneficial effect of ustekinumab in the treatment of axial disease in patients with AS. Furthermore, pooled data of Psummit 1 and 2 demonstrated a beneficial structural effect of the drug. Ustekinumab is now approved for PsA treatment in Europe.

Multiple anti-IL-17 agents have been and are being investigated in psoriatic disease. Recent publications on the use of brodalumab, ixekizumab and secukinumab—all monoclonal antibodies targeting the IL-17 pathway—have demonstrated PASI 75 skin responses in the range of 75–80% (Leonardi et al, 2012; Papp et al, 2012; Papp et al, 2013). At present, the 2 pivotal studies with secukinumab in PsA have been published and that drug is approved for PsA in Europe, and the 2 other agents are under investigation for PsA (and AS) in phase III studies. In the first pivotal study 606 patients with psoriatic arthritis were randomly assigned in a 1:1:1 ratio to receive intravenous secukinumab (at a dose of 10 mg per kilogram) at weeks 0, 2, and 4, followed by subcutaneous secukinumab at a dose of either 150 mg or 75 mg every 4 weeks, or placebo. ACR20 response rates at week 24 were significantly higher in the group receiving secukinumab at doses of 150 mg (50.0%) and 75 mg (50.5%) than in those receiving placebo (17.3%) ($p<0.001$ for both comparisons with placebo). In a second study, a phase 3, double-blind, placebo-controlled study, 397 patients were randomly assigned to receive secukinumab 300 mg (n=100), 150 mg (n=100), 75 mg (n=99), or placebo (n=98). A

significantly higher proportion of patients achieved an ACR20 at week 24 with secukinumab 300 mg (54 [54%] patients; odds ratio versus placebo 6.81, 95% CI 3.42-13.56; $p<0.0001$), 150 mg (51 [51%] patients; 6.52, 3.25-13.08; $p<0.0001$), and 75 mg (29 [29%] patients; 2.32, 1.14-4.73; $p=0.0399$) versus placebo (15 [15%] patients). Secukinumab is now approved for PsA treatment in Europe.

As for TNF blockers studies, in trials with ustekinumab and secukinumab continuation of previous CSDMARD treatment (usually methotrexate) was permitted, and the observed level of response was similar in patients receiving biological drug monotherapy, compared with those receiving the combination with a CSDMARD.

Abatacept, a selective T cell costimulation modulator, was investigated in a 6-month, double-blind, placebo-controlled, phase II study. Three different dosing regimens (3 mg/kg, 10 mg/kg and 30/10 mg/kg (two initial doses of 30 mg/kg, followed by 10 mg/kg) were compared with placebo. Intravenous drug was administered at days 1, 15 and 29, and every 4 weeks thereafter. ACR 20 responses were seen in 19%, 33%, 48% and 42% in the placebo, abatacept 3 mg/kg, abatacept 10 mg/kg and abatacept 30/10 mg/kg groups, respectively (with the two higher dosing groups showing a statistically significant difference with placebo). Physical function also improved significantly at 10 mg/kg, and less joint damage was demonstrated by MRI evaluation (Mease et al, 2011). These results suggest that the approved abatacept dosage for RA, may also be an effective treatment option for PsA.

Over recent years, small molecules inhibiting intracellular signalling pathways have entered the therapeutic field of RA, with tofacitinib, an orally administered JAK inhibitor, being the first of this new therapeutic class to receive marketing approval in the USA for treatment of moderate-to-severe RA. Efficacy of this drug in psoriasis has been demonstrated (Bachelez et al, 2015) and results of phase III studies with tofacitinib in PsA are awaited.

Apremilast, another small molecule inhibiting phosphodiesterase 4, has been investigated in a number of clinical trials in PsA. In one of the phase III randomized clinical trial, 504 patients were randomised (1:1:1) to placebo, Apremilast 20 mg twice a day (BID) or Apremilast 30 mg BID. At week 16, significantly more Apremilast 20 mg BID (31%) and 30 mg BID (40%) patients achieved ACR20 versus placebo (19%) ($p<0.001$). Efficacy of Apremilast in PsA has been confirmed also in patients with active skin disease : in patients with baseline psoriasis body surface area involvement $\geq 3\%$, significantly more Apremilast 30 mg twice daily patients achieved 50% reduction from baseline Psoriasis Area and Severity Index score (41%) versus placebo (24%; $p=0.0098$) at week 16. Apremilast is now approved for PsA treatment in Europe.

8.1.6 Global recommendations for management of PsA

Recently the international GRAPPA group and EULAR published updated recommendations for the treatment of PsA, including the use of TNF blockers (figures 18 and 19). The GRAPPA group takes an approach that

focuses on the different domains of psoriatic disease, and describes evidence-based treatments for each domain. When instituting a certain treatment, the efficacy should be monitored by the physician with the aim of maximally controlling all aspects of the disease. As mentioned in the introduction to this paragraph, the physician will—in an individual patient—treat with a combination of drugs that can be combined safely together, or will use a single drug capable of tackling the different disease manifestations. The EULAR management recommendations mainly deal with peripheral arthritis. A step-up treatment schedule is proposed, starting with NSAIDs, over csDMARDs (with methotrexate as anchor drug), then biological agents, usually a TNF blocker. In this algorithm the physician will take prognostic factors, toxicity and inadequate response to the prior level of treatment into account. Usually—when standard (csDMARD) treatments such as methotrexate, sulfasalazine, ciclosporin or leflunomide over a period of 3 to 6 months have failed—the recommendations for the initiation of a TNF blocker require a disease activity with at least one or more swollen and tender joint. Treatment decisions about patients with predominant severe enthesitis or dactylitis have to be made on an individual basis, but there is consensus that biological agents targeting TNF are probably the first-choice drugs. In cases of predominant axial involvement, the ASAS/EULAR treatment guidelines for axial SpA should be followed.

A clear effect of treatment with bDMARDs or tsDMARDs should be seen after at least 12 weeks of treatment, with rheumatological manifestations exhibiting an earlier response than skin and/or nail disease.

8.2 IBD-associated SpA

The treatment of the peripheral arthritis in patients with IBD is, in general, the same as for other SpA, but concomitant active gut inflammation, both in CD and ulcerative colitis (UC), may complicate the traditional treatment approach. We will again review the different treatment modalities.

8.2.1 NSAIDs

As with other SpA, NSAIDs are the first choice of treatment for axial disease, but this drug class should also be started for peripheral arthritis. However, in IBD, they should be given with caution because some data suggest that they may cause an exacerbation of intestinal symptoms, mainly in UC; these relapses of quiescent IBD in the large intestine may appear after a few days of NSAID treatment in susceptible patients. The role of Cox-2 selective agents such as celecoxib and etoricoxib, is not entirely clear. Although these agents seem to have a better safety profile for upper gastrointestinal tract lesions, there are no systematic data on their safety in IBD. Nevertheless, two prospective controlled studies of patients with IBD and rheumatic symptoms who were evaluated for IBD flares while receiving Cox-2 selective agents versus placebo, suggested no higher incidence of flares with the active drug compared with placebo (El Miedany et al, 2006; Sandborn et al, 2006). Based on these data, a short trial of a Cox-2 selective agent may be considered in patients with quiescent IBD who have active rheumatological symptoms related to SpA.

It is well known that a significant percentage of patients with SpA have subclinical (microscopic) inflammatory gut lesions resembling those seen in CD. Since chronic use of NSAIDs can lead to ulcerations in the stomach and the small and large intestine, one might hypothesise that some of these lesions are the consequence of administration of this type of drug. However, virtually all ileocolonoscopy studies in patients with SpA have shown the absence of any association between these gut lesions and the use of NSAIDs (similar percentage of gut lesions in patients with and without NSAID use). Moreover, most NSAID-induced gut lesions are found proximal to the ileum, whereas the majority of subclinical IBD lesions are found in the ileocaecal region and colon.

8.2.2 Glucocorticoids

Intra-articular glucocorticoid injections may be beneficial in monoarticular or oligoarticular flares. Oral glucocorticoids may reduce peripheral synovitis, but have no effect on axial symptoms (as mentioned above). Their systematic use is justified only if they are required for control of the bowel disease. Controlled ileal release (CIR) budesonide, a glucocorticoid that has high affinity for the glucocorticoid receptor but low systemic activity owing to extensive first-pass hepatic metabolism, may be used as an alternative to prednisone when treating bowel symptoms; placebo-controlled trials have shown that CIR budesonide at 9 mg/day is effective in patients with mild to moderately active Crohn's ileitis and/or right colon involvement. No trials in SpA have yet been performed, and the effect of CIR budesonide on peripheral arthritis or spondylitis was not examined in the CD trials. However, a placebo-controlled trial comparing prednisolone 7.5 mg versus CIR budesonide 3 or 9 mg daily in patients with RA yielded similar efficacy results for the prednisolone and the budesonide 9 mg group (Kirwan et al, 2004); this suggests that if CIR budesonide is prescribed for active gut disease, there might also be beneficial effects on peripheral arthritis.

8.2.3 csDMARDs

Comparable to their use in PsA, csDMARDs have been used by clinicians for the treatment of peripheral arthritis associated with IBD, but again, well-designed, controlled studies are lacking.

Sulfasalazine, which has been successfully used to treat colonic inflammation in UC and CD, has been found to be effective in the treatment of the peripheral arthritis accompanying SpA, especially if intestinal inflammation is present. It may also have a favourable effect on the peripheral arthritis in IBD, but, as mentioned before, will not influence axial symptoms. Despite the clinical effect of sulfasalazine on peripheral joint manifestations in SpA, the drug does not seem to prevent the development of IBD.

Azathioprine and its principal metabolite 6-mercaptopurine have been used successfully for more than 30 years in patients with CD for (1) induction of gastrointestinal remission in steroid-refractory disease, (2) as a

steroid-sparing agent, (3) in fistulising disease and (4) for maintenance treatment. However, despite some efficacy in RA, the drug has not been studied for treatment of the arthritis of CD or UC.

Low-dose methotrexate successfully used in the treatment of RA and in some cases of refractory IBD, has not yet been shown to be effective in joint inflammation associated with CD or UC.

Leflunomide is an isoxazole derivative approved for the treatment of RA and PsA. It has only been studied in a small open-label trial of 12 patients with CD who were intolerant to azathioprine: clinical improvement was noted in eight of 12 patients, suggesting that further study in controlled trials is warranted.

Gold salts, D-penicillamine and antimalarial drugs are ineffective.

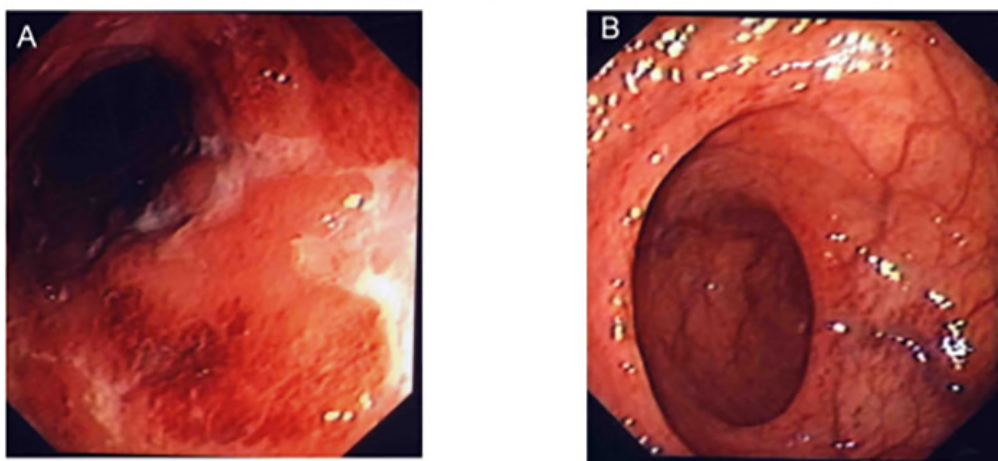
8.2.4 TNF-blocking agents

In the 1990s, it was shown that treatment with a single infusion of infliximab is highly effective in the short-term treatment of intestinal involvement in treatment-resistant CD (figure 22), even resulting in the closure of enterocutaneous fistulae.

Figure 19 Efficacy of anti-TNF α therapy in chronic inflammatory bowel disease. Ileocolonoscopy in Crohn's disease. (A) Before treatment with infliximab: presence of important ulcerations. (B) After treatment with infliximab: disappearance of inflammation and ulcerations. TNF, tumour necrosis factor.

Efficacy of Anti-TNF- α -Therapy in Chronic Inflammatory Bowel Disease

Ileocolonoscopy in a patient with Crohn's disease



A : before anti-TNF therapy: colitis and ulcers
B : after treatment with infliximab: normal findings

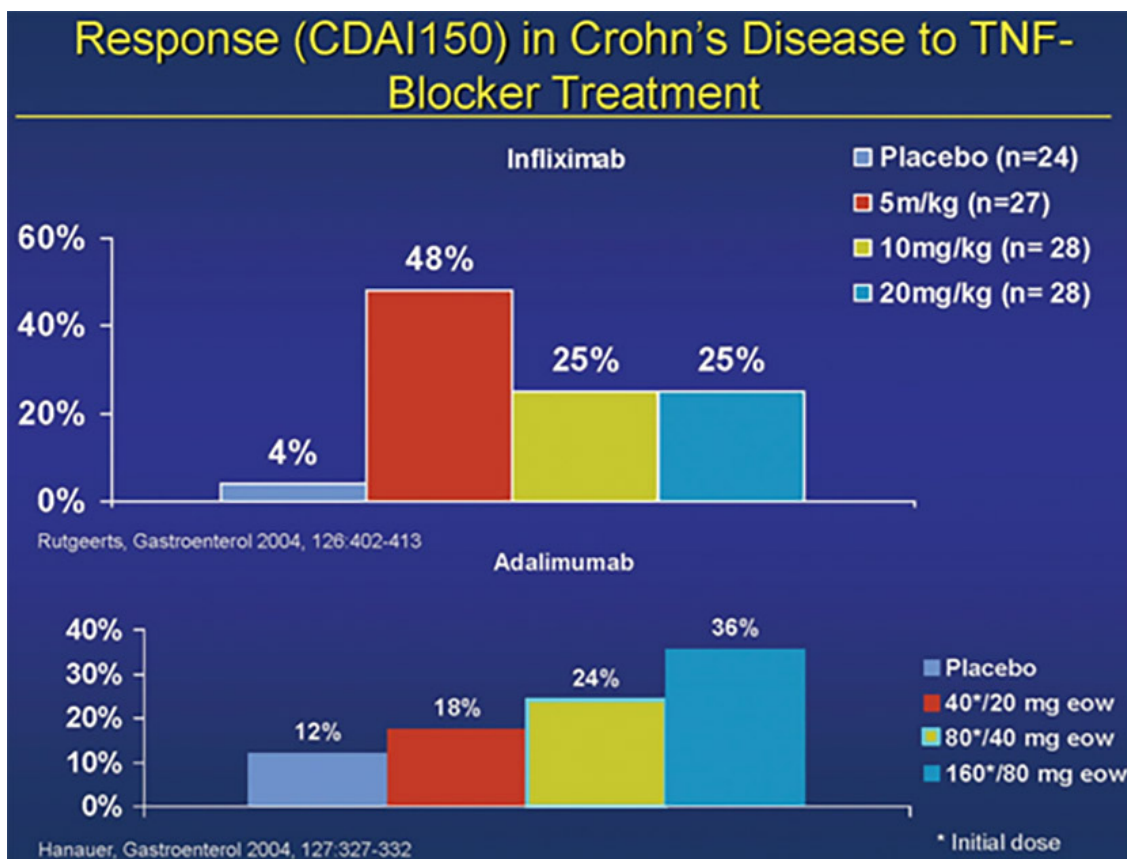


As a consequence of these pilot findings, multiple placebo-controlled, phase III studies were performed investigating the efficacy and safety of anti-TNF agents in active IBD. Both induction schedules and maintenance regimens were studied, the latter showing that maintenance treatment in moderate to severe CD prolonged the response and remission of the disease (Rutgeerts, 2004). Infliximab and adalimumab are approved by the European Medicines Agency for the treatment of CD and UC, and golimumab has recently received approval for the treatment of UC. Although phase III studies with certolizumab in CD showed efficacy, the drug has only been approved for use in the USA, but not in the European union.

The first observations that infliximab treatment might also be useful for the treatment of resistant peripheral joint and axial manifestations in patients with CD, came from an open pilot study: four patients with treatment-resistant or fistulising CD, but at the same time also active axial and/or peripheral SpA, were treated with 5 mg/kg infliximab. Beside remission of gut inflammation, a significant improvement of articular and axial symptoms was seen in all patients. In one patient the disease flared after approximately 3 months, but re-treatment with the same dose of infliximab induced a new remission (figure 23).

Although no formal placebo-controlled study has been performed in SpA associated with IBD, there is little doubt that infliximab is also highly efficacious in this indication. In the ACCENT I trial, evaluating the efficacy of a re-treatment regimen of infliximab in patients with active CD, maintenance treatment also resolved extra-intestinal manifestations, such as arthritis. An Italian open study evaluated the efficacy of a loading dose regimen of 5 mg/kg infliximab in 24 patients with SpA associated with active (n = 16) or quiescent (n = 8) CD. Infliximab improved both gastrointestinal and overall articular symptoms (axial disease, peripheral arthritis, enthesitis). In patients with inactive CD at baseline, infliximab prevented IBD flares during the follow-up period.

Figure 20 Effect of anti-TNF α therapy on articular symptoms in Crohn's disease. Efficacy of infliximab (intravenous infusion of 5 mg/kg body weight; infusions were given at weeks 0, 16 and 34) in a patient with CD and spondyloarthritis. Effect on C-reactive protein (CRP) level and the number of swollen joints (SJC). Gastrointestinal and articular disease flared approximately 3 months after infliximab treatment; re-treatment with the same dose induced a new remission. TNF, tumour necrosis factor. (Reproduced with permission of Elsevier from Van den Bosch et al, *Lancet* 2000;356:1821–2.)



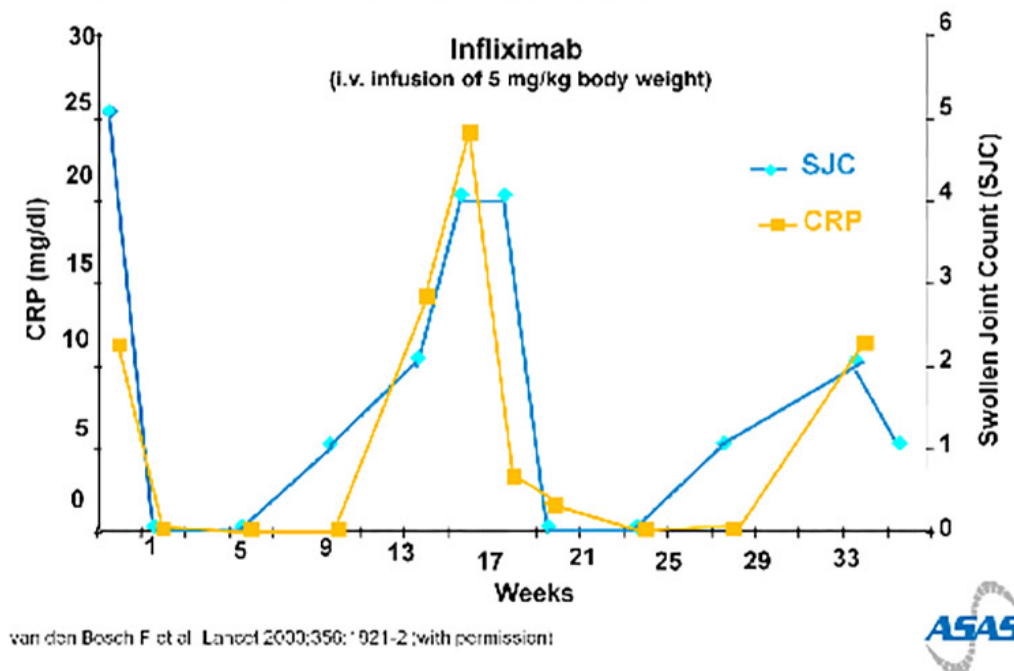
The combined published evidence in the gastroenterology and rheumatology literature shows that there is little doubt that monoclonal antibodies targeting TNF are effective for treatment of both gut and joint lesions.

A particular scientific challenge, however, is that more TNF α blockers are effective in axSpA than they are in IBD. Etanercept is an example of such a drug with discordant efficacy. Despite its very good efficacy in the treatment of AS, an 8-week, randomised, double-blind, placebo-controlled trial showed no signs of efficacy in patients with active CD. Braun et al (2007) surveyed all data on the occurrence of IBD in patients with AS exposed to anti-TNF therapy during different placebo-controlled trials and their open-label extension studies: flares or new onset of IBD were seldom seen in patients treated with infliximab, but the reactivation of IBD (especially of UC) was relatively common with etanercept (figure 24); interpretation of the adalimumab data was difficult because of the significantly smaller number of patient-years. The biological basis for this

discrepancy is still being studied: reasons may include differences in bioavailability and pharmacodynamics, as well as cell biological effects (induction of apoptosis) that may differ from one TNF α -blocking agent to another.

Figure 21 Flares or new forms of IBD in patients with AS treated with TNF-blocking agents. Low but different incidence of acute IBD in patients with AS receiving anti-TNF α therapy. AS, ankylosing spondylitis; IBD, inflammatory bowel disease; TNF, tumour necrosis factor. (Adapted from Braun et al, *Arthritis Rheum* 2007;57:639–47.)

Effect of Anti-TNF α -Therapy on Articular Symptoms in Crohn's Disease



8.2.4 Other bDMARD agents

Ustekinumab is a human monoclonal antibody with high affinity for the p40 subunit of IL-12 and IL-23. A double-blind, placebo-controlled, cross-over trial was conducted in 104 patients with moderate-to-severe Crohn's disease. Patients were given subcutaneous placebo at weeks 0-3, then ustekinumab at weeks 8-11; subcutaneous ustekinumab at weeks 0-3, then placebo at weeks 8-11; intravenous placebo at week 0, then ustekinumab at week 8; or intravenous ustekinumab at week 0, then placebo at week 8. Clinical response rates for the combined groups given ustekinumab and placebo were 53% and 30% ($P = .02$), respectively at weeks 4 and 6, and 49% and 40% ($P = .34$), respectively at week 8. In a subgroup of 49 patients who were previously given infliximab (neither primary nor secondary non-responders), clinical response to ustekinumab was significantly greater than the group given placebo ($P < 0.05$) through week 8. Ustekinumab is now approved for Crohn's disease treatment in Europe.

An integrin antagonist, vedolizumab binds to the $\alpha_4\beta_7$ integrin which is expressed specifically by a subset of gastrointestinal-homing T lymphocytes. The binding of $\alpha_4\beta_7$ integrin to mucosal address in cell adhesion

molecule-1 expressed on the surface of mucosal endothelial cells is a crucial component of the gut-selective homing mechanism for lymphocytes. The results of two trials (one in Crohn's disease and another in ulcerative colitis) have led to the approval of this drug for both forms of IBD. The trial in Crohn's disease included 368 patients who were randomly assigned to receive vedolizumab or placebo at weeks 0 and 2. At week 6, a total of 14.5% of the patients 1 who received vedolizumab and 6.8% who received placebo were in clinical remission. In the ulcerative colitis trial, 374 patients received vedolizumab (at a dose of 300 mg) or placebo intravenously at weeks 0 and 2. A response was defined as a reduction in the Mayo Clinic score (range, 0 to 12, with higher scores indicating more active disease) of at least 3 points and a decrease of at least 30% from baseline, with an accompanying decrease in the rectal bleeding sub score of at least 1 point or an absolute rectal bleeding sub score of 0 or 1. Response rates at week 6 were 47.1% and 25.5% among patients in the vedolizumab group and placebo group, respectively (difference with adjustment for stratification factors, 21.7 percentage points; 95% confidence interval [CI], 11.6 to 31.7; $P < 0.001$).

8.3 Reactive arthritis

Reactive arthritis is also discussed in chapter 14, Infection and Arthritis. NSAIDs are also the mainstay of treatment for reactive arthritis. This can, as for the other SpA, be supplemented by joint injections with glucocorticoids. Activation of a (latent) infection in the joint has not been reported. Data on the use of csDMARDs are limited. In most patients reactive arthritis is a self-limiting disease and therefore DMARD treatment should only be considered if chronic arthritis persists for more than 4–6 months.

As already discussed above, sulfasalazine was effective for peripheral arthritis in a placebo-controlled study of patients with SpA, including those with reactive arthritis. Azathioprine and other csDMARDs have been used with some success in patients with severe reactive arthritis; however, no controlled data are available. Several case reports and small open-label studies have reported a good efficacy of TNF-blocking agents for the treatment of reactive arthritis refractory to conventional treatment, without reactivation of the triggering infection. But again, no controlled data are available.

Reactive arthritis is triggered by a preceding gastrointestinal or urogenital infection, and bacteria or parts of bacteria can be detected in the synovial fluid and synovial membrane of patients, which raises the question as to whether a short or long-term (eg, 3 months) antibiotic treatment regimen might be of some benefit. However, neither regimen has been found to be effective for arthritis. Only when *Chlamydia trachomatis* is detectable in the urogenital tract should this infection be treated with an antibiotic for 10–14 days to prevent relapses of arthritis.

Since it was suggested that undifferentiated peripheral SpA may be an expression of reactive arthritis, in which the triggering infectious agent cannot be detected, an aetiological attempt was carried out in three studies using antimicrobial drugs. In two of the studies, a 3-month course of ciprofloxacin or doxycycline did not

produce favourable results in comparison with placebo. Recently, Carter et al tested the combination of doxycycline and rifampicin in a small group of patients with undifferentiated SpA. These two drugs were administered for a 9-month period. A significant improvement was seen in pain, morning stiffness, swollen and tender joint count in comparison with the patients of the control group who were given doxycycline only. These promising data certainly need to be confirmed in larger studies.

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Summary points

- ➔ Treatment of the predominant axial and predominant peripheral manifestations of the spondyloarthritis (SpA) partly differs and partly overlaps.
- ➔ Physiotherapy is the most important non-pharmacological treatment in SpA.
- ➔ Non-steroidal anti-inflammatory drugs (NSAIDs), tumour necrosis factor (TNF) blockers and IL-17 inhibitors are the only effective drugs for the treatment of axial SpA while conventional disease-modifying antirheumatic drugs may have a role in the management of peripheral SpA.
- ➔ Consequently, NSAIDs should be preferred for the treatment of axial SpA. The aim should be to achieve patients free of symptoms.
- ➔ TNF-blocker treatment is indicated in axial Spondyloarthritis (axSpA) and psoriatic arthritis (PsA) after failure of conventional treatment.
- ➔ IL-17 blockers are indicated in ankylosing spondylitis (AS) after failure of conventional treatment.
- ➔ TNF blockers and IL-17 are highly effective for the treatment of AS (TNF blockers also in non-radiographic SpA). A significant improvement of disease activity, function, spinal mobility and reduction of acute phase reactant is fast and can normally be seen days to a few weeks after the start of treatment.
- ➔ TNF blockers also reduce active inflammation of sacroiliac joints and spine in patients with axSpA as shown by MRI.
- ➔ TNF blockers are also highly effective for the treatment of PsA, as well as IL12/23 blocker and IL17 blocker. There is evidence for a good efficacy for other forms of peripheral SpA.
- ➔ Structural damage (erosions/joint space narrowing) is stopped by TNF blockers, IL12/23 blocker and IL17 blocker in PsA, while existing data does not allow to suggest that TNF blockers prevent ankylosis in patients with AS. There is evidence that NSAIDs can inhibit ankylosis.
- ➔ For extra rheumatic manifestations of SpA several bDMARDs (e.g. TNF blockers, but also IL 17 and IL23 blockers) have shown to be effective for the treatment of inflammatory bowel disease, psoriasis and in the reduction of flares of uveitis. Conversely, it is worth noting that etanercept and IL-17 blockers are not effective for the treatment of IBD; furthermore, etanercept has not proved to reduce uveitis flares.

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EULAR on-line course on Rheumatic Diseases

Management of spondyloarthritis

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IN-DEPTH DISCUSSION I

**The Management of Acute Anterior Uveitis associated
with SpondyloArthritis**

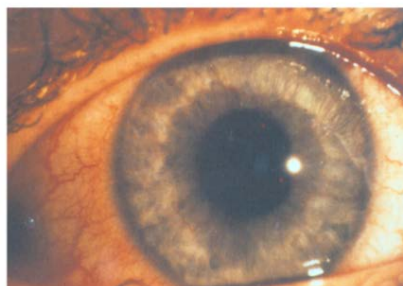
Acute anterior uveitis (AAU) is the most common form of uveitis, with an annual incidence rate of about 8 cases per 100000 population (1). The disease primarily affects only the anterior chamber of the eye. AAU is a prominent manifestation of spondyloarthritis with a strong link to HLA-B27, occurring in 30-40% of patients with axial Spondyloarthritis (axSpA). Acute inflammation of the uvea can be the first presenting symptom of the disease. In a study among 433 patients with different types of uveitis, 44 cases (almost 10%) of SpA were detected, whereas others showed a percentage up to 50% of previously undiagnosed cases of SpA among uveitis patients (2-4). The occurrence of AAU is increased in the HLA-B27 positive population, with a lifetime cumulative incidence of 0.2 % in the general population compared with 1% in the HLA-B27 positive population (5). In an observational survey of 902 SpA patients with a HLA-B27 positivity of 76%, uveitis prevalence was 32.2% (95% confidence interval [95% CI] 29.1–35.3%), and was the most common extraarticular feature of SpA. Factors independently associated with uveitis were HLA-B27 positivity (adjusted odds ratio [OR_{adj}] 2.97 [95% CI 1.83–4.81], $P < 0.0001$) and disease duration (OR_{adj} 1.28 [95% CI 1.16–1.41], $P < 0.0001$ for ≥ 10 years). (6) Banares and colleagues also described a relationship between anterior uveitis and bowel inflammation (in 60% of patients with AS-related uveitis), with a close relationship between the recurrence of uveitis and the presence of chronic intestinal inflammation (7)

An attack of AAU has a sudden onset and is typically unilateral (although in subsequent flares the other eye may become involved): local redness, photophobia, but most of all ocular pain are the cardinal symptoms. Inflammation can lead to debris, which accumulates in the anterior chamber and may cause papillary and lens dysfunction with blurring of vision. In some cases – when adequate treatment is delayed – glaucoma and severe visual impairment may occur, but most of the time, with local treatment, the uveitis subsides over a period of 6 to 12 weeks.

Figure 1: Characteristics of Acute Anterior Uveitis (reproduction from the ASAS slide kit)

Eye: Acute Anterior Uveitis in Spondyloarthritis

- Acute onset
- Unilateral
- Anterior
- Spontaneous remission
- Recurrent
- Related to HLA B27



In SpA patients with sudden symptoms of a painful, red eye, it is recommended to refer the patient to the ophthalmologist as soon as possible (figure 1).

Treatment of Uveitis

In most cases AAU can be successfully treated by the ophthalmologist with local treatment with corticosteroids and cycloplegic agents (mydriatics). Sometimes subconjunctival injections with corticosteroids are necessary to control inflammation in the anterior chamber. In most cases there is no residual visual impairment.

There seems to be consensus among ophthalmologists that in patients with 3 or more flares of AAU during a 1-year period or with recurrence of inflammation close to cessation of the topical therapy, further systemic treatment is indicated. In such cases oral corticosteroids (up to 60 mg daily) and/or immunosuppressive drugs may become necessary. Because of the low prevalence of uveitis, new systemic treatments have historically been implemented into clinical practice based upon their success in controlling other autoimmune inflammatory diseases, with subsequent anecdotal evidence based on small case studies published by uveitis specialists.

NSAIDs

NSAIDs are the cornerstone of pharmacologic treatment in patients with axSpA. They were however also used (before the emergence of topical corticosteroids) in the treatment of uveitis (8-11). In a study by Fiorelli et al, 59 patients with recurrent anterior uveitis were treated with continuous oral NSAID therapy (celecoxib: n=30; diflunisal: n=29) (12). In both groups the average number of relapses decreased from 2,84 attacks per person-year follow-up before start of systemic NSAID therapy to 0,53 attacks while on treatment ($p<0,001$). Patients remained in remission for an average of 18,22 months.

Sulfasalazine

There is some evidence that the use of sulfasalazine reduces the recurrence rate of AAU (13,14): in this open, prospective study the number of uveitis flares decreased from 3,4 in the pre-treatment year to 0,9 ($p=0,007$). Benitez-del-Castillo et al randomised 22 AS patients with recurrent attacks of AAU to receive either sulfasalazine (n=10) or no treatment (n=12) (15). During a follow-up period of 36 months, a statistically significant difference in favour of sulfasalazine was observed regarding the number of recurrences; new episodes of uveitis in the sulfasalazine group were also less severe.

Methotrexate

In severe chronic, non-infectious uveitis, a number of immunomodulatory drugs are introduced by ophthalmologists in order to control inflammation and avoid undesirable side effects of chronic high-dose, oral corticosteroid therapy. In a survey among uveitis specialists (16), inquiring about practice patterns regarding

the prescription of corticoid-sparing therapy, methotrexate was the most commonly used initial treatment for anterior, intermediate, and posterior/panuveitis (85%, 57%, and 37%, respectively). However, given the fact that methotrexate is not efficacious for the treatment of axial symptoms of SpA, and the potential side effects of this drug, it does not seem a logical treatment choice in patients with recurrent attacks of AAU associated to axial SpA. It could be considered in patients with SpA and predominant peripheral synovitis, where methotrexate could – despite the lack of controlled studies on its efficacy – be a treatment option.

Biologic DMARDS:

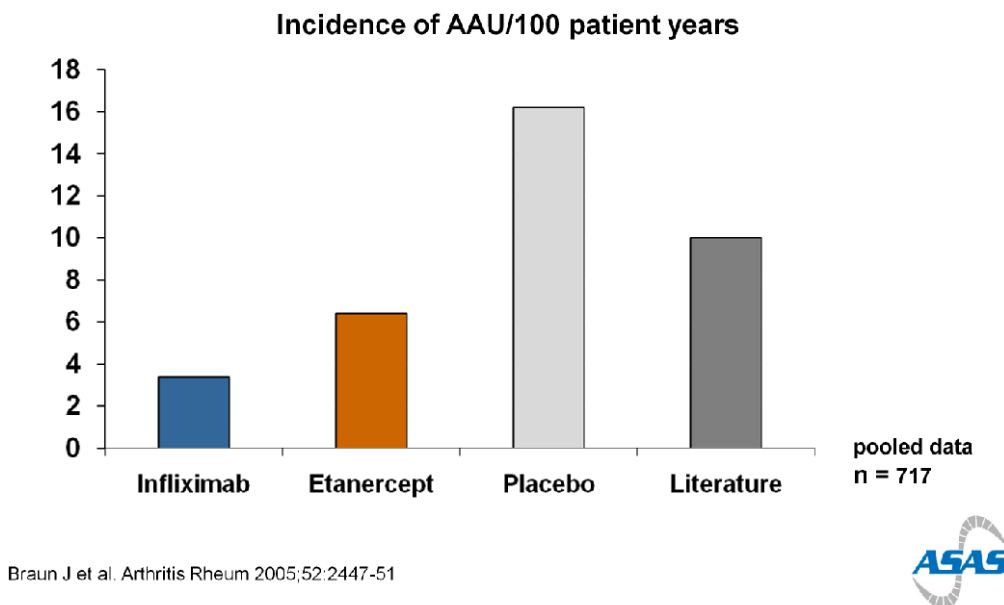
- **Anti-TNF agents**

In the previous decade, the advent of TNF-blockers has dramatically changed our treatment algorithm of patients with active SpA. Not only do these drugs have a profound effect on both axial and peripheral manifestations of SpA, but they also have a beneficial impact on other typical locomotor manifestations such as enthesitis and dactylitis, and finally also on the SpA extra-articular manifestations. At this moment, 5 different anti-TNF agents are indicated for the treatment of signs and symptoms of axSpA and PsA: etanercept (a soluble TNF-receptor fusion protein), infliximab (only for AS and PsA), adalimumab and golimumab (all anti-TNF monoclonal antibodies), and certolizumab (an anti-TNF Fab-fragment conjugated to PEG).

Infliximab is an adequate treatment of SpA, decreases the recurrence rate of uveitis and is effective as treatment for refractory uveitis (17). In contrast to systemic treatment with infusions, intraocular injections with infliximab are toxic, inducing intraocular inflammation (18,19). The efficacy of etanercept on uveitis is doubted, as etanercept does not seem to prevent a relapse in combination with methotrexate (20) and it was suggested that etanercept might even trigger attacks of uveitis (21). However, a comparison of three randomised studies with etanercept in AS showed a lower number of cases with uveitis in the etanercept-treated patients compared with placebo (22) indicating that etanercept does inhibit the recurrence of uveitis. An analysis of 4 placebo-controlled studies and 3 open-label studies with TNF-blocking agents in AS (where attacks of uveitis were reported by the patients) showed a frequency of flares of anterior uveitis in the placebo-group of 15.6 per 100 patient-years, compared with 7.9 per 100 patient-years in the etanercept group and only 3.4 per 100 patient-years in the infliximab-treated patients (figure 2) (23).

Figure 2: Decreased incidence of Acute Anterior Uveitis with anti-TNF (reproduction from the ASAS slide kit)

Decreased Incidence of Acute Anterior Uveitis (AAU) in Patients on Anti-TNF α -Therapy



Both etanercept and infliximab were statistically significant better than placebo; infliximab was more, although not significantly, effective than etanercept. A more recent study from France analysed retrospectively the frequency of anterior uveitis relapses before and after treatment with any of the three TNF blockers (24). A clear and significant reduction of uveitis relapses was observed when treatment with either infliximab or adalimumab was started; however, in case of etanercept therapy, no change in the relapse rate was seen.

Reports on the efficacy of adalimumab for uveitis are based on a large, prospective study in 1250 AS patients that received open-label treatment for up to 20 weeks (25): 15 uveitis flares per 100 patient-years were noted before start of adalimumab treatment; the overall rate of flares was reduced with 51% in all patients with better results seen in those patients that had a prior history of uveitis. In another study, AS patients that were treated with adalimumab because of high disease activity, were also screened by an ophthalmologist regarding uveitis. This study demonstrated a significant decrease (73%) of the recurrence rate of uveitis during adalimumab treatment (26).

Recent reports indicate that golimumab and certolizumab also seem to be effective for the treatment of refractory uveitis in patients suffering from immune-mediated inflammatory diseases, including axSpA (27-29). In a post-hoc analysis of a Certolizumab vs. placebo randomized trial in patients with axSpA: 38 of 218 certolizumab-randomized patients (17.4%) and 31 of 107 placebo-randomized patients (29.0%) had past uveitis history at baseline. The rate of uveitis flares was significantly lower in the certolizumab group (3.0 [95%

confidence interval (95% CI) 0.6-8.8] per 100 patient-years) than in placebo (10.3 [95% CI 2.8-26.3] per 100 patient-years) and were similar between AS (4.4 [95% CI 2.3-7.7] per 100 patient-years) and nr-axial SpA (5.6 [95% CI 2.9-9.8] per 100 patient-years) in the 96-weeks extension follow-up period (30).

Finally, recent American recommendations for ophthalmologists considered that infliximab or adalimumab may be used as corticosteroid-sparing treatment for patients with chronic uveitis resulting from seronegative spondyloarthropathy or with severe, vision-threatening or debilitating uveitis requiring systemic immunosuppressive agents or as adjunctive therapy to corticosteroid treatment in acute disease (31).

- **Other bDMARDs:**

Secukinumab, an IL-17 has been reported to be efficacious in the treatment of uveitis in a phase 2 clinical trial, where 37 patients with active non-infectious uveitis requiring a corticosteroid-sparing immunosuppressive therapy were randomized to 3 different doses of **secukinumab**. Higher secukinumab doses lead to higher responder rates and remission rates (32)

No data has been reported yet with regard to the effect of IL12/23 inhibitors in SpA-related uveitis.

Conclusion

It can be concluded that in most cases, attacks of acute anterior uveitis respond very well to (local) treatment by the ophthalmologist. Continuous use of NSAIDs (when indicated for the rheumatological manifestations) and/or sulfasalazine treatment may decrease the number of recurrent flares. In cases of refractory uveitis or a high uveitis recurrence rate, treatment with TNF blocking agents can be successful, especially if the treatment is indicated for high disease activity of SpA. Adalimumab and infliximab (and probably also the other monoclonal antibodies) seem to be more effective in lowering the recurrence rate of uveitis compared to etanercept.

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EULAR on-line course on Rheumatic Diseases

Management of spondyloarthritis

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IN-DEPTH DISCUSSION II

Choice of biologic DMARDs in relation to extra-articular manifestations in Spondyloarthritis

Spondyloarthritis (SpA) is a chronic inflammatory disease with either predominant axial symptoms of the spine and sacroiliac joints (axial SpA, including ankylosing spondylitis) or predominant peripheral manifestations, such as arthritis, enthesitis, or dactylitis (peripheral SpA). Next to these spinal and articular symptoms, many patients with SpA also suffer from extra-articular manifestations (EAMs).

Spondyloarthritis-concept related EAMs include anterior uveitis (25-30%), psoriasis (10-25%) or inflammatory bowel disease (IBD) (5-10%). The treatments, used for the rheumatological manifestations of the disease, such as NSAIDs, DMARDs and TNF-blocking agents may have a differential effect on these EAMs, and therefore the presence of these manifestations should be taken into account when taking therapeutic decisions.

Uveitis.

Acute anterior uveitis is an acute attack with inflammation of the uvea and can be the first presenting symptom of the disease. In a study among 433 patients with different types of uveitis, 44 cases (almost 10%) of SpA were detected, whereas others showed a percentage up to 50% of previously undiagnosed cases of SpA among uveitis patients (1-3). The occurrence of acute anterior uveitis is increased in the HLA-B27 positive population, with a lifetime cumulative incidence of 0.2 % in the general population compared with 1% in the HLA-B27 positive population (4).

The attacks of uveitis are usually recurrent and unilateral. The symptoms are sudden ocular pain with redness and photophobia. Inflammation can lead to debris, which accumulates in the anterior chamber and may cause papillary and lens dysfunction with blurring of vision. In some cases glaucoma and severe visual impairment occurs if adequate treatment is delayed, but most of the time, with local treatment, the uveitis subsides spontaneously within 3 months. In SpA patients with sudden symptoms of a painful, red eye, it is recommended to refer the patient to the ophthalmologist as soon as possible.

In most cases acute uveitis can be successfully treated by the ophthalmologist with local corticosteroids and mydriatics. Sometimes high oral dosage of prednisone (up to 60 mg daily) is necessary to control inflammation. In most cases there is no residual visual impairment.

Some data suggest that continuous use of NSAID's show efficacy for uveitis flares. There is some evidence that the use of sulfasalazine reduces the recurrence rate of uveitis (5, 6). Other immunosuppressive drugs used by the ophthalmologists to treat refractory uveitis, such as azathioprine and methotrexate, do not have much efficacy on the disease activity of SpA.

Some TNF-blocking agents, can be used for both indications, active disease of SpA as well as refractory uveitis. Infliximab is an adequate treatment of SpA, decreases the recurrence rate of uveitis and is effective in refractory uveitis (7, 8). The efficacy of etanercept, on uveitis is doubted, as etanercept does not seem to prevent a relapse in combination with methotrexate (9) and it was suggested that etanercept might even trigger an attack of

uveitis (10). However, a comparison of three randomised studies with etanercept in AS showed a lower number of cases with uveitis in the etanercept-treated patients compared with placebo (11) indicating that etanercept inhibits the recurrence of uveitis.

An analysis of 4 placebo-controlled studies and 3 open-label studies with TNF agents in AS showed a frequency of flares of anterior uveitis in the placebo-group of 15.6 per 100 patient-years, compared with 7.9 per 100 patient-years in etanercept group and 3.4 per 100 patient-years in the infliximab treated patients (8). The attacks of uveitis during these studies were reported by the patients and no follow up studies or ophthalmologic controls were performed.

Reports on the efficacy of adalimumab for uveitis are based on a large, prospective study in 1250 AS patients that received open-label treatment for up to 20 weeks (12): 15 uveitis flares per 100 patient-years were noted before start of adalimumab treatment; the overall rate of flares was reduced with 51% in all patients, with better results seen in those patients that had a prior history of uveitis. In a prospective study, AS patients were treated with adalimumab because of high disease activity, and screened by an ophthalmologist for uveitis as well. This study demonstrated a significant decrease (73%) of the recurrence rate of uveitis (13) during adalimumab treatment.

Recent reports show that golimumab (14,15) and certolizumab also seem to be effective in refractory uveitis (16).

It can be concluded that in most cases, attacks of anterior uveitis respond very well to (local) treatment by the ophthalmologist. In cases with refractory uveitis or a high uveitis recurrence rate, treatment with TNF blocking agents can be successful, especially if the treatment is indicated for high disease activity of SpA. Adalimumab and infliximab seem to be more effective in lowering the recurrence rate of uveitis compared to etanercept, and certolizumab and golimumab are effective in refractory uveitis.

Psoriasis

Psoriasis is a common skin disease with plaque lesions and nail deformities and is primarily treated by the dermatologist. Psoriatic arthritis occurs in 5-20% of the people with psoriasis and can present as a symmetrical polyarthritis, resembling rheumatoid arthritis, but with additional involvement of the DIP-joints (17). Axial disease occurs in about 5% of the psoriasis patients with asymmetrical sacroiliitis in one-third of the cases and spondylitis without sacroiliitis in the rest. Enthesitis and dactylitis are common, especially in the oligoarticular form of the disease. In SpA, patients with psoriatic arthritis excluded, psoriasis occurs in approximately 5-10%.

In case of scaling skin lesions or nail changes suspicious for psoriasis in SpA it is recommended to refer the patients to a dermatologist.

Skin manifestations of psoriasis usually respond very well to local corticosteroids or PUVA therapy.

In case of psoriatic arthritis, NSAID's and intra-articular injections with corticosteroid are effective in mono- or oligoarthritis (18), but these treatments do not influence skin disease. Methotrexate is widely used in daily clinical practice for the treatment of skin disease and arthritis, despite the lack of randomized controlled trials to support this (18). Leflunomide is also effective for both psoriasis and peripheral arthritis, but not for the axial manifestations of SpA (19).

TNF alfa blockers, such as infliximab, etanercept, adalimumab, certolizumab and golimumab are efficacious on the skin and nail lesions of psoriasis (table 1) (15). In some cases treatment of SpA with TNF blocking agents can result in a new paradoxical manifestations of psoriasis, such as palmoplantar pustulosis (20). New biologicals, such as the interleukin (IL) 12/23 inhibitor ustekinumab (21) and the anti-IL17A monoclonal antibody secukinumab (22), are very effective for psoriasis and psoriatic arthritis (and for AS for secukinumab while results of placebo-controlled trials with ustekinumab in patients with AS are awaited).

Inflammatory Bowel Disease

Inflammatory Bowel disease includes Crohn's disease and ulcerative colitis and is primarily treated by the gastro-enterologist. Approximately 10% of the IBD patients develop SpA. On the other hand, the chance of SpA patients to develop IBD is 5-10%. Asymptomatic inflammatory bowel disease is described in a high percentage of SpA patients (up to 60%) and can be detected by endoscopy of the colon and terminal ileum (23). During follow up studies, it appeared that up to 20% of the SpA patients with chronic gut inflammation eventually develop Crohn's disease (24). Another indication that diseases as SpA and IBD show some overlap comes from a study on serological markers of IBD. In this study, a high percentage (55%) of AS patients without abdominal complaints had a positive tests for pANCA, ANCA or Omp-C ASCA antibodies (25). In case of persistent or frequently recurring diarrhoea and/or blood or mucus production with the stools it is advised to refer SpA patients to the gastro-enterologist in order to perform an ileocolonoscopy.

Treatment of IBD by the gastro-enterologist is based on immunosuppressive drugs and anti-TNF. Although good quality evidence is lacking, the use of NSAIDs is assumed to worsen colitis manifestations, therefore it is advised that SpA patients with IBD should minimise the use of these drugs, perhaps with the exception of celecoxib, which does not seem to increase the risk of exacerbation of IBD (26). The use of sulfasalazine can be beneficial for both SpA as well as IBD. Other immunosuppressive drugs used for the treatment of IBD, such as azathioprine, have no proven efficacy in SpA (27). Of the TNF blocking agents only infliximab and adalimumab are effective in both Crohn's disease and ulcerative colitis (28-31). Golimumab shows efficacy in ulcerative colitis but is not tested in Crohn's disease (32) whereas certolizumab is effective in Crohn's disease but not tested for ulcerative colitis (33). Etanercept was evaluated in a small trial for Crohn's disease and did not show

efficacy (34), while there is even data to suggest that new manifestations of IBD might occur during treatment of SpA with etanercept (35-37) (table 1).

Regarding new mode-of-action biologics, ustekinumab was shown to be effective in patients with moderate to severe Crohn's disease that was resistant to TNF antagonists (38); patients with an initial response had significantly increased rates of response and remission with ustekinumab as maintenance therapy. Interestingly, the anti-IL17A agent secukinumab was ineffective in a placebo-controlled proof-of-concept study in 59 patients with Crohn's disease, with unexpectedly also higher rates of adverse events compared with placebo (39).

Table 1: TNF inhibitors and extra-spinal manifestations in SpA

	Arthritis	Uveitis	Ulcerative colitis	Crohn's disease	Psoriasis
infliximab	+	+	+	+	+
adalimumab	+	+	+	+	+
etanercept	+	+/-	-	-	+
golimumab	+	+	+	?	+
certolizumab	+	+	?	+	+

Legend table 1: + effective, - not effective, ? no data

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Conclusions

In SpA physical exercises and NSAID's are the choice of treatment. In case of peripheral arthritis, sulphasalazine can be added as a useful DMARD. In case of insufficient response to NSAIDs, TNF blockers are very effective in SpA. These drugs all work very well on the axial manifestations as well as on arthritis, enthesitis and dactylitis. For skin and nail psoriasis, TNF antagonists also have a proven beneficial effect and other biological drugs targeting the IL-12/23 or IL-17 pathway have also been approved for treatment of moderate-to-severe psoriasis.

Concerning the treatment of other extra spinal manifestations, anterior uveitis can be treated adequately by the ophthalmologist with local treatment. In refractory cases or a high recurrence rate, treatment with

adalimumab and infliximab seems to be more effective for this indication compared to etanercept, with emerging positive data for golimumab and certolizumab, pointing towards a global better efficacy of monoclonal antibodies compared to the TNF-receptor fusion protein. The same phenomenon is observed in cases of SpA with concurrent IBD. The use of NSAIDs should be limited to short, intermittent courses. When anti-TNF therapy becomes necessary in SpA patients with IBD, monoclonal antibodies should be prescribed, since etanercept was shown to be ineffective for the treatment of Crohn's disease.

In second line of biologic drugs, after anti TNF alpha failure, ustekinumab and secukinumab can be used in case of active psoriasis, probably also in case of active or recurrent uveitis; in case of active IBD, secukinumab should be avoided and ustekinumab preferred. Overall, it is important to realize that in SpA extra-articular manifestations do occur frequently and should be taken into account when treatment choices have to be made (40).

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Measuring disease activity and damage in inflammatory arthritis

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LEARNING OUTCOMES

- ➔ Describe and explain which assessments are available to assess disease activity and damage in patients with rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis
- ➔ Explain the difference between response and status criteria
- ➔ Apply assessments in the follow-up of patients in clinical practice
- ➔ Interpret data from clinical trials using the discussed assessments

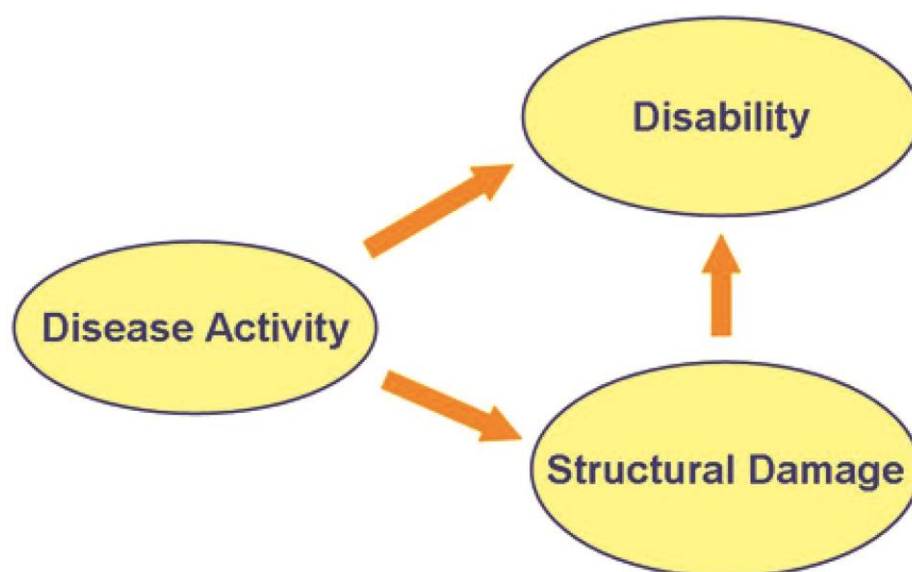
In daily clinical practice every clinician is using implicit and explicit assessments. An example of an implicit assessment is 'the patient is doing well', and an example of an explicit assessment is 'on a 10-point scale the patient's global health is 8 (with 10 being the best possible)'. It has been recognised for many years that for optimal treatment, monitoring of outcomes with explicit assessments is essential. This chapter describes the principles of assessment and the most frequently used assessments in monitoring after the diagnosis has been made. The content focuses on the application in clinical practice and the interpretation of published data from studies. For the general introduction, rheumatoid arthritis (RA) has been used as the classical representative of the inflammatory joint diseases. The sections on the specific assessments are tailored towards the three individual diseases: rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis.

1 General

1.1 Concept of disease activity, function and damage

In RA there is a clear relationship between disease activity, function, and damage (figure 1). Both in early and late disease there is a close relationship between disease activity and (physical) function. Moreover, in all stages, disease activity causes damage that is visible on, for example, radiographs and magnetic resonance imaging (MRI). In longstanding disease there is a close relationship between damage and function. To get a complete picture of the disease, these three aspects (disease activity, function, damage) need to be assessed. The most widely applied instrument to assess function is the Health Assessment Questionnaire (HAQ). The assessment of function is beyond the scope of this chapter (for more detailed information see chapter 9 on pathogenesis and clinical aspects of RA).

Figure 1 Relationship between disease activity, structural damage and disability in rheumatoid arthritis.



Importantly the assessment of disease activity can be based on a clinical evaluation by a health professional (e.g. swollen joint count), on technical investigations (e.g. laboratory tests, imaging, etc.), but also on so-called patient reported outcomes. These are assessments that are reported by the patient, which deal with different aspects of disease activity (e.g., morning stiffness, pain), but also with function as assessed by the HAQ. Patient-reported measures have gained a lot of interest in recent years as these are of great importance to the patient. However, the combination of patient-reported measures with clinical assessments, laboratory and imaging results gives the most complete picture.

1.2 Why is it important to measure (tailor-made treatment)?

It has been shown in several studies that a subjective global assessment of disease activity by doctors underestimates the amount of inflammation (disease activity). This is true, both if the doctor's global assessment (e.g. on a visual analogue scale) is compared with clinical disease activity measures or with inflammation as assessed by ultrasound. A few decades ago it was of less importance if a patient still had some residual disease activity, as no effective treatments were available. Currently, treatments are available that can bring about complete disease remission. To be able to provide optimal treatment to a patient (so called tailor-made treatment) it is important to be well informed about the actual disease activity. The present goal is to help a patient as quickly as possible into longstanding remission. Regular disease activity assessments are necessary to judge if this goal has been reached or whether adjustments to treatment need to be made. For example, the TICORA (Tight Control in RA) trial (Grigor et al, 2004) showed that treatment with predefined goals of disease activity, and adjustment of treatment according to the level of disease activity, resulted in more patients entering remission compared to traditional clinical practice. Other trials applying this so-called "treat-to-target" principle and comparing various treatment strategies with predefined treatment goals are the BeSt trial (BeSt is the Dutch acronym for "Behandelstrategieën", which stands for treatment strategies, Goekoop-Ruiterman et al, 2010) and the Belgian CareRA trial (acronym for "Care for early RA", Verschueren et al, 2016).

Overall, there is a causal relationship between clinically assessed disease activity (e.g., by the number of swollen joints) and the development of damage in joints. This is true even when individual joints are assessed: swelling in a particular joint leads to damage in the same joint. Vice versa, absence of swelling in an individual joint is directly linked to repair of damage in the same joint, while repair does not occur in joints with persistent swelling. However, this relationship is not always as expected. Some patients in clinical remission still show progression of radiographic damage. On the other hand, in some studies (e.g. in the ATTRACT study, Smolen et al, 2005) patients treated with a TNF blocker, especially if in combination with methotrexate, show less radiographic damage even if there is persistent disease activity. More information is needed to understand these data fully. However, this indicates that imaging is important in addition to disease activity assessment for a full understanding of what is happening to a patient.

1.3 Core set (definition)

Many instruments are available to assess disease activity in inflammatory diseases. Before the implementation of core sets, these were all used according to the personal preference of the investigators in various studies. But if different instruments are included in various clinical trials it is hard to compare data across trials. Moreover, if many assessments are included in a clinical trial there are problems with multiple statistical tests, and there is always the risk of presenting only the data with positive results. To overcome these problems, core sets have been defined for the inflammatory diseases. A **core set** is a *group of assessments that should be included and reported in each study as a minimum*. In addition, other measures may be used to examine a specific study question.

The definition and use of core sets has led to a standardisation of clinical trial design and reporting. Core sets are defined for use in studies but sometimes also for use in clinical practice.

1.4 Single versus composite measures (pros and cons)

As the inflammatory diseases are heterogeneous, no single instrument can describe the disease process well for every patient. For example, some patients have a relatively normal erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) with a high number of swollen joints; for other patients this may be the other way round. Examining only the ESR would not give a correct reflection of the level of disease activity in these two patients. But both ESR and the number of swollen joints give some information about the underlying process of inflammation. The many available instruments reflect different parts of the underlying disease process, and several of them overlap partly or largely. This concept has led to the development of **combined disease activity measures (composite scores)**. These combine the information from various instruments that describe the underlying disease process, but with minimum overlap.

In general, composite scores more accurately reflect the overall state of the disease compared to individual measures; this does not dispute the fact that there may be times when single construct measures are more appropriate for judging a specific outcome, because the intervention is directed primarily at one construct and not necessarily meant to produce a global change. The most widely used composite measure is the Disease Activity Score (DAS), which has been shown to have a closer relationship with radiographic progression and function than single variables. Another advantage is that it can be used to better describe disease activity across patients with different expressions of the disease process. Furthermore, the overall advantage of using composite scores is their wider applicability to various groups of patients and the reduction in sample size needed in clinical trials to obtain the same power to detect a difference between groups.

1.5 Response versus status measures

Core sets include individual assessments and in trial reports these should be presented for the group at baseline as well as at follow-up and over the treatment period. This information is presented at a group level and is hard to interpret for a clinician. If the average number of swollen joints is reduced from 12 to seven, what does this tell us about the benefit for an individual patient? Moreover, single instruments do not give the full picture of disease activity. These two factors led to the development of **response criteria**. The application of response criteria demonstrates whether a patient has responded to a certain treatment. The advantage for the interpretation is that the clinician now gets information on how many patients respond to a certain treatment. This can more easily be translated into useful information for making treatment decisions in clinical practice. Response criteria are mainly used in clinical trials and less in clinical practice. The main disadvantage is that response criteria compare only the follow-up assessment with baseline but do not take into account what is happening in between. For example, if a patient shows a sustained response after 2 weeks of treatment or after 50 weeks of treatment, both are counted as responders at the end of the trial at week 52. Thus, time to response and stability of response are important factors that also need to be taken into account.

In order to increase interpretability, disease activity measures require criteria for identifying disease activity states (or status) and improvement (or response criteria). **Response measures** help to determine whether treatments really work—that is, whether they actually produce clinically important improvement—allowing investigators, clinicians, regulators and patients to determine the efficacy (or lack thereof) of a given intervention and to communicate about response using the same metric. **Disease activity states (status measures)** measure clinical disease activity at specific time points and are important for supporting decisions about entry into clinical trials, for supporting treatment changes, and for defining therapeutic goals.

The baseline value always plays an important role during each follow-up assessment if based on a response criterion—for example, at weeks 2, 12, 24, 52 there is always a comparison with the baseline value. Especially with a longer follow-up, this is a disadvantage. In addition, responder status does not give, or only partially gives, information about the level of disease activity reached. Here the adage applies: ‘it is good to be better, but it is better to be good’. To assess if a patient is in a ‘good condition’, or has low disease activity or is in remission or in a ‘patient-acceptable symptom state (PASS)’, various composite measures with validated cut-offs have been developed. The effect of treatment on an individual patient can be best described if the information on both the response and the achieved level of disease activity is used.

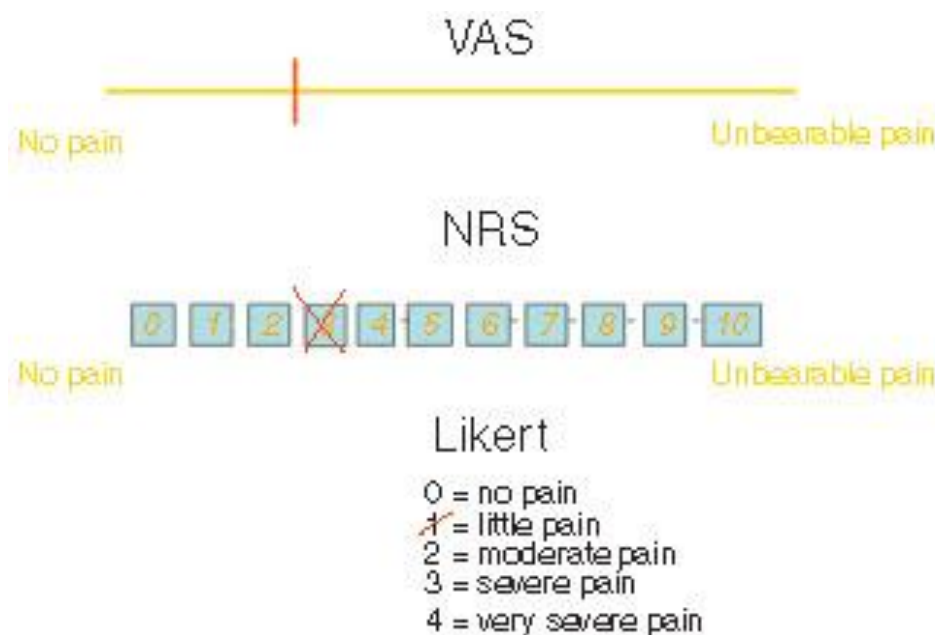
PASS is a relatively new concept. This is the maximum level of symptoms (which can be defined separately—for example, pain and function) with which patients consider themselves to be well for a certain period of time. In defining PASS, various definitions for time have been used, ranging from no time specified (current

state), or the next few months, to the rest of the patient's life. Validation of PASS for various diseases, across languages and cultures, and testing for stability over time is underway.

1.6 Answer modalities

For the patient-reported instruments various answer modalities can be used. Most widely used are the (horizontal) visual analogue scale (VAS), the numerical rating scale (NRS) and the verbal rating scale (Likert) (figure 2). The VAS is usually a horizontal line marked at the left and right ends with the two extreme options in wording (e.g. no pain and most extreme pain) and no marks on the line. The patient is asked to tick the line describing his or her situation best. The VAS is usually 10 cm long and can be measured in millimetres or centimetres. The assessment from the left (e.g. no pain) to the tick gives the result. The NRS is a line with numbers reflecting the entire range, most frequently from 0 to 10. At the extremes the same wording is presented as for the VAS. Again the patient is asked to tick the number that describes his or her situation best. The value can be read off immediately. The Likert scale describes the various possibilities with words—for example, no pain, a little pain, moderate pain, severe pain, and very severe pain. The patient selects the word that describes his or her situation best.

Figure 2 Visual analogue scale (VAS), numerical rating scale (NRS), and Likert scale.



The disadvantage of the Likert scale is that it is difficult in multicultural situations to obtain the exact meaning of scale terms in another language. Moreover, the distance between the various categories is not equal and consequently a change from very severe to severe pain is not necessarily the same as an improvement from severe to moderate pain. The theoretical advantage of the VAS is that there are 101 different answer options with possibly higher sensitivity to change. In a comparative study the reproducibility and sensitivity to change of the VAS and NRS were similar. Moreover, patients preferred the NRS over the VAS. Other advantages of the

NRS are that there can be no errors in making a copy (resulting in a line that is no longer exactly 10 cm) or measuring the distance, and that the NRS can also be applied in telephone interviews. Whenever the VAS is further mentioned in this module it could also be replaced by an NRS. In clinical practice, especially, the NRS seems to be the most feasible answer modality (Van Tubergen et al, 2002).

2 Rheumatoid arthritis

2.1 Core set

Box 1 presents the American College of Rheumatology (ACR) core set for RA. In summary, this includes: three VAS (the doctor and patient global assessment of disease activity and patient perception of pain), two joint counts (the number of tender joints and the number of swollen joints assessed by the physician), one laboratory measure (ESR or CRP), a measure for function (usually the HAQ), and a measure for damage in trials of at least 1 year's duration.

Box 1 American College of Rheumatology (ACR) core set

- Tender joint count
- Swollen joint count
- Patient pain assessment
- Patient global assessment
- Doctor global assessment
- Function
- Acute phase reactant
- Radiographic analysis

Important patient-reported outcomes not included in the core set are related to fatigue and sleep. These are important complaints and might therefore yield additional information. Several instruments to assess fatigue in detail are available, but also a simple VAS on the level of fatigue can already provide sufficient information. Furthermore, to obtain a more complete picture of the disease impact on the lives of rheumatoid arthritis patients, composite patient-reported outcome measures like the RA Impact of Disease (RAID) instrument should be considered in future trial design (Gossec et al, 2011).

Joint counts have always been the backbone of RA disease activity evaluation. There are several joint counts in use (table 1). These differ in the number of joints assessed. Joint counts range from 28 to 74 for swelling, and from 28 to 76 for tenderness. Some scores give a weight to the abnormality and others just score absence or

presence. Moreover, most joint counts assess the number of tender and swollen joints independently, but few scores combine tenderness and swelling. These last scores are not popular. On a group level, reduced joint counts with 28 joints perform as well as more extensive joint counts, and giving weight to the level of tenderness or swelling does not improve the performance of a score. However, the 28-joint counts do not include the feet and this might be inappropriate in clinical practice in individual patients. The most commonly used joint counts will be described in more detail.

Table 1 Joint counts in rheumatology

Joint	74/76 joints	66/68 joints swelling/tenderness	Ritchie articular index (53 joints) tenderness	44 joints swelling	28 joints swelling tenderness
Temporomandibular	+	+	+ [†]		
Sternoclavicular	+	+	+ [†]	+	
Acromioclavicular	+	+	+ [†]	+	
Shoulder	+	+	+	+	+
Elbow	+	+	+	+	+
Wrist	+	+	+	+	+
MCP	+	+	+ [‡]	+	+
PIP (hands)	+	+	+ [‡]	+	+
DIP (hands)	+	+			
Hip	+*	+*	+		
Knee	+	+	+	+	+
Ankle	+	+	+	+	
Talocalcaneal			+		
Tarsus	+	+	+		
MTP	+	+	+ [‡]	+	
PIP (feet)	+	+			
DIP (feet)	+				

*Hip joints are not assessed for swelling.

†Both sides calculated as a single unit.

‡Each group of joints from each side calculated as a single unit.

DIP, distal interphalangeal; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

The Ritchie articular index (figure 3A) is a weighted joint score based on tenderness. All joints are assessed separately. However, the proximal interphalangeal (PIP) joints of each hand, the metacarpophalangeal (MCP) joints of each hand, the metatarsophalangeal (MTP) joints of each foot, the temporomandibular joints, the sternoclavicular joints, and acromioclavicular joints are calculated as a single unit. The highest score for a

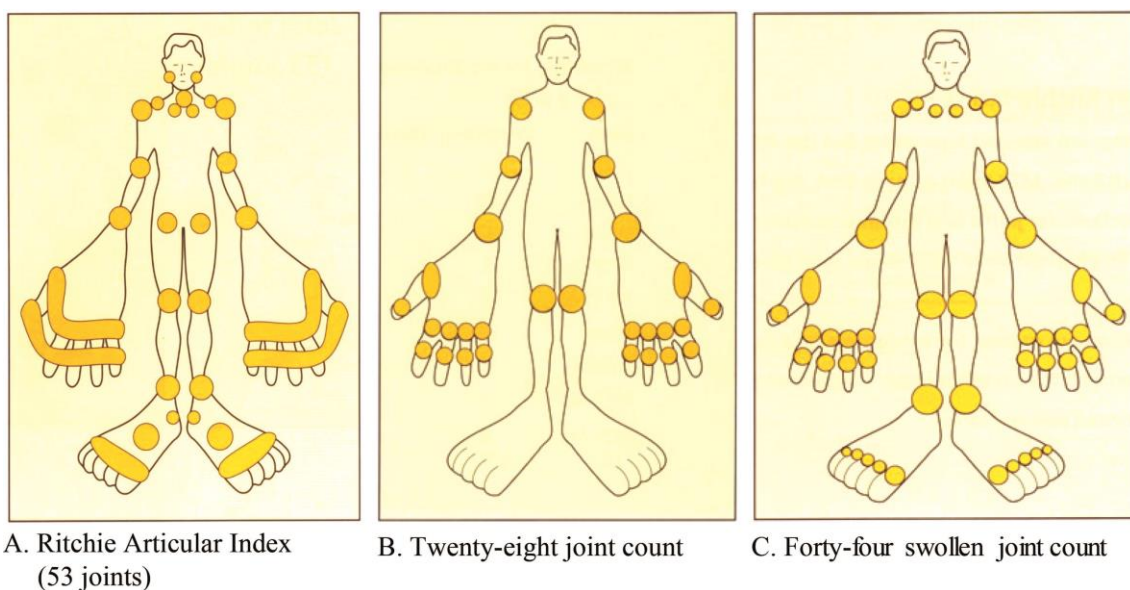
single joint gives the score for the group. The joints are graded for tenderness on a 0–3 scale, with 0 = no tenderness, 1 = pain on pressure, 2 = pain and winced, and 3 = winced and withdrew.

The 68-tender joint count is not graded, resulting in a range of 0 to 68.

The 28-joint count excludes mainly the ankles and feet and is again not graded, with a range from 0–28 (figure 3B).

For the assessment of swelling the following joint counts are widely used: the 66-, 44- (figure 3C) and 28-joint counts. All are ungraded and range from 0–66, 0–44, and 0–28, respectively.

Figure 3 Commonly used joint counts.



2.2 Composite measures

For the assessment of disease activity in RA several composite measures have been developed. A widely used composite disease activity score is the **DAS** or one of its modifications. The original DAS comprises *four* variables, including the Ritchie articular index, the 44-swollen joint count, ESR, and patient global assessment of wellbeing (box 2) (*Van der Heijde et al, 1993). The VAS on global wellbeing can either be omitted, resulting in a DAS based on *three* variables, or is frequently replaced by the patient global assessment of disease activity. As these two VAS are closely linked, results with either of the two VAS are comparable. In the DAS with three variables a constant correction factor is included to ensure comparability between DAS4 and DAS3 (on a group level). The multiplication factors in the formulae are derived statistically to obtain the most informative combination of the assessments.

Box 2 DAS formulas

- **DAS (four variables):** $0.54 \times v(\text{Ritchie}) + 0.065 \times (\text{SJC44}) + 0.33 \times \ln(\text{ESR}) + 0.0072 \times (\text{general health})$
- **DAS (three variables):** $0.54 \times v(\text{Ritchie}) + 0.065 \times (\text{SJC44}) + 0.33 \times \ln(\text{ESR}) + 0.22$
- **DAS-CRP (four variables):** $0.54 \times v(\text{Ritchie}) + 0.065 \times (\text{SJC44}) + 0.17 \times \ln(\text{CRP} + 1) + 0.0072 \times (\text{general health}) + 0.45$
- **DAS-CRP (three variables):** $0.54 \times v(\text{Ritchie}) + 0.065 \times (\text{SJC44}) + 0.17 \times \ln(\text{CRP}+1) + 0.65$

CRP, C reactive protein (mg/L); DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; ln, natural logarithm; SJC44, 44-swollen-joint count.

At a later stage the **DAS28** was developed to replace the Ritchie articular index and the 44-swollen-joint count with the more feasible 28-joint count for both tenderness and swelling (box 3) (*Prevoo et al, 1995). In general, the values for the DAS28 are somewhat higher than the values of the DAS. This can also be seen on the cut-off levels for remission and low disease activity (see below).

Box 3 DAS28 formulas

- **DAS28 (four variables):** $0.56 \times v(\text{TJC28}) + 0.28 \times v(\text{SJC28}) + 0.70 \times \ln(\text{ESR}) + 0.014 \times (\text{general health})$
- **DAS28 (three variables):** $[0.56 \times v(\text{TJC28}) + 0.28 \times v(\text{SJC28}) + 0.70 \times \ln(\text{ESR})] \times 1.08 + 0.16$
- **DAS28-CRP (four variables):** $0.56 \times v(\text{TJC28}) + 0.28 \times v(\text{SJC28}) + 0.014 \times \text{GH} + 0.36 \times \ln(\text{CRP} + 1) + 0.96$
- **DAS28-CRP (three variables):** $[0.56 \times v(\text{TJC28}) + 0.28 \times v(\text{SJC28}) + 0.36 \times \ln(\text{CRP}+1)] \times 1.1 + 1.15$

CRP, C reactive protein (mg/L); DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; ln, natural logarithm; GH, general health; SJC28, 28-swollen-joint count; TJC28, 28-tender-joint count.

Formulas for DAS and DAS28 using CRP instead of ESR are available (box 2 and 3). The DAS28 CRP was found to be related to radiographic progression and function; however, this was less pronounced as was demonstrated for the DAS28 ESR and the two measures are not exchangeable (Wells et al, 2009). Also other studies showed that DAS/DAS28 with ESR versus DAS28 with CRP do not behave similarly. At the individual level DAS28 CRP is often lower than DAS28 ESR, particularly in females and patients with long disease duration. Therefore, switching between different types of DAS scores in daily clinical practice should be avoided. An online DAS/DAS28 calculator is available at: <http://www.das28.nl/das28/DAScalculators/dasculators.html>.

In recent years two new composite scores have been published summing five variables from the ACR core set without transformation and without weighting (box 4). However, owing to the differences in range of the various variables there is an implicit weighting in these scores.

Box 4 SDAI and CDAI formulas

- **SDAI (five variables):** SJC28 + TJC28 + Patient global health (VAS; 0–10) + Physician global (VAS; 0–10) + CRP(mg/dL)
- **CDAI (four variables):** SJC28 + TJC28 + Patient global health (VAS; 0–10) + Physician global (VAS; 0–10)

CDAI, Clinical Disease Activity Index; CRP, C reactive protein; SDAI, Simplified Disease Activity Index; SJC28, 28-swollen joint count; TJC28, 28-tender joint count; VAS, visual analogue scale.

The **Simplified Disease Activity Index (SDAI)** is the sum of the 28-swollen joint count, the 28-tender joint count, and the patient and investigator global assessments of disease activity on a 10 cm VAS and CRP in mg/dL (*Aletaha et al, 2005). The **Clinical Disease Activity Index (CDAI)** is a modification of the SDAI without the laboratory parameter CRP to allow immediate clinical assessment.

Finally, at the individual level, it is important to highlight that the doctor should be critical about the result of any composite score (as for any type of assessment). For example, in patients with chronically elevated acute-phase reactants not related to RA, the disease activity may be overestimated by the RA-unrelated high CRP/ESR value, and in patients with RA and fibromyalgia disease activity may also be overestimated if fibromyalgia is contributing to patient global assessment and level of tenderness in the joints.

2.3 Response criteria

There are two widely applied types of response criteria for RA: the ACR response criteria and the European League Against Rheumatism (EULAR) response criteria (*Felson et al, 1995; *van Gestel et al, 1996). The **ACR criteria** (box 5) are based on the variables included in the core set. These criteria are referred to as the ACR20, ACR50 and ACR70 response criteria, depending on the required percentage of improvement. A response in both tender and swollen joint counts is obligatory; in addition, three out of the five remaining variables should show a response.

Box 5 ACR improvement criteria

≥20% (ACR20), ≥50% (ACR50) and ≥70% (ACR70) improvement in:

- Tender joint count
- Swollen joint count

and ≥20% (ACR20), ≥50% (ACR50) and ≥70% (ACR70) improvement in three of the following:

- Patient pain
- Patient global
- Assessor global
- Disability
- Acute phase response (ESR/CRP)

ACR, American College of Rheumatology; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

The **EULAR response criteria** are based on the DAS or on the DAS28 (tables 2 and 3). EULAR response criteria are defined as ‘no’, ‘moderate’ or ‘good’ response. The ACR response criteria are based on a percentage change only, in contrast to the EULAR criteria, which are based on an absolute improvement and the level of disease activity achieved.

Table 2 EULAR response criteria

DAS at end point	Improvement in DAS from baseline		
	>1.2	>0.6 and ≤1.2	≤0.6
≤2.4	Good	Moderate	None
>2.4 and ≤3.7	Moderate	Moderate	None
>3.7	Moderate	None	None

DAS remission <1.6. DAS, Disease Activity Score.

Table 3 EULAR response criteria

DAS28 at end point	Improvement in DAS28 from baseline		
	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	Good	Moderate	None
>3.2 and ≤5.1	Moderate	Moderate	None
>5.1	Moderate	None	None

DAS28 remission <2.6. DAS28, 28-joint Disease Activity Score.

2.4 Remission, low disease activity

In addition to response criteria, cut-off points to define if a patient is in (clinical) remission or in a state of low disease activity have been developed for the various composite measures (table 4). These measures are becoming more important because they are used as the current treatment goal.

Table 4 Cut-off values for various composite measures

Disease activity	DAS	DAS28	SDAI	CDAI
High	>3.7	>5.1	>26	>22
Moderate	≤3.7	≤5.1	≤26	≤22
Low	≤2.4	≤3.2	≤11	≤10
Remission	<1.6	<2.6	≤3.3	≤2.8

CDAI, Clinical Disease Activity Index; DAS, Disease Activity Score; DAS28, 28-joint Disease Activity Score; SDAI, Simplified Disease Activity Index.

Remission is now included as an endpoint for clinical trials and observational studies and is also a major therapeutic target in clinical practice. Remission should be understood as a near complete suppression of

disease activity or absence of any discernible disease activity. Due to limitations in the various definitions of remission and recognizing its importance as a crucial goal in current RA management, ACR and EULAR set up a task force to redefine the concept and published a new definition in 2011 (box 6) (*Felson et al, 2011). Since in the clinical setting CRP is sometimes not available at every visit, an alternative definition of remission without CRP was proposed for daily practice.

Box 6 ACR/EULAR 2011 provisional definition of RA remission

For clinical trials:

Boolean-based definition

At any time point, patient must satisfy all of the following:

- Tender joint count ≤ 1
- Swollen joint count ≤ 1
- Patient global assessment ≤ 1 (0–10 scale)
- C reactive protein ≤ 1 mg/dL

Index-based definition

- Simplified Disease Activity Index score ≤ 3.3

For clinical practice:

Boolean-based definition

At any time point, patient must satisfy all of the following:

- Tender joint count ≤ 1
- Swollen joint count ≤ 1
- Patient global assessment ≤ 1 (0–10 scale)

Index-based definition

- Clinical Disease Activity Index score ≤ 2.8

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis.

2.5 Frequency of monitoring

The minimum frequency of monitoring for implementing effective treatment during the active phases of the disease is 3-monthly. When a patient is in persistent remission, this can be reduced to 6-monthly follow-ups.

2.6 Imaging assessment

2.6.1 Conventional radiographs

Radiographic imaging is the imaging method most widely used in the diagnosis of RA and to follow the course of the disease and effectiveness of treatment (*Van der Heijde et al, 2004).

A series of radiographs comprises the simplest and cheapest permanent record of the cumulative joint damage caused by the disease. Damage assessed on radiographs is a direct consequence of disease activity, as well as other destructive pathophysiological processes. There is also a close relationship between radiographic damage and other outcome measures, such as functional ability and work disability. As damage is largely

irreversible, structural damage on radiographs is a reflection of cumulative disease activity in the past.

However, more and more reports have shown that repair of damage is possible to some extent. Repair occurs most frequently in patients receiving biologic treatment and in joints with improved swelling (Lukas et al, 2010). More information is needed on how frequently this repair does occur, the significance of the repair (e.g., is a joint with repair functioning better than a joint without signs of repair?), how long it takes to see repair, and how repair may be best assessed.

2.6.1.1 Which abnormalities?

Many abnormalities in joints can be detected on plain films in RA (figure 4). These include soft tissue swelling and proliferation, juxta-articular and diffuse osteoporosis, marginal bony erosions, subchondral cysts, joint space narrowing (JSN) as a consequence of cartilage loss, subluxation and misalignment, ankylosis, sclerosis, and osteophytes in severely damaged joints. Both erosions and JSN are the most specific features in RA and can be assessed reliably. Moreover, they give additive information. Erosions are present in about 80% of patients in most longitudinal cohorts. The majority of patients develop the first erosions within the first year after onset. Erosions both in hands and feet are common early features, often appearing in the feet earlier than in the hands. The wrist is the most common joint for early JSN.

Figure 4 Structural damage in rheumatoid arthritis (arrows showing erosions, lines showing joint space narrowing).



2.6.1.2 Which joints?

Films of the hands and feet are sufficient for both diagnostic and evaluation purposes. Hands and feet are the joints affected in most patients, abnormalities on radiographs can be seen more easily in small joints than in large joints, and structural damage in small joints reflects damage in large joints. Already in the mid-1980s, Scott et al showed in a cross-sectional group of patients that there is a good correlation between damage seen in the hands and that in other joints. This has been confirmed in an inception cohort of middle-aged women, followed up for 12 years. The correlation between damage in the hands and feet and that in large joints was as high as 0.76 (Drossaers-Bakker KW et al, 2000). This indicates that films of hands and feet are satisfactory to follow the course of disease and to monitor efficacy of treatment in individual patients. Films of large joints should only be taken if clinically indicated. An essential finding in that same study was that no patients without erosions in hands and feet showed erosive changes in the large joints. Although RA is a symmetrical disease, imaging of only one hand and one foot would result in considerable loss of information.

2.6.2 Scoring methods: general introduction

The information from radiographs is especially useful if it is quantified. Several scoring methods, which will be discussed later in this chapter, are available.

Selection of the most appropriate scoring method is largely dependent on the setting in which it will be applied. For example, in clinical practice and large cohort studies, feasibility is of major importance, while in clinical trials sensitivity to change drives the selection of a method. Selection of the scoring method also depends on whether data are needed to show progression over a short or a long follow-up period, or are important at a single point in time.

This chapter describes the methods that are used most frequently in research and clinical practice. For a historical overview of all published scoring methods we refer to the literature. Methods applying a global score, and based mainly on the Larsen method, are presented below. This is followed by the presentation of more detailed scoring methods, based mainly on the Sharp method. Table 5 summarises the various characteristics of the scoring methods.

Global score each joint

- ➡ Larsen score (global score combining erosion/JSN; also large joints)
- ➡ modified Larsen score (simplification with better resolution)
- ➡ Scott modification Larsen score (other grading)

Detailed score each joint

- ➡ Ratingen score (only % surface erosion of each joint)
- ➡ Sharp's method (score erosions, JSN separately; only hands)
- ➡ Genant's modification of Sharp's method (can include the feet)
- ➡ Van der Heijde's modification of Sharp's method (also the feet)
- ➡ Simple Erosion Narrowing Score (SENS) (same joints as vd Heijde)

2.6.3 Global assessment for each joint**2.6.3.1 Larsen score (hands and feet +/- large joints)**

The Larsen score applies a grade from 0 to 5 to individual joints (Larsen et al, 1977). This is the only method that can be applied to both large and small joints and a reference atlas with the grades for the various joints is available. The scoring is mainly a combination of erosions and JSN, resulting in a global grade. The original Larsen scoring method includes soft tissue swelling and juxta-articular osteoporosis in grade 1. Only from grade 2 onwards are definite abnormalities, such as erosions, present. Grade 5 represents mutilating abnormality. Several modifications of this scoring system have been published, the most important modification being for use in longitudinal studies. Most studies include only the joints of the hands, wrists and feet. The information in table 5 is based on the original method applied to hands, wrists and feet. In the original Larsen score, the wrist is evaluated as a single joint. In total 32 joints are scored (0-5) and this leads to a scoring range for hands and feet from 0 to 160. The modification by Larsen has amended both the sites to be evaluated as well as the grading, for a more uniform evaluation in studies (Larsen et al, 1995). Most striking is the deletion of soft tissue swelling and osteoporosis for grade 1. Now erosions <1 mm and slight JSN are graded as 1. The number of areas in both hands and feet has been changed. The interphalangeal (IP) and MCP joints of the thumb are no longer included, and neither are the IP nor metatarsophalangeal (MTP) joints of the big toe. In this modification the wrist is scored in quadrants. Therefore, the number of joints assessed remains as 32.

Table 5 Comparison of radiographic scoring methods for rheumatoid arthritis

	Larsen method	Scott modification of Larsen method	Ratigen method	Sharp method	Genant modification of Sharp method	van der Heijde modification of Sharp method	Simple Erosion Narrowing Score (SENS)
<i>Films</i>							
Hands	X	X	X	X	X	X	X
Feet	X	X	–	–	X	X	X
Large joints	X*	–	–	–	–	–	–
<i>Joints included</i>							
PIP/IP	X	X	X	X	X	X	X
MCP	X	X	X	X	X	X	X
Wrist	X	X	X	X	X	X	X
MTP	X	X	–	–	X	X	X
IP1	X	X	–	–	X	X	X
<i>Features scored</i>							
Erosions	–	–	X	X	X	X	X
JSN	–	–	–	X	X	X	X
Misalignment	–	–	–	–	–	X	X
Global	X	X	–	–	–	–	–
<i>Number of joints per hand/foot scored for</i>							
Erosions	–	–	19	17	14	22	22
JSN	–	–	–	18	13	21	21
Misalignment	–	–	–	–	–	‡	‡
Global	16	16	–	–	–	–	–
<i>Range per joint</i>							
Erosions	–	–	0–5	0–5	0–3+ [†]	0–5/0–10 [§]	0–1
JSN	–	–	–	0–4	0–4 [†]	0–4	0–1
Malalignment	–	–	–	–	–	‡	‡
Global	0–5	0–5	–	–	–	–	–
Total	0–160	0–200	0–190	0–314	0–202	0–448	0–86

*Large joints are assessed separately; the remaining information in this table is based on hands and feet.

†Scored per 0.5.

‡Combined with the JSN score.

§Erosions for hands 0–5, for feet 0–10.

IP, interphalangeal; JSN, joint space narrowing; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

2.6.3.2 Scott modification of Larsen's method (hands and feet)

The modification by Scott et al in 1986 is frequently used when the 'Larsen' method is applied. The authors redefined the grading and applied it to the same 32 joints as in the original Larsen method. Moreover, the

wrist is scored as a single joint, but is weighted by a factor of 5 to obtain the total score (0-25). This produces a range for hands and feet of 0–200 (total score of 2 wrists (0-25) and 30 other joints (0-5)).

2.6.3.3 Ratingen score (hands and wrists only)

In this modification of the Larsen score, the grading is entirely based on the surface area of the joints destroyed by erosions (Rau et al, 1998). This is graded from 0 to 5: grade 1, <20%; grade 2, 21–40%; up to grade 5, >80% destroyed. In total 38 joints of the hands including the wrists are scored (0-5), resulting in a range of 0–190.

2.6.4 Detailed scoring methods

2.6.4.1 Sharp's method (hands and feet)

Sharp's method was the first published description of a detailed scoring system for erosions and JSN separately for joints in the hands and wrists. The Sharp method used at present is the modification described in 1985 (Sharp et al, 1985). This reduced the number of joints scored from originally 27 for both erosions and JSN to 17 areas for erosions and 18 for JSN for each hand, which simplified the scoring.

Moreover, the method was developed and validated for scoring the joints of the hands, but nowadays the same methodology is also applied to the joints of the feet (cfr infra: Genant and van der Heijde modification). **Erosions** are scored from 0 to 5 for each joint. Scores are applied as: 0, no erosion; 1, one discrete erosion or involvement of <21% of the joint area by erosion; 2, two discrete erosions or involvement of 21% through 40% of the joint; 3, three discrete erosions or involvement of 41% through 60% of the joint; 4, four discrete erosions or involvement of 61% through 80% of the joint; 5, extensive destruction involving >80%. **JSN** is scored on a 0–4 scale, representing focal narrowing (score 1), joint space loss of <50% (score 2), joint space loss of >50% (score 3), and complete joint space loss or ankylosis (score 4). Subluxation or luxation is not included in the score. The erosion score and the JSN score can be used separately but are usually summed to get the total score.

2.6.4.2 Genant's modification of Sharp's method (hands and feet)

A modification of the Sharp method is described by Genant, which extended the scale for progression from a six-point scale (0 to 5) to an eight-point scale with 0.5 increments from 0 to 3+ for erosions, and from a five-point scale (0 to 4) to a nine-point scale with 0.5 increments from 0 to 4 for JSN (Genant, 1983). This score is applied in 14 joints of each hand and wrist for erosions and in 13 joints for JSN. This results in a total score range of 0–202. Frequently, this is normalised to a 200-point scale.

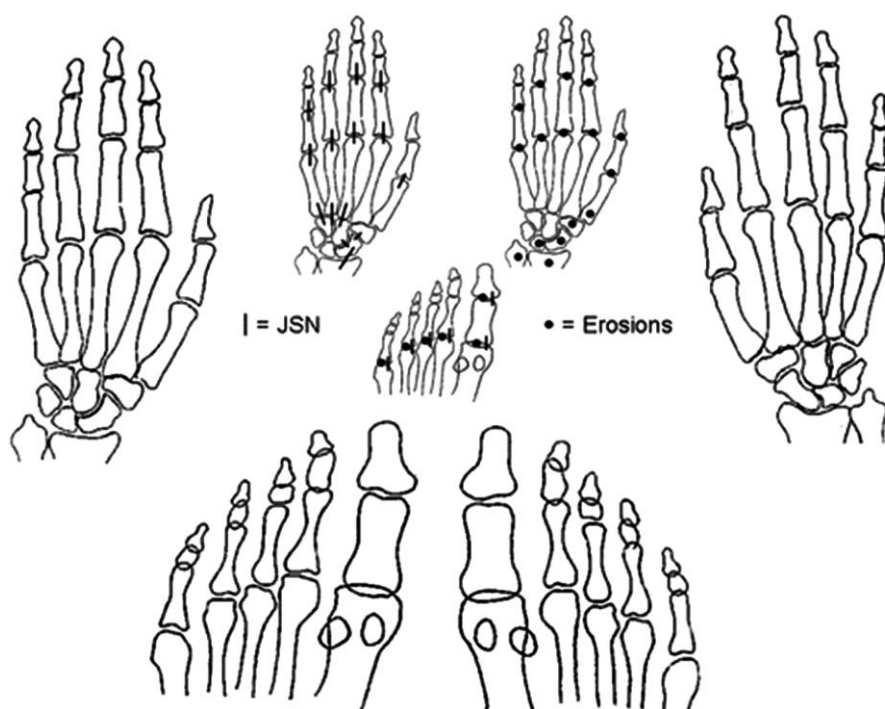
2.6.4.3 van der Heijde's modification of Sharp's method (hands and feet)

The main modification by van der Heijde was the addition of six joints for each foot to the scoring system (see figure 5) (van der Heijde, 1999). Moreover, in the hands one site for erosions and three sites for JSN were deleted from the scoring areas as compared with the Sharp's method as described in 1985, leaving 16 sites for erosions and 15 for JSN for each hand. The scoring of **erosions** in the hands remained the same with a range of 0–5 for each joint. However, for the scoring of erosions in the feet the scoring range was expanded to 10 per joint, with a maximum of five for the metatarsal and phalangeal site of the joint. Another major difference is that subluxation and luxation (misalignment) are integrated in the grading of JSN. **JSN** is scored on a 0–4 scale, with the same grading as described for the Sharp method. But in this modification a score of 3 can also be applied in the case of subluxation of a joint and a score of 4 in the case of complete luxation. These features are mostly scored in MCP joints and MTP joints. In total 2x6 sites in the feet (maximum 10) and 2x16 sites in the hands (maximum 5) are scored for erosions (range 0-280). For JSN 2x6 sites in the feet and 2x15 sites in the hands ((maximum 4) are scored (range 0-168). The scoring range for the total score is 0–448 (erosion score + JSN score).

2.6.4.4 Simple Erosion Narrowing Score (hands and feet)

The Simple Erosion Narrowing Score (SENS) is based on the same joints included in the van der Heijde modification of Sharp's method for hands and feet (figure 5). Instead of scoring the joints for erosions and JSN, this is a simple counting of the number of eroded joints and the number of narrowed joints. A score of 1 is applied if a site is eroded and also for each narrowed site. In total 16 joints per hand are scored for erosions and 15 for JSN, and six joints per foot for both erosions and JSN, leading to a scoring range from 0 to 86. A score form that can be used for the SENS is available (figure 5).

Figure 5 Scoring sheets for radiographs (*Simple Erosion Narrowing Score (SENS) method*). JSN, joint space narrowing.



2.6.5 Assessment of structural damage in clinical practice

Several scoring methods are available for use in clinical trials. Most widely used are the Larsen and Sharp methods with several modifications. However, they are not very practical for use in clinical practice. Therefore, the above-described SENS method was developed and tested. The method is easy to learn and easy to apply in clinical practice and takes only a few minutes. An increase of 1 in the score (equivalent to a newly eroded or narrowed joint) can be considered as progressive disease. It is recommended that annual radiographs of hands and feet are taken, and also for patients in clinical remission. If patients remain in persistent remission and do not show progression of structural damage, the frequency of taking radiographs can be reduced.

2.7 Magnetic resonance imaging

Conventional radiography, although the most widely used imaging method in RA, has limitations. It is not sensitive for detecting early disease manifestations such as soft tissue inflammation—that is, it cannot be used to assess current disease activity and it does not visualise the earliest stages of bone erosion. In contrast, magnetic resonance imaging (MRI) and ultrasonography (US) allow direct visualisation of early inflammatory as well as early destructive joint changes in RA (McQueen et al, 2007; Østergaard et al, 2008).

2.7.1 Which abnormalities?

MRI provides multiplanar tomographic imaging with unprecedented soft tissue contrast, without the use of ionising radiation, and allows assessment of all the structures involved in arthritic disease—that is, synovial

membrane, intra- and extra-articular fluid collections, cartilage, bone, ligaments, tendons, and tendon sheaths. It has been shown to be more sensitive than clinical examination and radiography for detection of inflammatory and destructive joint changes in early RA. MRI and histopathological signs of synovial inflammation are closely correlated and in a study of MCP joints in patients with early and established RA, mini-arthroscopy confirmed the presence of bone pathology in all joints with MRI bone erosions and histological and macroscopic synovitis in all joints with MRI synovitis (Ostendorf et al, 2001).

A high level of agreement between MRI and computed tomography (CT) -the 'gold standard' reference for detection of bony destruction- for detection of bone erosions in RA wrists and MCP joints (concordance at 87–90% of sites) documents that MRI erosions represent true bone damage (Perry et al, 2005).

2.7.2 Which joints and how to acquire images?

Most MRI studies in RA have investigated knee, wrist or finger joints. Reports on other peripheral joints are few in number and not essentially different. The few studies available on MRI of the feet do not suggest any advantage in imaging feet rather than wrists and hands. Although only one formal comparison with follow-up of other joints exists, *MRI of unilateral MCP joints and wrist joints* are most commonly recommended, while MRI of other joints should only be obtained if specifically clinically indicated.

Compared with radiography, MRI offers clear advantages, but also disadvantages such as increased cost and lower availability. However, MRI costs represent only a fraction of the total expense incurred in the management of patients with RA, when the costs of treatment of RA with biological agents or of the indirect costs of sick leave/early retirement are considered. Nevertheless, reducing the cost of MRI would be advantageous and would encourage clinicians to use MRI more often. Dedicated extremity MRI units are being used increasingly because they offer improved patient comfort at lower cost than conventional whole-body MRI units. The best of the dedicated low-field MRI units provide similar information on erosions and synovitis as conventional high-field whole-body MRI. However, performance characteristics of different machines differ widely, emphasising the need for careful testing.

Optimal MRI assessment of synovitis requires the use of intravenous gadolinium contrast, while assessment of bone oedema and erosions does not. Thus, for assessment of synovitis, bone oedema and erosions, a *pre- and post-contrast T1-weighted sequence in two planes* plus a *T2-weighted fat-saturated or short tau inversion recovery (STIR) sequence* is recommended.

2.7.3 Methods for assessment

Numerous pathologies can be visualised by MRI, but systematic methods for assessing RA activity and damage have focused on synovitis, bone marrow oedema and bone erosions. MRI allows quantitative (contrast uptake ('enhancement') rate after intravenous injection (only synovitis) or synovial membrane volume) as well as less

detailed (qualitative: presence/absence; semi-quantitative: scoring) evaluation of synovitis and bone erosions. In clinical practice a qualitative description of the images is used, whereas the more laborious quantitative assessments are used for research purposes.

The most commonly used assessment method is the Outcome Measures in Rheumatology (OMERACT) RA MRI scoring system (**RAMRIS**), which involves semi-quantitative assessment of synovitis, bone erosions, and bone oedema in RA hands and wrists. Recently also a RAMRIS JSN scoring system (joint space narrowing) was developed and validated (Glinatsi et al, 2015). In addition, scoring methods for tenosynovitis are currently under validation. The RAMRIS (box 7) was developed and validated through interactive multicentre studies through OMERACT and EULAR collaborations. A consensus on MRI definitions of important joint pathologies and a 'core set' of basic MRI sequences has also been presented (box 7).

RAMRIS erosion scores are closely correlated with erosion volumes estimated by MRI and CT, and good intra- and inter-reader reliability and a high level of sensitivity to change have been reported. This supports the suitability of RAMRIS for use in monitoring activity and damage in RA, after proper training and calibration of readers. A EULAR–OMERACT RA MRI reference image atlas has been developed, providing an easy-to-use tool for standardised RAMRIS scoring of MR images for RA activity and damage by comparison with standard reference images (*Østergaard et al, 2005).

Box 7 OMERACT MRI in rheumatoid arthritis (RA) group recommendations of a ‘core set’ of basic MRI sequences, MRI definitions of important RA joint pathologies and an RA MRI scoring system (OMERACT 2002 RAMRIS)

‘Core set’ of basic MRI sequences

It is suggested that future MRI studies, which intend to assess inflammatory as well as destructive changes in RA joints, should at least include the following:

- Imaging in two planes* with T1-weighted images before and after IV gadolinium contrast†
- A T2-weighted fat saturated sequence or, if the latter is not available, a short tau inversion recovery (STIR) sequence

**Imaging in two planes can be acquired by obtaining a two dimensional sequence in two planes, or a three dimensional sequence with isometric voxels in one plane allowing reconstruction in other planes.*

†IV gadolinium injection is not essential if destructive changes alone (bone erosions) are considered important.

Definitions of important RA joint pathologies

- Synovitis: An area in the synovial compartment that shows above-normal post-gadolinium enhancement* of a thickness greater than the width of the normal synovium
- MRI bone erosion: A sharply marginated bone lesion, with correct juxta-articular localisation and typical signal characteristics†, which is visible in two planes with a cortical break seen in at least one plane‡
- MRI bone oedema: A lesion§ within the trabecular bone, with ill-defined margins and signal characteristics consistent with increased water content

**Enhancement (signal intensity increase) is judged by comparison of T1-weighted images obtained before and after IV gadolinium contrast.*

†On T1-weighted images: loss of normal low signal intensity of cortical bone and loss of normal high signal intensity of trabecular bone. Quick post-gadolinium enhancement suggests the presence of active, hypervascularised pannus tissue in the erosion.

‡Other focal bone lesions, including metastases, must obviously be considered, but are generally distinguishable with associated imaging and clinical findings.

§May occur alone or surrounding an erosion or other bone abnormalities; high signal intensity on T2-weighted fat-saturated and STIR images and low signal intensity on T1-weighted images.

Scoring system

- Synovitis: Synovitis is assessed in three wrist regions (the distal radioulnar joint; the radiocarpal joint; the intercarpal and carpometacarpophalangeal joints) and in each metacarpophalangeal (MCP) joint. The first carpometacarpophalangeal joint and the first MCP joint are not scored. Synovitis is scored from 0 to 3.
- Bone erosions: Each bone (wrists: carpal bones, distal radius, distal ulna, metacarpal bases; MCP joints: metacarpal heads, phalangeal bases) is scored separately from 0 to 10.
- Bone oedema: Each bone is scored separately (as for erosions) from 0 to 3.
- Sum scores: Sum scores of synovitis, erosion and oedema, respectively, are calculated by summation of individual joint scores, as a total sum or separately in the evaluated wrist and 2nd–5th MCP joints. For synovitis, the possible range of sum scores of unilateral 2nd–5th MCP joints, wrist joint and both are 0–12, 0–9 and 0–21, respectively. Corresponding values for bone erosion are 0–80, 0–150 and 0–230, while for bone oedema the values are 0–24, 0–45 and 0–69.

IV, intravenous; MRI, magnetic resonance imaging; OMERACT, Outcome Measures in Rheumatology; RAMRIS, Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system.

2.7.4 Predicting and monitoring disease activity and damage: implications for clinical practice

MRI synovitis can be assessed with high reproducibility and is sensitive to change. In patients with clinical remission, MRI synovitis is common and has been shown to predict subsequent erosive progression (Bøyesen et al, 2010). MRI bone oedema is an independent predictor of subsequent radiographic progression in early RA (figure 6) and MRI measured inflammation is sensitive to change during treatment (Haavardsholm et al, 2008 and 2009; Hetland et al 2009) . MRI has also been shown to detect inflammation in RA patients experiencing progression in joint damage despite clinical remission (Brown et al, 2008). This supports the use of MRI detected inflammation for predicting the disease course, monitoring response to therapy, and defining remission in selected cases.

Figure 6 Bone marrow oedema in early rheumatoid arthritis patients (in the radius and hamate) is an independent predictor of subsequent radiographic joint damage (bone marrow oedema can only be visualised by magnetic resonance imaging).



MRI may also be used in early RA patients with normal radiographs to determine whether a patient has erosions. However, care should be taken (including requiring erosions to be visible in two planes) to avoid overestimation of erosive disease, and proper training is essential since erosion-like changes may be seen in patients without RA. Several studies have shown that MRI is more sensitive than radiography for monitoring erosive progression—that is, damage in the individual joint regions. MRI of a few joints is also reported to be more sensitive than radiography of many joints, using the Sharp/van der Heijde method, which is generally considered the most sensitive radiographic method. In established RA, RAMRIS scoring of unilateral wrist and MCP joints was more sensitive to change than Sharp/van der Heijde radiographic scoring of bilateral hands,

wrist and forefeet. Early MRI erosion progression could therefore be considered as a valid measure of structural damage that could substantially decrease sample size and study duration if used as structural damage end point in RA clinical trials (Baker et al, 2016).

2.8 Ultrasonography

US has several advantages. It has low running costs, is patient friendly, relatively easily accessible, and is interactive with the patient. The examination involves no ionising radiation, is multiplanar and visualises joint structures in real time. A Doppler examination provides haemodynamic information on the examined tissue. US enables quick examination of several joints in different body regions during one session and is easy to repeat, making follow-up examinations convenient and comfortable for the patient. However, the assessment of joints with US is limited as ultrasound cannot penetrate bone, and because of intra-machine and inter-reader variability and the lack of systems for assessment of activity and damage that have been tested longitudinally in follow-up studies.

2.8.1 Which abnormalities?

US can visualise inflammatory as well as destructive RA changes. It allows assessment of synovitis, both by detecting thickening of the synovial membrane of inflamed joints, bursae or tendon sheaths by grey scale (B-mode) US and by disclosing, and potentially quantifying, increased synovial blood flow using Doppler techniques. At knee and hip joints, the power Doppler signal has been found to correlate well with histological assessment of synovial membrane microvascular density. Although no similar data are available for small joints, there is strong agreement between US and MRI for the detection of synovial inflammation. High-frequency probes are required for satisfactory examination of the small joints of the hands and feet. US can also detect fluid in joints, bursae and tendon sheaths and may be used to evaluate the integrity of tendons and ligaments, as well as for imaging of enthesal inflammation.

It has been reported that US is more sensitive for visualising bone erosions in RA finger joints than conventional radiography. It is comparable to MRI in this respect, but inferior to MRI for detection and follow-up of erosions in wrists. Its sensitivity for detecting bone erosions is markedly site-dependent (high in easily accessible joints but low in anatomically complicated joints), owing to the fact that US cannot penetrate bone. Where accessibility is optimal, US registration of bone erosions shows high agreement with assessments by MRI and CT.

2.8.2 Which joints?

The exact number and localisation of joints that should be examined by US to obtain the best monitoring of RA has not yet been clarified. Based on cross-sectional data systems, incorporating a reduced number of joints has been suggested but needs further testing.

2.8.3 Methods for assessment

No generally accepted overall system for the assessment of RA activity and damage exists, but important advances have been made recently. In working groups under OMERACT and EULAR banners, definitions of important joint pathologies have been reported and a series of reproducibility studies performed, aiming at international consensus. Even though standardisation and validation is still incomplete, US is widely used in clinical practice in several countries for guiding injections and for investigating joint inflammation.

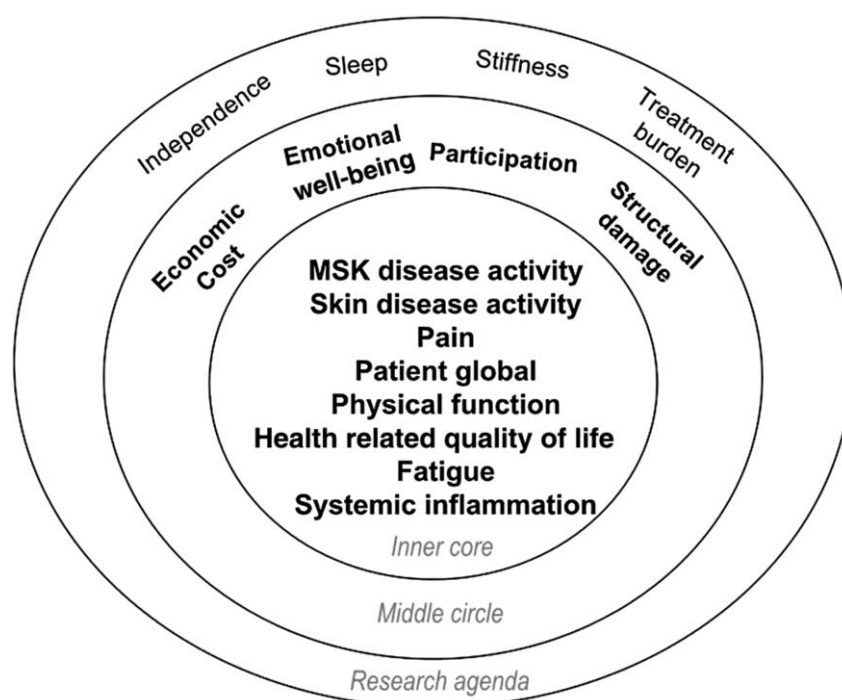
2.8.4 Predicting and monitoring disease activity and damage: implications for clinical practice

US grey scale synovitis of the wrist has been shown to be an independent predictor of subsequent bone erosions (Bøyesen et al, 2011). There is also accumulating evidence that a Power Doppler signal within synovial hypertrophy is associated with subsequent damage of the bone. However, further studies are still needed with regards to the prognostic role of US in RA (Naredo et al, 2005; Taylor et al, 2004; Janta et al, 2016; D'Agostino et al, 2016). US is, on the other hand, a sensitive measure of inflammation and has been shown to be sensitive to change during treatment, thus accentuating its role in disease monitoring of RA patients (Naredo et al, 2008).

3 Psoriatic arthritis

3.1 Core set

The GRAPPA-OMERACT PsA Working group recently updated the core set of outcomes to be measured in psoriatic arthritis (PsA) clinical trials. The updated PsA Core domain set includes: musculoskeletal disease activity (which now includes enthesitis, dactylitis, and spine symptoms in addition to peripheral arthritis) and skin disease activity (including nail disease), pain, patient global assessment, physical function, HRQoL, fatigue and systemic inflammation. Changes compared to the 2006 Core Domain set include moving fatigue and systemic inflammation to the inner circle (to be collected in all trials of PsA) and moving structural damage, participation, and emotional wellbeing to the middle circle (strongly recommended but not feasible to access in all clinical trials). Four new items were also added to the research agenda for further study (stiffness, independence, treatment burden, and sleep) (Orbai et al, 2016).

Figure 7 Psoriatic arthritis core set (Orbai et al, 2016)

In principle, all joint counts applied in RA are also used in PsA. However, as involvement of the distal interphalangeal (DIP) joints is a main characteristic of PsA, these are typically included in joint counts for this disease. Frequently, 68 tender and 66 swollen joints are employed. In some instances these have been extended, with the DIP joints of the feet and the carpometacarpal joints of the hands included to yield a full 78 tender and 76 swollen joint count.

3.2 Assessment tools for psoriatic arthritis

There has been great progress in the assessment of patients with PsA. Several assessment tools have been validated and new tools continue to be developed. A summary of these tools is presented in table 6. Some of these measures will be highlighted below. Further details can be found in the literature (*Mease PJ, 2011).

Table 6 Assessment tools for psoriatic arthritis

Measures	Specific tools
Peripheral joint assessment	Tender/swollen joint count (extended joint counts are preferred)
Axial joint assessment	ASDAS, BASDAI, BASFI, BASMI
PsA composite measures and response criteria	DAS/DAS28, DAPSA, CPDAI, PASDAS, AMDF, PsAJAI, PsARC and ACR response criteria
Skin assessment	PASI, BSA, target lesion, Global
Enthesitis assessment	Mander, MASES, Leeds, Berlin, SPARCC, 4-point
Dactylitis assessment	Leeds, present/absent, acute/chronic
Patient global	VAS (global, skin + joints)
Physician global	VAS (global, skin + joints)
Function/HRQoL	HAQ, SF-36, PsAQoL, DLQI

ACR, American College of Rheumatology; AMDF, Arithmetic Mean of Desirability Functions; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BSA, body surface area; CPDAI, Composite Psoriatic Disease Activity Index; DAS, Disease Activity Score; DAPSA, Disease Activity in Psoriatic Arthritis; DLQI, Dermatology Life Quality Index; HAQ, Health Assessment Questionnaire; HRQL, Health Related Quality of Life; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; PASI, Psoriasis Area and Severity Index; PASDAS, Psoriatic Arthritis Disease Activity Score; PsA, psoriatic arthritis; PsAJAI, Psoriatic Arthritis Joint Activity Index; PsAQoL, Psoriatic Arthritis Quality of Life; PsARC, Psoriatic Arthritis Response Criteria; SF-36, 36-Item Short Form Health Survey; SPARCC, Spondyloarthritis Research Consortium of Canada; VAS, Visual Analogue Scale.

3.3 Composite measures

A summary of composite disease activity scores proposed in psoriatic arthritis and the components of each score are presented in table 7.

Table 7 Summary of Composite Disease Activity Scores proposed in Psoriatic Arthritis

	ACR	DAS/ DAS28/ EULAR	PSARC	DAPSA	cDAPSA	CPDAI	mCPDAI	CPDAI- JED	PsAJAI	PASDAS	ADMDF/ GRACE Index	MDA
TJC/SJC	X	X	X	X	X	X	X	X	X	X	X	X
PGA	X	X	X	X	X				X	X	X	X
PhGA	X		X						X	X		
Patient pain	X			X	X				X			X
Dactylitis						X	X	X		X		
Enthesitis						X	X	X		X		X
Spinal involvement						X						
Skin involvement						X	X				X	X
Acute phase reactants	X	X		X					X	X		
Physical function (HAQ)	X					X	X		X		X	X
HRQoL						X				X	X	
PGA of joint involvement											X	

ACR, American College of Rheumatology response criteria; AMDF, Arithmetic Mean of Desirability Function; CPDAI, Composite Psoriatic Disease Activity Index; mCPDAI, modified CPDAI; CPDAI-JED, CPDAI joints, entheses, dactylitis; DAPSA, Disease Activity in Psoriatic Arthritis; cDAPSA, clinical version of the DAPSA; DAS, Disease Activity Score; DAS 28, 28-joint Disease Activity Score; EULAR, European League Against Rheumatism response criteria; GRACE Index, GRAppa Composite Exercise Index (GRACE index = [1-AMDF]); HAQ, Health Assessment of Questionnaire; HRQoL, Health related quality of life; MDA, Minimal Disease Activity; PASDAS, Psoriatic Arthritis Disease Activity Score; PGA, Patient Global Assessment; PhGA, Physician Global Assessment; PsAJAI, Psoriatic Arthritis Joint Activity Index; PsARC, Psoriatic Arthritis Response Criteria; TJC/SJC, Tender Joint Count/Swollen Joint Count.

The **DAS** and **DAS28** as described for RA have been widely used in PsA. They have been shown to be useful in polyarticular disease but there are concerns about the validity of their use in the general PsA population, namely in patients with oligoarticular disease, in patients with involvement of the DIP joints of the hands and in patients with predominantly lower limb involvement.

The Disease Activity in PsA (**DAPSA**) score largely assesses the articular component of the disease (box 8). Cut-offs for disease activity states and response criteria according to the DAPSA and the clinical DAPSA (cDAPSA) have been developed. The following DAPSA cut-offs were proposed: for remission, $DAPSA \leq 4$; for low disease activity, $4 < DAPSA \leq 14$; for moderate disease activity, $14 < DAPSA \leq 28$; for high disease activity, $DAPSA > 28$. Derived cDAPSA cut-offs were similar and the investigators arbitrarily proposed to reduce the cDAPSA cut-off between moderate and high disease activity by one point compared with the DAPSA, to account for the putative higher levels of CRP in patients with these levels of disease activity: for remission, $cDAPSA \leq 4$; for low disease activity, $4 < cDAPSA \leq 13$; for moderate disease activity, $13 < cDAPSA \leq 27$; for high disease activity, $cDAPSA > 27$. The following DAPSA response criteria were proposed: minor response, 50% change in DAPSA; moderate response, 75% change; major response, 85% change. Discriminative validity was assessed using Qui-square statistics.

The Composite Psoriatic arthritis Disease Activity Index (**CPDAI**) assesses disease activity in five domains: skin, joint, enthesis, dactylitis and spine; a score of 0 = not involved, 1 = mild, 2 = moderate or 3 = severe involvement, is attributed to each domain based on pre-defined criteria, resulting in a final score from 0–15.

The Psoriatic Arthritis Joint Activity Index (**PsAJAI**) is the weighted sum of scores given in case of a least 30% improvement in each of six measures with weights of 2 given to tender joint count, CRP level, and physician global assessment of disease activity. Weights of 1 are given to the remaining 30% improvement measures, including pain, patient global assessment of disease activity, and HAQ. PsAJAI range is 0–9 with a preliminary definition of response being a PsAJAI ≥ 5 .

Two novel indices were recently proposed, the **Psoriatic Arthritis Disease Activity Score (PASDAS)**, (box 8), developed in analogy to the DAS/ASDAS, and the **Arithmetic Mean of Desirability Functions (AMDF)**, which uses the arithmetic mean of 8 transformed empirically selected variables and arbitrary cut-offs (tender and

swollen joint counts, HAQ, patient VAS for global assessment, patient VAS for skin, patient VAS for joints, psoriasis area and severity index (PASI), and PsA quality-of-life index (PsAQoL)). Further validation and comparative studies are required until a final consensus can be reached about the best measure(s) to use in PsA.

Box 8 Psoriatic arthritis (PsA) composite measures

Disease Activity in PsA (DAPSA) score

SJC66 + TJC68 + Patient global (VAS, 0–10) + Pain (VAS, 0–10) + CRP

PsA Disease Activity Score (PASDAS)

$$0.18 \times \sqrt{\text{Doctor global VAS}} + 0.159 \times \sqrt{\text{Patient global VAS}} - 0.253 \times \sqrt{\text{SF36-PCS}} + 0.101 \ln(\text{SJC66} + 1) + 0.048 \ln(\text{TJC68} + 1) + 0.23 \times \ln(\text{Leeds enthesitis count} + 1) + 0.377 \ln(\text{tender dactylitis count} + 1) + [0.102 \ln(\text{CRP} + 1) + 2] \times 1.5$$

CRP, C reactive protein (mg/dL for DAPSA and mg/L for PASDAS); PSC, physical component scale of SF36; ln, natural logarithm; VAS, visual analogue scale.

3.4 Response criteria

Three response criteria are in use for PsA: the PsA response criteria (**PsARC**), developed specifically for PsA, and **the ACR and EULAR response criteria**, originally developed for RA. To achieve a PsARC response a patient has to achieve two of the following, one of which has to be a joint count and no worsening of any measure: tender or swollen joint count improvement of at least 30% (worsening defined as an increase of at least 30%), patient global improvement by 1 point on a 5-point Likert scale, or doctor global improvement on the same scale (worsening defined as an increase of one point). All three response criteria can discriminate placebo from active treatment in clinical trials. The incidence of an ACR 20 response is typically lower than a PsARC response, although for the PsARC a 30% improvement is required. It has been suggested that this may be because only one of the joint counts needs to have improved and assessments such as acute phase reactants and HAQ are not included. Validation of the current criteria and further development of the PsARC are continuing. Development and validation of response criteria for other composite measures is ongoing.

3.5 Remission, low disease activity

Criteria to define minimal disease activity (**MDA**) have been proposed and validated by Coates et al (2010*). Patients are classified as having MDA if their score is equal to or below the predefined cut-off for five of seven outcome measures: tender joint count ≤ 1 ; swollen joint count ≤ 1 ; PASI ≤ 1 or body surface area ≤ 3 ; patient pain VAS score ≤ 15 (0–100 scale); patient global disease activity VAS score ≤ 20 (0–100 scale); HAQ score ≤ 0.5 ; and tender entheses points ≤ 1 .

3.6 Frequency of monitoring

Little information is available about the optimum frequency of monitoring. However, the guidelines for monitoring clinical disease activity for RA seem to be applicable also to PsA (3-monthly during active disease and reduced to 6-monthly follow-ups if a patient is in remission/MDA).

3.7 Imaging assessment

3.7.1 Conventional radiographs

Radiographic imaging is the most widely used imaging method in PsA. Although there are similarities with RA, there are also major differences in, for example, the type and site of lesions as well as the joints affected. Whereas RA is characterised by mainly osteodestructive lesions, in PsA there are both osteodestructive and osteoproliferative manifestations, which may even coexist not only in the same patient but also in the same joint.

3.7.1.1 Which abnormalities?

Characteristic radiographic features of PsA include joint erosions, JSN, bony proliferation including periarticular and shaft periostitis, osteolysis, ankylosis, spur formation, and spondylitis. Abnormalities are seen in the phalangeal tufts and at the sites of attachments of tendons and ligaments of the bone. Although erosive changes in early PsA are marginal as in RA, they become irregular and ill-defined with disease progression because of periosteal bone formation adjacent to the erosions. In severe cases, erosive changes may progress to development of pencil-in-cup deformity or gross osteolysis. These features are typical of arthritis mutilans.

3.7.1.2 Which joints?

Joint involvement in PsA is often asymmetrical and may be oligoarticular. Asymmetrical erosions may be visible radiographically in the carpus and in the MCP, PIP and DIP joints of the hands, but the DIP joints are often the first to be affected. The hands tend to be involved much more often than the feet with a ratio of nearly 2:1. Erosive changes and bone proliferation in the feet usually involve the IP and MTP joints: the IP joint of the great toe is most often affected. Radiographs of the hand are most important in the follow-up of patients, but addition of films of the feet makes the picture more complete.

Spondylitis is a characteristic feature of PsA and may be difficult to distinguish from AS radiographically. Syndesmophytes occur in both PsA and AS, but in PsA they may be Para marginal and do not appear in consecutive vertebrae. Sacroiliitis is relatively common and often unilateral.

3.7.2 Scoring methods: general introduction

Development and validation of scoring methods for PsA are less advanced than for RA. All the presently used methods have as their basis the scoring methods used for RA. Table 8 summarises the two global scoring methods and two detailed scoring methods, which will be described below.

Global score each joint

- ➡ Modified Steinbrocker score (hands-feet)
- ➡ Ratingen method for PsA (separately destruction-proliferation)

Detailed score each joint

- ➡ Sharp method (RA, but 2 extra scores erosion, 1 extra score JSN)
- ➡ Van der Heijde modification of Sharp method

3.7.3 Global assessment for each joint

3.7.3.1 Modified Steinbrocker score

The modified Steinbrocker score was developed at the PsA clinic at the University of Toronto (Rahman et al, 1998). Each joint is scored on a 0–4 scale, where 0 is normal; 1 reflects juxta-articular osteopenia or soft tissue swelling; 2 is the presence of erosion; 3 is the presence of erosion and JSN; 4 is total joint destruction, either lysis or ankylosis. This score is applied to 14 joints in each hand and six joints in each foot. The range of the score is from 0 to 160.

3.7.3.2 Psoriatic Arthritis Ratingen Score

The Psoriatic Arthritis Ratingen Score (PARS) includes 40 joints of the hands and feet (Wassenberg et al, 2001). All joints are scored separately for destruction and proliferation. The **destruction score** is based on the amount of joint surface destruction on a **0–5 scale**, with 0, normal; 1, one or more definite erosions with an interruption of the cortical plate of >1 mm but destruction of <10% of the total joint surface; 2, destruction of 11–25%; 3, destruction of 26–50%; 4, destruction of 51–75%; 5, destruction of >75% of the joint surface. The **proliferation score** considers any kind of bony proliferation typical for PsA on a **0–4 scale**, with 0, normal; 1, bony proliferation measured from the original bone surface of 1–2 mm or, if the margins of the proliferation cannot be distinguished from the original bone surface, clearly identifiable bone growth not exceeding 25% of the original diameter of the bone; 2, bony proliferation of 2–3 mm or bone growth between 25–50%; 3, bony proliferation >3 mm or bone growth >50%; 4, bony ankylosis. The destruction score with a range from 0 to 200 and the proliferation score with a range from 0 to 160 are summed to give the **total score** (0–360).

Table 8 Comparison of radiographic scoring methods for psoriatic arthritis

	Modified Steinbrocker (Global score)	Ratingen method for PsA (Global score)	Sharp method (Detailed score)	van der Heijde modification of Sharp method (Detailed score)
<i>Films</i>				
Hands	X	X	X	X
Feet	X	X	X	X
Large joints	–	–	–	–
<i>Joints included</i>				
DIP	X	X	X	X
PIP/IP	X	X	X	X
MCP	X	X	X	X
Wrist	X	X	X	X
MTP	X	X	X	X
IP1	X	X	X	X
<i>Features scored</i>				
Erosions	–	X	X	X
JSN	–	–	X	X
Misalignment	–	–	–	X
Proliferation	–	X	–	–
Global	X	–	–	–
<i>Number of joints per hand/foot scored for</i>				
Erosions	–	40	27	26
JSN	–	–	25	26
Misalignment	–	–	–	*
Proliferation	20 (14/6)	40	–	–
Global	–	–	–	–
<i>Range per joint</i>				
Erosions	–	0–5	0–5	0–5/0–10 [†]
JSN	–	–	0–4	0–4
Malalignment	–	–	–	*
Proliferation	–	0–4	–	–
Global	0–4	–	–	–
Total	0–160	0–360	0–470	0–528

*Combined with the JSN score.

[†]Erosions for hands 0–5, for feet 0–10.

DIP, distal interphalangeal; IP, interphalangeal; JSN, joint space narrowing; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

3.7.4 Detailed scoring methods

3.7.4.1 PsA scoring method based on Sharp scoring method for RA

The erosion scale used in RA has a range of 5 per joint (cfr supra 2.6.4.1). The erosion scale was expanded with the scores of 6 and 7 to accommodate more extensive bone destruction seen in many cases of PsA, such as gross osteolysis or a pencil-in-cup lesion. However, the scores of 6 and 7 are not added to get the total erosion score, but these features are kept separately. The **erosion score** is applied to 21 joints in each hand (0-5) and six joints in each foot (0-5), resulting in a range of 0–210 for hands and 0–60 for feet. The **scoring of JSN** is on a scale of 0–4 and is used as for RA with the addition of widening (score 5), which is automatically scored when gross osteolysis is present. Again the score for widening is not included in the total narrowing score but analysed as a separate feature. The JSN score is applied to 20 joints in each hand (0-4) and five joints in each foot (0-4), leading to a range of 160 for hands and 40 for feet.

3.7.4.2 Sharp/van der Heijde modified scoring method for PsA

A scoring system similar to that used in RA is applied to PsA (van der Heijde et al, 2005). The same joints are scored for erosions (16 in the hands and 6 in the feet) and JSN (15 in the hands and 6 in the feet), with the addition of the eight DIP joints (=both hands) for erosions and the eight DIP joints (=both hands) and two IP joints of the thumb for JSN. Again, the maximum score for erosions is 5 in the joints of the hands and 10 in the joints of the feet. **Scores for erosions** are applied as follows: 0, no erosions; 1, discrete erosion; 2, large erosion not passing the middle-line; 3, large erosion passing the middle-line; a combination of the above scores may lead to the maximum of 5 per entire joint in the hands; and 5 at each site of the joint (for the entire joint a maximum of 10) in the feet. The so-called **JSN score** is based on the following features: 0, normal; 1, asymmetric or minimal narrowing up to a maximum of 25%; 2, definite narrowing with loss of up to 50% of the normal space; 3, definite narrowing with loss of 50–99% of the normal space or subluxation; 4, absence of a joint space, presumptive evidence of ankylosis or complete luxation. Gross osteolysis and pencil-in-cup lesions are scored separately. In the final **summary score**, joints with one of these abnormalities get the maximum score assigned for both erosions and for JSN. The total range for erosions is 200 for the hands, 120 for the feet; the total range for JSN is 160 for the hands and 48 for the feet, giving a total possible score of 528.

3.7.5 Assessment of structural damage in clinical practice

No recommendation exists on the assessment of structural damage in routine clinical practice in PsA. The methods are not validated sufficiently. Based on feasibility, the modified Steinbrocker approach seems the most appropriate candidate, but little is known about its usefulness and validity for monitoring disease in clinical practice.

3.8 Magnetic resonance imaging

The clinical appearance of PsA is diverse, involving the spine, sacroiliac (SI) joints, peripheral joints and/or entheses and, accordingly, imaging findings vary. Imaging in PsA (Ory et al, 2005; McQueen et al, 2006) has received less research scrutiny than in RA and AS, but this is likely to change, as MRI outcome measures are increasingly being used in clinical trials of new therapeutic agents.

3.8.1 Which abnormalities?

PsA shares clinical manifestations with RA and spondyloarthritis (SpA) and also shares MRI features. Peripheral PsA synovitis appears to be similar to RA synovitis on MRI. Similarly, PsA bone erosions do not have disease-specific MRI features. MRI bone oedema can involve any of the wrist or finger bones. As in other spondyloarthritides, enthesitis, dactylitis and spondylitis can be seen. Enthesitis may occur adjacent to peripheral and axial joints, often associated with synovitis and sometimes with bone oedema. Dactylitis has been shown on MRI to be due to tenosynovitis with effusion, sometimes associated with synovitis in nearby finger or toe joints. Diffuse soft tissue oedema may overlie areas of dactylitis, synovitis or bone oedema. There are few MRI studies in axial PsA, but as in AS, findings in SI joints and the spine include bone oedema, erosions, periarticular fat accumulation and sclerosis.

3.8.2 Which joints?

PsA affects both axial and peripheral joints and entheses, and a general agreement on which joints to image to assess PsA activity and damage has not been established and possibly needs to be individualised, based on the disease pattern.

3.8.3 Methods for assessment

Most studies report only qualitative MRI assessments of the different pathologies of PsA. Quantitative assessment of contrast uptake has been reported in one study. No generally accepted or validated methods for assessment of PsA activity or damage exist. An OMERACT PsA MRI scoring system (**PsAMRIS**) has been developed for use in PsA hands (Østergaard et al, 2009). Discussions of appropriate MRI sequences and consensus MRI definitions of important pathologies are also provided. The scoring system has been shown to be reliable in hands and feet (McQueen et al, 2009; Glinatsi et al, 2015), however further testing and validation of the score is warranted.

3.8.4 Predicting and monitoring disease activity and damage: implications for clinical practice

It remains to be determined whether any MRI features predict subsequent joint damage in PsA.

MRI has disclosed evidence of subclinical arthritis in a high proportion of patients with psoriasis alone, suggesting that PsA may be a much more common disorder than has previously been suspected and that MRI could improve disease activity assessment in PsA.

3.9 Ultrasonography

Little research into the use of US in PsA has been carried out. However, in peripheral joints and entheses, the same advantages and disadvantages as for RA apply. US is not suited for assessment of axial disease, as changes are generally located at sites inaccessible to US examination.

3.9.1 Which abnormalities?

In areas accessible to US examination in the limbs of patients with PsA, US can be used to assess synovitis (synovial hypertrophy or Doppler signal, or both), joint effusion, bone erosions, tenosynovitis and enthesitis. For instance, enthesitis at the Achilles tendon is identified by US much more frequently than on clinical examination in patients with psoriasis and PsA. However, the sonographic findings are non-specific, as they may also occur in other diseases such as osteoarthritis and RA. US may be a useful tool for assessing dactylitis and visualising tenosynovitis, joint effusion, and synovitis.

3.9.2 Which joints?

PsA affects both axial and peripheral joints and entheses and a general agreement on which joints to image to assess activity and damage has not been established. This possibly needs to be individualised, based on the disease pattern.

3.9.3 Methods for assessment

Only qualitative US assessments of the different pathologies of PsA have been reported. No generally accepted or validated methods for assessment of PsA activity or damage exist.

3.9.4 Predicting and monitoring disease activity and damage: implications for clinical practice

It remains to be determined whether any US features predict subsequent joint damage in PsA. The value of longitudinal monitoring by US in patients with PsA for joint and enthesal manifestations, although likely, has not been scientifically documented.

4 Axial spondyloarthritis

4.1 Core set

Many instruments are available which can be used to assess axial SpA (*Machado et al, 2011). The Assessment in SpondyloArthritis international Society (ASAS) has proposed several core sets for use in clinical trials to

evaluate disease-controlling anti-rheumatic treatment, symptom-modifying anti-rheumatic drugs and physical therapy, as well for use in clinical practice (Zochling et al, 2006). All core sets comprise several domains and for each domain one or several instruments have been selected. Table 9 presents the domains and respective instruments for the various core sets, which will be discussed in more detail. The domains of *pain*, *patient global assessment of disease activity*, *morning stiffness*, *fatigue*, *spinal mobility* and *physical function* are included in all core sets. All the assessments described in this chapter were initially developed for AS but are currently applied both in radiographic (i.e., AS) and non-radiographic axial SpA. These assessments are presented in detail in the ASAS handbook (*Sieper et al, 2011), which can be accessed at the Annals of the Rheumatic Diseases website (<http://www.ard.bmj.com>) or the ASAS website (<http://www.ASAS-group.org>).

Patient global assessment: The patient is asked to place a mark on a VAS or an NRS to represent their response to the question: ‘How active was your spondylitis on average last week?’

Pain: Patients are asked two questions about the pain experienced, on average, over the previous week—‘How much spine pain did you experience due to AS?’ and ‘How much spine pain did you experience at night due to AS?’ Patients indicate their response on a VAS or NRS.

Spinal stiffness: The patient is asked, ‘On average last week, for how long after you woke up did you experience stiffness in your spine?’ This is recorded in minutes or on a VAS with a maximum score of 2 h. Often also the intensity of spinal stiffness is assessed by the question, ‘How would you describe the overall level of morning stiffness you have had from the time you wake up?’ The final result for spinal stiffness is the average of duration and intensity of morning stiffness.

Fatigue: One general question is asked about the average level of fatigue in the previous week, ‘How would you describe the overall level of fatigue/tiredness you have experienced?’ This, too, is answered on a VAS or NRS.

Physical function: Two indexes are available to assess functional capacity: the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Dougados Functional Index (Calin et al, 1994; Dougados et al, 1988). The **BASFI** consists of 10 questions, answered on a VAS or NRS. The final score is the average of the scores for the 10 questions, ranging from 0 (no limitation in function) to 10 (maximal limitation) (box 10). The **Dougados Functional Index** has 20 questions, which are answered on a 3-point or 5-point verbal rating scale and summed to give a total score. The answers are scored 0, 1 and 2 or 0, 0.5, 1, 1.5 and 2, respectively, to ensure that the final score always falls in the range 0–40. Both functional indexes have been shown to be valid and sensitive in differentiating between groups of patients with a different level and/or improvement in physical function. There seems to be little difference between the two instruments in their sensitivity to change. The BASFI is the most commonly used instrument. Several language versions can be found on the website <http://www.ASAS-group.org> (accessed 7 September 2016).

Table 9 Specific instruments for each domain in core sets for DC-ART, SMARD, physical therapy and clinical record keeping

Domain	Instrument
Function*	BASFI
Pain*	NRS/VAS [§] , past week, spine, at night due to AS <i>and</i> NRS/VAS, past week, spine, due to AS
Spinal mobility*	Chest expansion <i>and</i> modified Schober <i>and</i> occiput to wall <i>and</i> cervical rotation <i>and</i> (lateral spinal flexion or BASMI)
Patient global*	NRS/VAS, global disease activity past week
Peripheral joints and entheses [†]	Number of swollen joints (44-joint count) Validated entheses score, such as MASES, San Francisco and Berlin
X-Ray spine [‡]	Lateral lumbar spine <i>and</i> lateral cervical spine
Stiffness*	NRS/VAS duration of morning stiffness, spine, past week
Acute phase reactants [†]	CRP or ESR
Fatigue*	Fatigue question BASDAI

*Included in core sets for DC-ART, SMARD/physical therapy and clinical record keeping.

†Included in core sets for DC-ART and clinical record keeping.

‡Included in core set for DC-ART.

§Use of an NRS is preferred by ASAS.

AS, ankylosing spondylitis; ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; DC-ART, disease-controlling antirheumatic treatment; ESR, erythrocyte sedimentation rate; NRS, numerical rating scale; SMARD, symptom-modifying antirheumatic drug; VAS, visual analogue scale.

Box 9 Bath Ankylosing Spondylitis Functional Index (BASFI)

- Putting on your socks or tights without help or aid (e.g., sock aids)
- Bending forward from the waist to pick up a pen from the floor without an aid
- Reaching up to a high shelf without help or aids (e.g., helping hand)
- Getting up out of an armless dining room chair without using your hands or any other help
- Getting up off the floor without help from lying on your back
- Standing unsupported for 10 min without discomfort
- Climbing 12–15 steps without using a handrail or walking aid (one foot each step)
- Looking over your shoulder without turning your body
- Doing physically demanding activities (e.g., physiotherapy exercises, gardening or sports)
- Doing a full day's activities whether it be at home or at work

Spinal mobility: Assessment of the spinal mobility domain involves the use of the following five instruments:

- *Chest expansion.* The patient is asked to rest his/her hands on or behind their head. The difference between maximal inspiration and expiration is then measured anteriorly at the fourth intercostal level (e.g., 5.1 cm). The better of two such measurements should be recorded.
- *Modified Schober test.* The doctor makes a mark on the patient's skin on the imaginary line between the two superior, posterior iliac spines. A second mark is then made 10 cm higher than the first mark. The patient is asked to bend forward as far as he/she can and the distance between the two marks on the skin is measured. The increase in the distance is noted (e.g., if 14.3 cm is the distance measured between the lines when the patient is bent forward maximally, the recorded result would be 4.3 cm). The better of two tries is recorded.
- *Occiput-to-wall test.* The patient stands with the heels and back against a wall and with hips and knees as straight as possible. The chin should be held at the usual carrying level. The patient is asked to try as hard as he/she can to touch his/her head against the wall. The distance between the wall and the occiput is then measured in centimetres (e.g., 9.6 cm). The better of two tries is recorded. For the Bath Ankylosing Spondylitis Metrology Index (BASMI), the tragus-to-wall distance is used (see below). Comparison of the two measures showed that both behave similarly. Because the normal situation is clear for the occiput to wall (0) and not for the tragus to wall (dependent on the size of the head) there is a preference for use of the occiput-to-wall distance.
- *Lateral spinal flexion.* The patient stands as close to a wall as possible, with the shoulders level. The distance between the patient's middle fingertip and the floor is measured with a tape measure. The patient is asked to bend sideways as far as they can without bending the knees or lifting the heels, while keeping the shoulders against the wall. The new distance from middle fingertip to floor is measured and the difference between the two is noted. The better of two tries is recorded for full left and right lateral flexion. The mean of the left and right values gives the final result for lateral spinal flexion (expressed in centimetres to the nearest 0.1 cm)
- *Cervical rotation.* The patient sits straight on a chair; chin level, hands on the knees. The assessor places a goniometer at the top of the head in line with the nose. The assessor asks the patient to rotate the neck maximally to the left, follows with the goniometer, and records the angle between the sagittal plane and the new plane after rotation. A second reading is taken and the better of the two is recorded for the left side. The procedure is repeated for the right side. The mean of left and right is recorded in degrees (0–90°) (normal > 70°).

Peripheral involvement: The 44-swollen joint count should be assessed.

Enthesitis: A few validated enthesitis scores are available for clinical studies but none of these has yet been selected as the preferred instrument.

4.2 Composite measures

The most widely used composite measure in axial SpA is the Bath AS Disease Activity Index (**BASDAI**), an entirely patient-oriented outcome measure including an assessment of *back, pain of entheses, pain or swelling of peripheral joints, fatigue, and morning stiffness* (figure 8) (Garrett et al, 1994). This measure is often used in clinical trials but also in clinical practice, especially for defining disease activity for the start of TNF blockers. The BASDAI is closely linked to patient global assessment but not to the doctor global assessment of disease activity. Several language versions can be found on the website <http://www.asas-group.org> (accessed 7 September 2016).

A composite measure for the *assessment of spinal mobility* is also available: the **BASMI**. This is a combination of the lateral lumbar flexion, tragus-to-wall distance, modified Schober, cervical rotation and intermalleolar distance (as a measure of hip function) (figure 8). The intermalleolar distance is not a measurement endorsed by the ASAS. Figure 9 describes the measurement of the BASMI. Assessment on a 10-point scale or on a linear scale as presented in figure 9 is the best-answer modality.

Recently, a composite disease activity index combining domains considered relevant by patients and clinicians has been developed as an ASAS initiative (box 10) (Lukas et al, 2009; van der Heijde et al, 2009). The **AS Disease Activity Score (ASDAS)** comprises three items from BASDAI: (1) back pain (BASDAI question 2); (2) peripheral pain/swelling (BASDAI question 3); and (3) duration of morning stiffness (BASDAI question 6), as well as patient's global assessment and one acute phase reactant (CRP or ESR). The preferred formula is ASDAS-CRP; the alternative formula is ASDAS-ESR. For clinical use the ASDAS is grouped into inactive, moderate, high and very high disease activity (figure 10) (*Machado et al, 2010). These disease activity states apply to both formulas. However, at the individual level, ASDAS-CRP and ASDAS-ESR values should not be used interchangeably. An ASDAS online calculator is available at: http://www.asas-group.org/clinical-instruments/asdas_calculator/asdas.html.

Figure 8 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) on a numerical rating scale (NRS).

NRS BASDAI

Please tick the box which represents your answer.
All questions refer to last week (ie ☒ 10).

- 1 How would you describe the overall level of fatigue/tiredness you have experienced? Fatigue
- | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|----|
- None Very severe
- 2 How would you describe the overall level of AS neck, back or hip pain you have had? Spinal pain
- | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|----|
- None Very severe
- 3 How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had? Peripheral arthritis
- | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|----|
- None Very severe
- 4 How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure? Enthesitis
- | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|----|
- None Very severe
- 5 How would you describe the overall level of morning stiffness you have had from the time you wake up? Intensity of morning stiffness
- | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|----|
- None Very severe
- 6 How long does your morning stiffness last from the time you wake up? Duration of morning stiffness
- | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|----|
- 0 h 1 h 2 or more h

$$\text{BASDAI} = \frac{Q1 + Q2 + Q3 + Q4 + \left(\frac{Q5 + Q6}{2} \right)}{5}$$

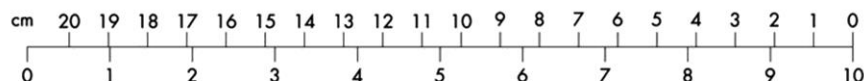
Figure 9 Bath Ankylosing Spondylitis Metrology Index (BASMI).**BASMI**

Bath ankylosing spondylitis metrology index, a combined index to assess the spinal mobility in patients with ankylosing spondylitis

Name: _____

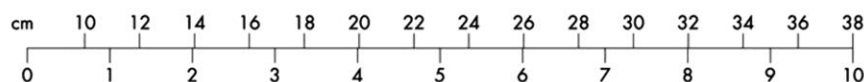
Date: _____

- 1 Lateral lumbar flexion: patient stands with heels and buttocks touching the wall, knees straight, shoulders back, hands by the side. The patient is then asked to bend to the right side as far as possible without lifting the left foot/heel or flexing the right knee, and maintaining a straight posture with heels, buttocks, and shoulders against the wall. The distance from the third fingertip to the floor when patient bends to the side, is subtracted from the distance when patient stands upright. The manoeuvre is repeated on the left side.



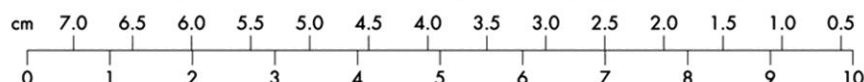
Mean of right/left

- 2 Tragus-to-wall distance: maintain same starting position as above. The distance between tragus of the ear and wall during maximal effort to draw the head back without raising the chin above its usually carrying level is measured on both sides to the nearest 0.1 cm, using a rigid ruler. Ensure no cervical extension, rotation, rotation, flexion or side flexion occurs.

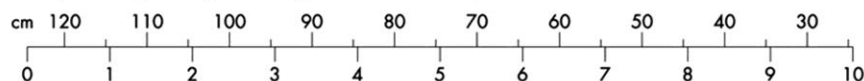


Mean of right/left

- 3 Lumbar flexion (modified schober): set marks in upright position at the level of the spinous process of L5 (found as the first process below the projected line across the back at the level of the top of the iliac crest) and 10 cm above the first mark. Measure distraction of the marks when the patient bends forward as far as possible, keeping the knees straight.

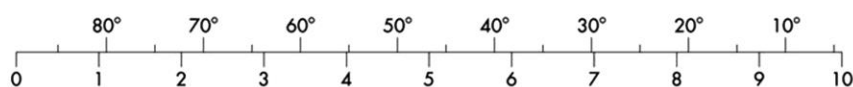


- 4 Intermalleolar distance: patient supine on the floor or a wide plinth, with the knees straight and the feet pointing straight up. Patient is asked to separate legs along the resting surface as far as possible. Distance between medial malleoli is measured.



- 5 Cervical rotation: patient supine on plinth, head in neutral position, forehead horizontal (if necessary head on pillow or foam block to allow this, must be documented for future reassessments). Gravity goniometer placed centrally on the forehead. Patient rotates head as far as possible, keeping shoulders still, ensure no neck flexion or side flexion occurs, Rotational angle to the right and to the left is measured.

If you do not have a gravity goniometer: patient sits with shoulders to the wall. Place goniometer to the wall above the patient's head. Patient rotates head as described above. Examiner aligns goniometer branch parallel to sagittal plane of the head.



Mean of right/left

BASMI:
(average
of 5 scores)

Box 10 ASDAS formulas**ASDAS-CRP**

$(0.12 \times \text{back pain}) + (0.06 \times \text{duration of morning stiffness}) + (0.11 \times \text{patient's global assessment}) + (0.07 \times \text{peripheral pain/swelling}) + [0.58 \times \ln(\text{CRP}+1)]$

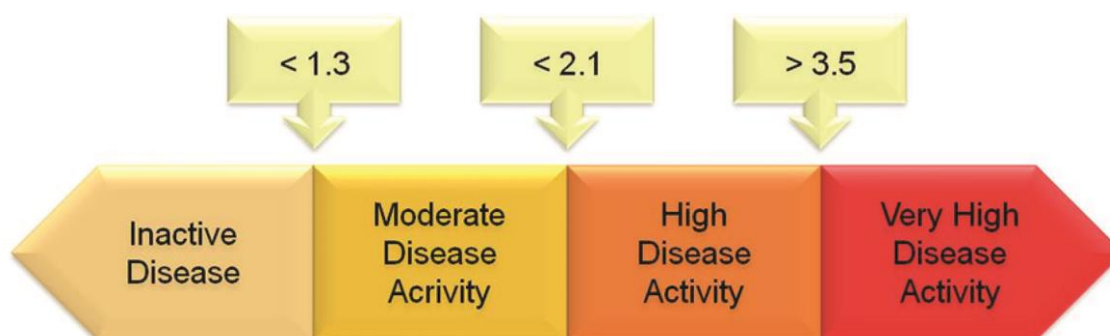
ASDAS-ESR

$(0.08 \times \text{back pain}) + (0.07 \times \text{duration of morning stiffness}) + (0.11 \times \text{patient's global assessment}) + (0.09 \times \text{peripheral pain/swelling}) + [0.29 \times \sqrt{\text{ESR}}]$

ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C reactive protein (mg/L); ESR, erythrocyte sedimentation rate (mm/h); Ln, natural logarithm.

All questions are scored using a 0–10 VAS/NRS. In ASDAS-CRP, when the conventional CRP is below the limit of detection or when the high sensitivity CRP is <2 mg/L, the constant CRP value of 2 mg/L should be used to calculate ASDAS-CRP.

Figure 10 The Ankylosing Spondylitis Disease Activity Score (ASDAS) cut-offs for disease activity states
(Source: Assessment of SpondyloArthritis international Society (ASAS) www.asas-group.org).



The ASDAS is a reliable measure of disease activity in both radiographic and non-radiographic axial SpA and is responsive to change during treatment (Pedersen et al, 2010). Evidence accumulated during recent years supports the replacement of the BASDAI and previously used response criteria (section 4.3) by the ASDAS tool and its disease activity status and improvement cut-offs (section 4.3). The ASDAS has been received extremely well by professionals working in the field of axial SpA and is already starting to replace the BASDAI. Indeed, the ASDAS is currently being used as an outcome measure in several clinical trials and observational studies. The availability of online, desktop and handheld ASDAS calculators, as well as a quick ASDAS calculator paper form (available at www.asas-group.org), will facilitate its implementation in clinical practice.

4.3 Response criteria

The **ASAS 20 response criteria** have been widely used in clinical trials in AS (Anderson et al, 2001). The ASAS 20 criteria are based on four variables: function (BASFI), morning stiffness (inflammation—mean of morning stiffness questions of BASDAI), patient global assessment of disease activity, and overall pain (figure 11). To fulfil the ASAS 20 response criteria, there should be a 20% improvement with a minimum of 1 unit (on a 10-point scale) in at least three of the four domains without worsening of 20% and 1 unit in the possible

remaining domain. Two more strict criteria have been developed: the ASAS 40 and ASAS 5/6 criteria. The **ASAS 40 criteria** are based on the same four domains with a requirement of an improvement of at least 40% and 2 units in three out of the four domains without any worsening in the possible fourth domain (figure 12) (Brandt et al, 2004). For the **ASAS 5/6 criteria** again the same four domains are assessed but now expanded with an acute phase reactant and a measure of spinal mobility. To fulfil the ASAS 5/6 criteria there should be at least a 20% improvement in at least five domains (figure 13).

Figure 11 The Assessment in SpondyloArthritis international Society (ASAS) 20 improvement criteria (www.asas-group.org).

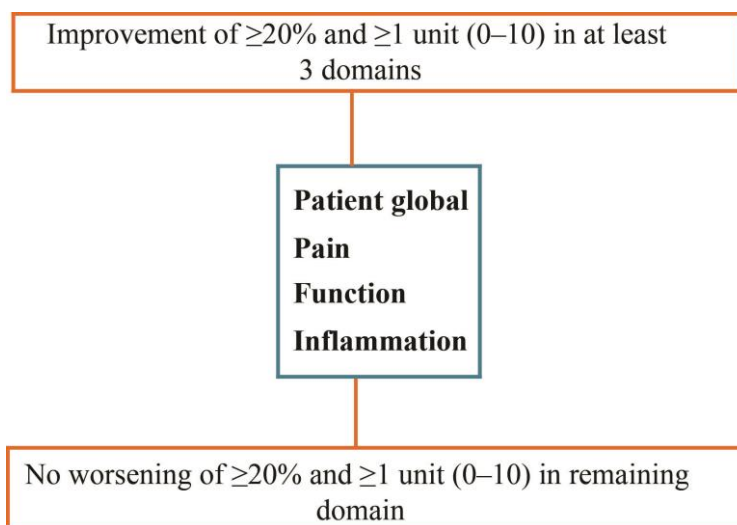


Figure 12 The Assessment in SpondyloArthritis international Society (ASAS) 40 improvement criteria (www.asas-group.org).

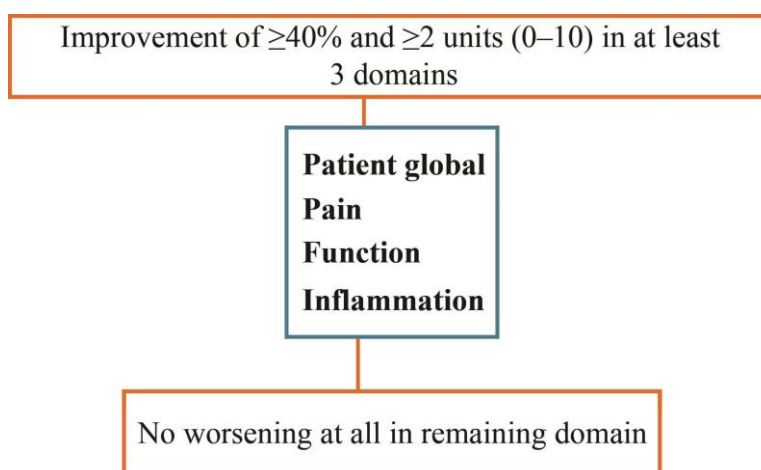
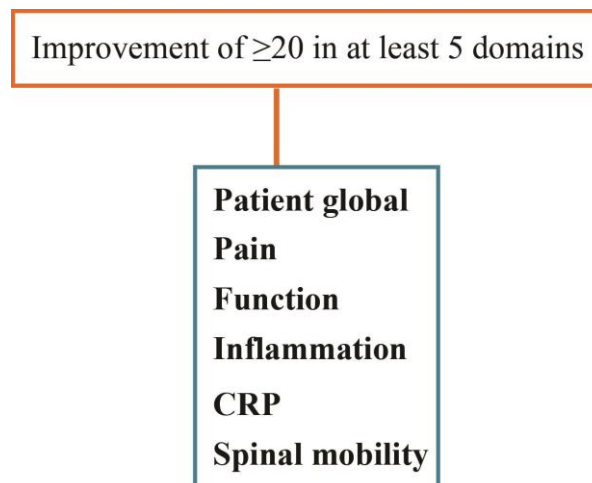
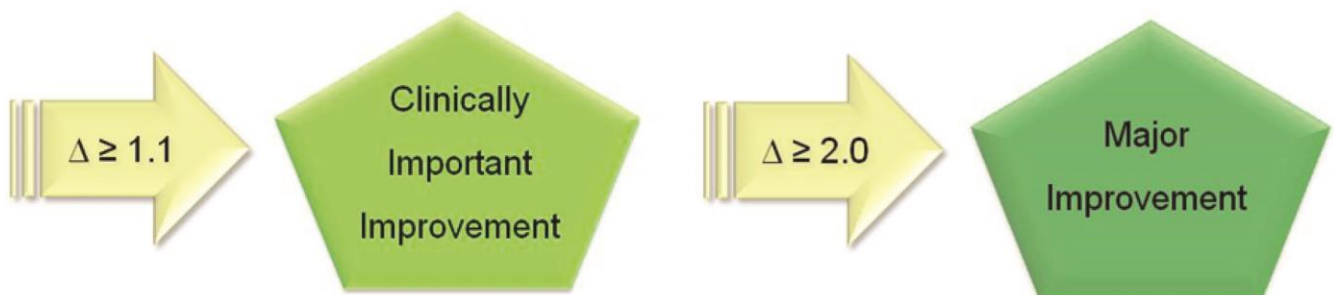


Figure 13 The Assessment in SpondyloArthritis international Society (ASAS) 5/6 improvement criteria. CRP, C reactive protein (www.asas-group.org).



Recently, **response criteria for the ASDAS** have been published. Clinically important improvement should be more than or equal to a 1.1 point improvement in ASDAS and a major improvement should be equal to or exceed 2.0 points (figure 13).

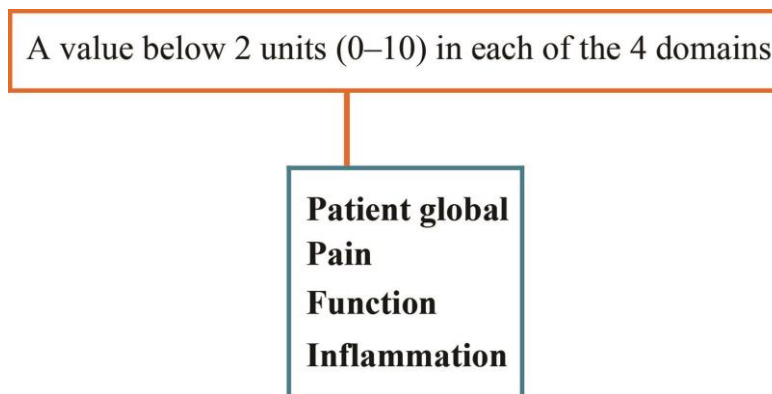
Figure 14 Selected cut-offs for improvement in the Ankylosing Spondylitis Disease Activity Score (ASDAS) (Source: Assessment of SpondyloArthritis international Society (ASAS) www.asas-group.org).



4.4 Remission, low disease activity

In addition to response criteria, **ASAS partial remission criteria** have been defined (figure 14). These are fulfilled if the value for all four domains included in the ASAS 20 response criteria is below 2. The **ASDAS cut off of <1.3** selected by ASAS to denote **inactive disease** also represents a remission-like state but the term ‘inactive disease’ was preferred by ASAS members, as remission is part of a broader concept that has not been completely defined in axial SpA and may include other features such as the absence of bone marrow oedema/osteitis (as determined by MRI). Compared with ASAS partial remission criteria, ASDAS inactive disease has the advantage of being independent of BASFI: patients with quiescent disease and a lot of structural damage who (as a consequence) have a high BASFI may never achieve ASAS partial remission, whereas they may more easily achieve ASDAS inactive disease.

Figure 15 The Assessment in SpondyloArthritis international Society (ASAS) partial remission criteria (www.asas-group.org).



4.5 The ASAS Health Index (ASAS HI)

The ASAS HI is a recently developed health index for patients with SpA based on the International classification of functioning, disability and health (ICF) core set for AS. It is important to emphasise that the ASAS HI is not a health-related quality of life instrument. It measures the burden or the impact of the disease, which encompasses different aspects of the disease (disease activity, structural damage, reduced mobility, reduced physical function, and reduced social participation) in an even more extensive way than health-related quality of life. The ASAS HI is a linear composite measure assessing ‘health’ in its broader sense and containing 17 items: (1) ‘Pain sometimes disrupts my normal activities’; (2) ‘I find it hard to stand for long’; (3) ‘I have problems running’; (4) ‘I have problems using toilet facilities’; (5) ‘I am often exhausted’; (6) ‘I am less motivated to do anything that requires physical effort’; (7) ‘I have lost interest in sex’; (8) ‘I have difficulty operating the pedals in my car’; (9) ‘I am finding it hard to make contact with people’; (10) ‘I am not able to walk outdoors on flat ground’; (11) ‘I find it hard to concentrate’; (12) ‘I am restricted in travelling because of my mobility’; (13) ‘I often get frustrated’; (14) ‘I find it difficult to wash my hair’; (15) ‘I have experienced financial changes because of my rheumatic disease’; (16) ‘I sleep badly at night’; (17) ‘I cannot overcome my difficulties’. The response option is dichotomous (‘I agree’ = score 1, or ‘I do not agree’ = score 0). All item scores are summed to give a total score that ranges from 0 (good functioning) to 17 (poor functioning). In addition, a questionnaire with a set of nine environmental factors (EF) has been proposed to address the issues of support/relationships, attitudes and health services. These EF items can act as a barrier or a facilitator and may influence the health of patients with axial SpA.

4.6 Frequency of monitoring

The frequency of monitoring in patients with axial SpA is variable and largely dependent on disease activity. With the availability of new treatments, monitoring of axial SpA is becoming more important.

4.7 Imaging assessment

4.7.1 Conventional radiographs

Radiography is the first imaging step in making the diagnosis of AS. The *anteroposterior (AP) view of the pelvis* gives sufficient information about the SI joints, making special projections unnecessary. *Lateral radiographs of the cervical and lumbar spine* give information on the severity and extent of the disease. The lateral radiograph of the thoracic spine is often difficult to interpret owing to over-projections of the ribs and other structures. AP films of the cervical spine are of little help in axial SpA; AP films of the lumbar spine do give extra information on the extent of syndesmophyte formation, although this information is rather limited and it is questionable whether it is worth the extra radiation and costs.

4.7.1.1 Which abnormalities?

The radiographic process in AS is dominated by osteoproliferation, although osteodestruction also occurs to a limited extent. Sclerosis, erosions, pseudodilatation and ankylosis are the major features. The value of the findings depends on the age of the patient because erosions and ankylosis are increasingly found in older people—this being regarded as a consequence of osteoarthritis. AS-related spinal changes can be differentiated into active (spondylitis, spondylodiscitis), structural osteodestructive (erosions), and structural hyperproliferative (enthesophytes, vertebral squaring, disc calcifications, syndesmophytes, bony bridging, vertebral ankylosis) changes. Syndesmophytes are characterised by a typical axial growth, which may lead to bridging between vertebrae in the outer, but sometimes also in the central, part of the annulus fibrosus. Furthermore, syndesmophytes may appear in the prediscal region between the intervertebral disc and the anterior intervertebral ligament.

4.7.1.2 Which sites?

Assessment of the *SI joints* is especially important for making a diagnosis (figure 16). Radiographs of the *spine* are most informative for assessing the extent of the disease and for following progression over time. *Hip* involvement is an important prognostic factor. However, radiographs of the hips should not be taken routinely, but only if clinically indicated. Moreover, if the SI joints need to be visualised, this can be done by the AP view of the pelvis, which has the major advantage of providing information about the hips as well. Assessment of peripheral joints should only be done if clinically indicated.

Figure 16 Both sacroiliac joints show some erosions, sclerosis, bony bridges, irregular joint space and ill-defined margins (bilateral grade 3 according to modified New York criteria: grade 0, normal; grade 1, suspicious for sacroiliitis; grade 2, small localised areas with erosions or sclerosis without alteration in joint width; grade 3, moderate/advanced sacroiliitis with one or more erosions, evidence of sclerosis, joint space narrowing or widening or partial ankylosis; grade 4: total ankylosis).



4.7.2 Scoring methods: general introduction

Three methods have specifically been designed for the assessment of structural damage in AS. Table 10 summarises the various characteristics of the scoring methods. All methods are suitable for assessing damage in the spine. In addition, scoring methods for the SI joints exist, as well as one specific method for assessment of the hips in AS.

Global spine

➔ BASRI (AP and lateral, SI joints, lumbar and cervical spine), BASRI hip, BASRI total

Detailed spine

➔ SASSS (lateral thoracic and lumbar spine, anterior and posterior corner)

➔ modified SASSS (lateral cervical and lumbar spine, anterior corner)

4.7.3 Global assessment of the spine

4.7.3.1 Bath Ankylosing Spondylitis Radiological Index

The Bath Ankylosing Spondylitis Radiological Index (BASRI) spine has three components: the SI joints, the lumbar, and the cervical spine (Calin et al, 1999). A global score ranging from 0 to 4 (normal, suspicious, mild, moderate, and severe) is applied to each component. The SI joints are scored according to the four grades of

the modified New York criteria (0-4). To assess the lumbar spine, lateral and AP views are used. The score for the lumbar spine, from the lower border of T12 to the upper border of S1, is a composite score of both views, taking all the affected levels into account in the score. The cervical spine was defined as extending from the lower border of C1 to the upper border of C7. Squaring, sclerosis, erosions, syndesmophytes and fusion are the features that are included. Syndesmophytes and fusion are the most important parts driving the scoring method. The BASRI spine is the sum of the mean score of the right and left SI joint (to one decimal place) plus the score of the lumbar spine plus the score of the cervical spine. The range for the BASRI spine is 2–12 (as patients with AS have sacroiliitis by definition, the minimum is 2). A similar grading system has been developed for the hips: the BASRI hip. The sum of the BASRI spine and BASRI hip is called the BASRI total, with a range from 2 up to 16.

Table 10 Comparison of radiographic scoring methods for ankylosing spondylitis

	BASRI	SASSS	Modified SASSS
<i>Films</i>			
AP pelvis	X	–	–
Lateral cervical spine	X	–	X
Lateral lumbar spine	X	X	X
AP lumbar spine	X	–	–
<i>Joints/vertebrae included</i>			
SI	X	–	–
Hip	X	–	–
Cervical spine	X	–	X
Lumbar spine	X	X	X
<i>Features scored</i>			
Erosions	–	X	X
Squaring	–	X	X
Sclerosis	–	X	X
Syndesmophyte	–	X	X
Global	X	–	–
<i>Number of sites per film scored for</i>			
Erosions	–	6 [‡]	12 [§]
Squaring	–	6	12
Sclerosis	–	6	12
Syndesmophytes	–	6	12
Global	3–4*	–	–
<i>Range</i>			
Per vertebra for erosions	–	0–1	0–1
Per vertebra squaring	–	0–1	0–1
Per vertebra for sclerosis	–	0–1	0–1
Per vertebra for syndesmophytes	–	2–3	2–3
Per joint/vertebra global	0–4	–	–
Total	2–12/16 [†]	0–72	0–72

**Without the hips, three sites (cervical, lumbar spine and SI joints) are scored, including the hips, four sites.*

†Without the hips the range is up to 12, including the hips the range is up to 16.

‡Four corners of six vertebrae are scored.

§The two anterior corners of 12 vertebrae are scored.

AP, anteroposterior; BASRI, Bath Ankylosing Spondylitis Radiological Index; SASSS, Stoke Ankylosing Spondylitis Spine Score; SI, sacroiliac.

4.7.4 Detailed assessment of the spine

4.7.4.1 Stoke Ankylosing Spondylitis Spine Score

The Stoke Ankylosing Spondylitis Spine Score (SASSS) is a detailed scoring system for the anterior and posterior site of the lumbar spine and includes the lower border of the 12th thoracic vertebra, all five lumbar vertebrae, and the upper border of the sacrum on a lateral view (Taylor et al, 1991). All four corners of each vertebra are examined and scored 1 for an erosion, sclerosis and/or squaring, 2 for a syndesmophyte, and 3 for total bony bridging, giving a maximum possible score of 72 (total of 24 corners).

4.7.4.2 Modified Stoke Ankylosing Spondylitis Spine Score

The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) is a modification of the SASSS and scores the anterior site of the lumbar and cervical spine at a lateral view (Creemers et al, 2005). The anterior corners of the cervical spine from the lower border of C2 to the upper border of T1, and the anterior corners of the lumbar spine from the lower border of T12 to the upper border of S1, are scored (total of 24 corners). The scoring of features is identical to the SASSS. The range is also 0–72. The **mSASSS** has been selected as the *preferred method for assessing structural damage in the spine* by ASAS and OMERACT, based on favourable reproducibility and sensitivity to change (Wanders et al, 2004).

4.7.5 Assessment of structural damage in clinical practice

Given the slow progression rate of structural damage in axial SpA, it is recommended that regular radiographs should be taken at an interval of ≥ 2 years. Either BASRI or mSASSS could be used as scoring methods. The disadvantage of the BASRI is the ceiling effect: patients may reach the maximum score while still showing progression. Another disadvantage is that an AP film of the lumbar spine is needed with extra radiation exposure, but this yields only limited extra information.

4.8 Magnetic resonance imaging

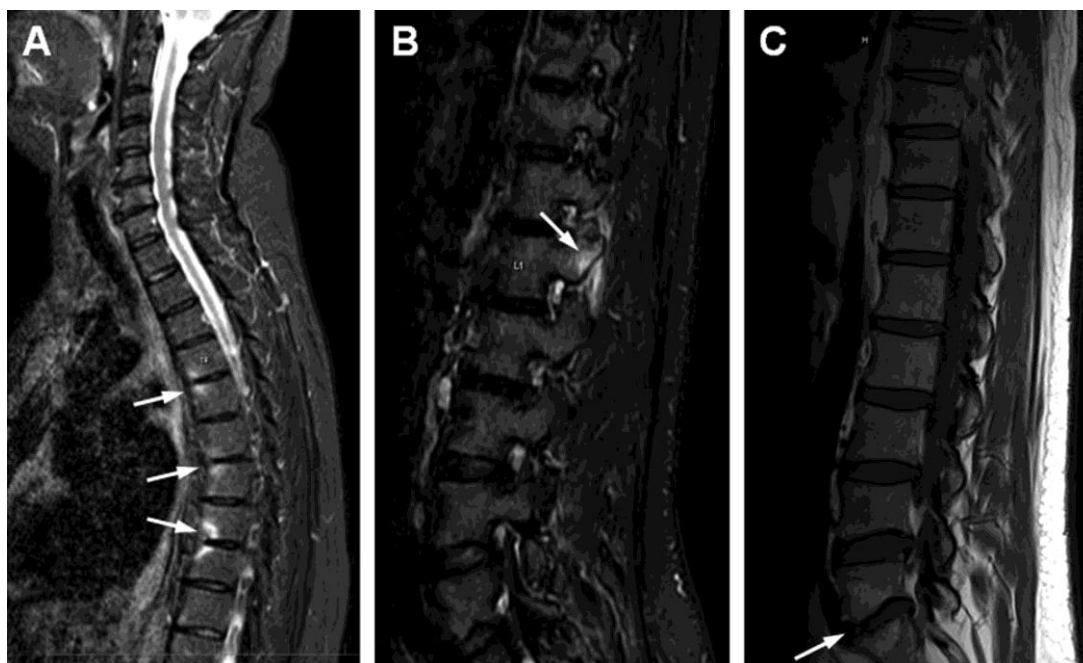
The axial skeleton is the main target for axial SpA and, owing to its ability to visualise inflammatory changes in bone and soft tissues, MRI is the most sensitive modality for imaging early spine and SI joint changes. Axial SpA

may also involve peripheral arthritis and enthesitis, which can also be visualised by MRI (Hermann et al, 2004; Maksymowych et al, 2006).

4.8.1 Which abnormalities?

Inflammatory lesions of the spine, which can be visualised by MRI, are: anterior/posterior spondylitis (figure 17A), spondylodiscitis and arthritis of the zygapophyseal (figure 17B), and costovertebral joints. Spinal structural lesions include: fatty deposition (figure 17C), erosions, syndesmophytes, and ankylosis. Findings indicating active disease in the SI joints (sacroiliitis) include juxta-articular bone marrow oedema (figure 18A), capsulitis, and enhancement of the joint space after contrast medium administration, while visible chronic changes include bone erosions, sclerosis, fatty deposition (figure 18B), and trans articular bone bridges/ankylosis. Enthesitis is also common and may affect the interspinous and supraspinous ligaments of the vertebral spine and the interosseous ligaments in the retroarticular space of the SI joints. Some patients also have disease manifestations in peripheral joints and entheses and these can be visualised by MRI as in other diseases.

Figure 17 (A) Anterior spondylitis: STIR image showing corner bone marrow oedema at T4/5, T6/7 and T8/9. (B) Arthritis of the zygapophyseal joints: STIR image showing inflamed facet joints at L1/2. (C) Fatty deposition: T1 image showing high signal intensity due to fatty deposition at L5/S1 anterior vertebral corners. STIR, short tau inversion recovery.



4.8.2 Which joints and how to acquire images?

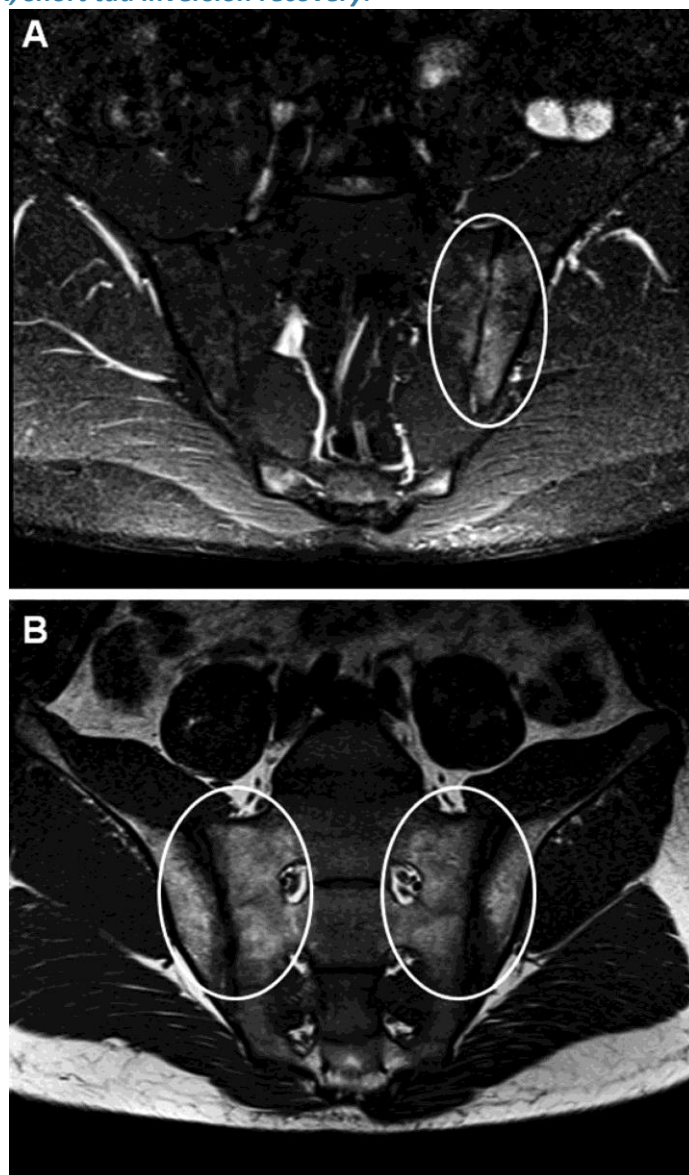
Most MRI studies of the SI joints have used only one imaging plane (semicoronal, i.e., parallel with the axis of the sacral bone). To be maximally sensitive for changes in the ligamentous portion of the SI joints, imaging in

two perpendicular planes is required. This is particularly important when MRI is used for diagnosis, though probably less important when used as an outcome measure in trials.

Similarly, the majority of MRI studies of the axial SpA spine involve only sagittal images, which are not optimal for visualising changes in the apophyseal and costovertebral joints. The importance of such changes remains to be determined.

There is general agreement that adequate MRI of the axial SpA spine, as of the SI joint, must at least include a *T1-weighted sequence without fat saturation* and a *STIR sequence in one plane*. To what extent further sequences -including post-contrast sequences and/or more planes- are needed, is debated and depends on the goal of the examination.

Figure 18 (A) Active left sacroiliitis (bone marrow oedema) in a patient with non-radiographic axial spondyloarthritis; affected bone marrow areas (oval line) are located periarticularly (STIR). (B) Fatty deposition in the same patient; T1 image showing high signal intensity due to fatty deposition (oval lines) at both sacroiliac joints. STIR, short tau inversion recovery.



4.8.3 Methods for assessment

Several scoring systems for assessment of disease activity in the SI joints and in the spine have been proposed. These have been tested against each other by the OMERACT-ASAS MRI in AS group and will be described below, followed by a description of the few systems available for assessment of chronic damage.

4.8.3.1 Activity: spine

Three different scoring systems have been developed and validated: the Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity (**ASspiMRI-a**) score, grading activity 0–6 per vertebral unit in 23 units; the **Berlin modification of the ASspiMRI-a score**, grading activity 0–3 per vertebral unit in 23 units; and the Spondyloarthritis Research Consortium of Canada (**SPARCC**) scoring system, scoring only the six vertebral units considered by the reader as the most abnormal, with additional points for ‘depth’ and high ‘intensity’ of the lesion (table 11). In an OMERACT–ASAS multireader exercise, the feasibility, reliability, sensitivity to change, and discriminatory capacity of all three scoring systems in patients with AS were demonstrated. The SPARCC method had the highest sensitivity to change, as judged by Guyatt’s effect size and the highest reliability as judged by the inter-reader intraclass correlation coefficient, but not if judged by the smallest detectable change (Lukas et al, 2007).

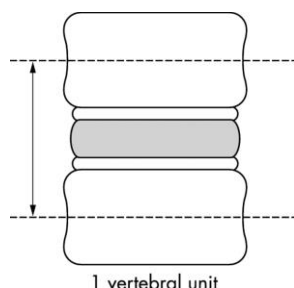
Table 11 MRI scoring methods for assessment of the spine in ankylosing spondylitis

	Activity			Damage
	SPARCC	ASspiMRI-a	Berlin	ASspiMRI-c
Images	Sagittal STIR	Sagittal post-Gd T1-weighted FS + sagittal STIR	Sagittal post-Gd T1-weighted FS + sagittal STIR	Sagittal T1-weighted
Area	Six most affected DVUs	All 23 DVUs	All 23 DVUs	All 23 DVUs
Features	Bone marrow oedema	Bone marrow oedema/enhancement and bone erosion	Bone marrow oedema/enhancement	Sclerosis, squaring, syndesmophytes and bridging/fusion
Grades	0–1 per DVU quadrant + 1 for depth ≥ 1 cm and 1 for high intensity of lesion	0–6 per DVU	0–3 per DVU	0–6 per DVU
Total score range	0–108	0–138	0–69	0–138

ASspiMRI-a, Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity; *ASspiMRI-c*, Ankylosing Spondylitis spine Magnetic Resonance Imaging-chronicity (Braun et al, 2003); *Berlin method* (Braun et al, 2004); *SPARCC*, Spondyloarthritis Research Consortium of Canada (Maksymowych et al, 2005).

DVU, disco vertebral unit defined as the region between two virtual lines through the middle of each vertebra and includes the intervertebral disc and the adjacent vertebral end plates (Figure 19); FS, fat saturated; Gd, intravenous injection of gadolinium-containing contrast agent; SpA, spondyloarthritis; STIR, short tau inversion recovery.

Figure 19: Definition of a DVU (Braun et al, 2004)



4.8.3.2 Activity: sacroiliac joints

Three main scoring approaches have been proposed, based on either global scores per quadrant or individual scores in consecutive semicoronal images through the joint (table 12).

Table 12 MRI scoring methods for assessment of the sacroiliac joints in ankylosing spondylitis

	Activity			Damage	
	SPARCC	Puhakka activity	Hermann activity	Puhakka damage	Hermann damage
Images	Semicoronal STIR	Pre- and post-Gd semicoronal and semi axial T1-weighted FS; semicoronal STIR	Semicoronal pre- and post-Gd T1-weighted FS and STIR	Pre-Gd semicoronal and semi axial T1-weighted and T1-weighted FS	Semicoronal pre- and post-Gd T1-weighted and T1-weighted FS
Area	SI joints, six consecutive semicoronal slices	SI joints, in two planes	SI joints, in semicoronal plane	SI joints, in two planes	SI joints, in semicoronal plane
Features	Bone marrow oedema	Bone marrow oedema, bone marrow enhancement, joint space enhancement	Bone marrow oedema, bone marrow enhancement	Erosion, sclerosis, joint space width	Erosion, sclerosis, joint space width, bone bridging/ankylosis
Grades	In each slice: 0–1 per quadrant + 1 for depth ≥ 1	Marrow oedema: 0–3 per quadrant; marrow enhancement: 0–3 per quadrant; joint	Global: 0–3 per quadrant	Erosion: 0–3 per quadrant; sclerosis: 0–3 per quadrant;	Global: 0–4 per joint

	cm and 1 for high intensity	space enhancement: 0–3 per joint		joint space: 0–3 per joint	
Total score range	0–108	0–60	0–24	0–60	0–8

Hermann method: Hermann et al, 2004; Puhakka method: Puhakka et al, 2003; SPARCC, Spondyloarthritis Research Consortium of Canada: Maksymowych et al, 2005.

FS, fat saturated; Gd, intravenous injection of gadolinium-containing contrast agent; SI, sacroiliac; STIR, short tau inversion recovery.

The presence and extent of bone marrow oedema in the cartilaginous portion of the joint is the primary MRI feature that is scored, although one method also scores inflammation in the joint space and the ligamentous portion of the joint.

In an OMERACT–ASAS multireader exercise, agreement between readers and sensitivity to change were compared and found somewhat better for the most detailed scoring method (the SPARCC method).

4.8.3.3 Damage: spine and sacroiliac joints

The only method proposed for scoring the AS **spine** is the Ankylosing Spondylitis spine Magnetic Resonance Imaging-chronicity (**ASspiMRI-c**) **score**, grading chronic changes (sclerosis, squaring, syndesmophytes and fusion) 0–6 per vertebral unit in 23 units (table 11).

A scoring method for chronic changes in the **SI joints (Puhakka)** scores bone erosions and sclerosis at four osseous positions per joint (the iliac and sacral sides of the cartilaginous and ligamentous portions of the joints, respectively), as well as the joint space width (table 12). Another approach (**Hermann**) scores each sacroiliac joint 0–4 based on a global assessment of erosion, sclerosis, joint space width and bone bridging/ankylosis (table 12). Validation of the methods for damage assessment is limited and their value has not yet been clarified.

4.8.4 Predicting and monitoring disease activity and damage: implications for clinical practice

MRI allows detection and monitoring of disease activity in the spine and SI joints with a higher sensitivity than any other imaging modality and has been a major improvement in both clinical trials and practice.

Data concerning the advantage of MRI for detection of damage in SI joints and the spine compared with radiography are ambiguous and further studies are needed to clarify the role of MRI for follow-up of axial SpA damage. The prognostic significance of MRI findings, if any, has not been clarified.

4.9 Ultrasonography

US is not suitable for the assessment of axial disease, as changes are generally located at sites inaccessible to US examination. In patients with peripheral involvement US can visualise such changes as in other diseases. US has proven to be a valuable assessment of enthesal disease in axial SpA patients (D'Agostino et al, 2003). Standardised scoring systems are available, but further validity testing is required (D'Agostino et al, 2009; de Miguel et al, 2009; Naredo et al, 2010).

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SUMMARY POINTS

- For a complete description of the burden of disease of a patient with an inflammatory rheumatic disease, information on disease activity, function and structural damage is needed.
- For rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (SpA) core sets are available including the minimum assessments that should be performed in the evaluation of a clinical trial or clinical practice, or both.
- Composite measures for disease activity in RA such as the Disease Activity Score (DAS), 28-joint DAS (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI) give a good indication of the level of overall disease activity and are useful in the evaluation of clinical trials and as a benchmark for tailor-made treatment.
- Response criteria in all inflammatory diseases (such as American College of Rheumatology (ACR) 20, EULAR, Assessment in SpondyloArthritis international Society (ASAS) 20, and Ankylosing Spondylitis Disease Activity Score (ASDAS) response criteria) provide limited information at the individual patient level, especially in view of longterm follow-up, and should be complemented by status scores (such as remission criteria).
- Films of hands and feet give sufficient information to determine the extent of damage on conventional radiographs in RA and follow the course of the development of damage. Several validated scoring systems exist for use in clinical trials ((modified) Sharp, Larsen method) and for use in clinical practice (Simple Erosion Narrowing Score (SENS)).
- In RA, magnetic resonance imaging (MRI) and ultrasonography (US) are highly sensitive techniques for detecting early inflammatory and destructive changes in RA joints. MRI is also sensitive to change in synovitis and erosions and is predictive of future radiographic progression.
- In axial SpA, MRI allows detection and monitoring of disease activity in the spine and sacroiliac joints with a higher sensitivity than any other imaging modality and has been a major improvement in both clinical trials and daily practice.
- The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) is the preferred method for assessing damage to the spine in axial SpA on conventional radiographs because of good reliability and sensitivity to change.
- In PsA, MRI and US can visualise activity and damage in axial (only MRI) and peripheral joints, but the value for monitoring and prognosticating PsA is not yet established.

Key references*

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8

module

EULAR on-line course on Rheumatic Diseases

Measuring disease activity and damage in inflammatory arthritis

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A previous version was coauthored by Pernille Bøyesen, Pedro Machado, Désirée van der Heijde and Mikkel Østergaard



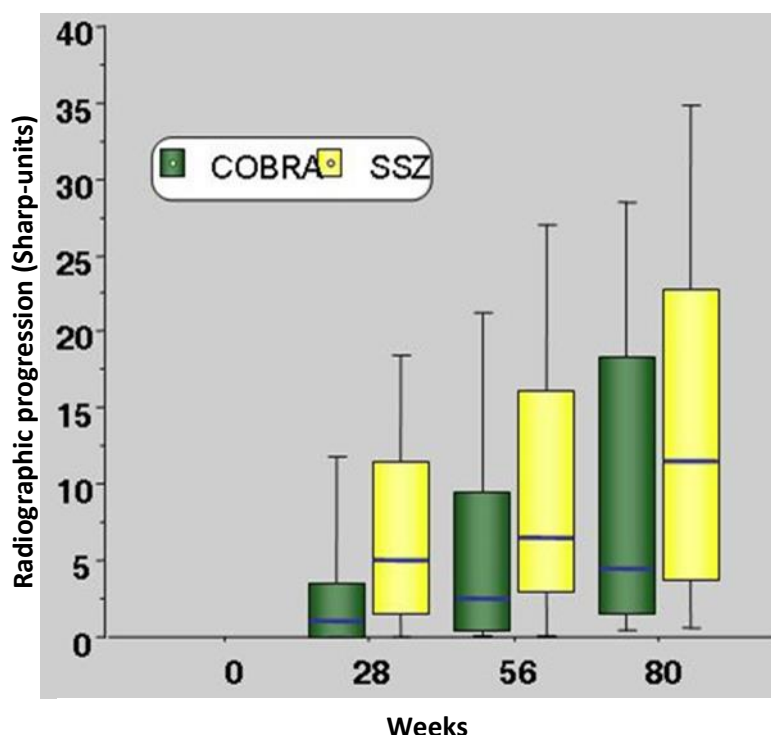
IN-DEPTH DISCUSSION I

Presentation and interpretation of radiographic data

Structural damage caused by inflammatory joint diseases evolves slowly over a long period of time, but with marked inter-individual variation. Scoring systems quantify the amount of damage. Sets of X-rays (e.g. hands and feet for RA) obtained with regular time intervals are scored and the sum score per patient reflects total damage at a time point. The within-patient difference occurring between two or more observations in time is considered to be the individual change (progression) score.

How to present radiographic data to the medical readership ?

A number of difficulties limit the interpretability of radiographic scores in clinical studies. The first problem is how to present radiographic data to the medical readership. Both in RA and in AS, radiographic progression scores are not normally distributed. Only a small fraction of all patients show substantial progression of damage and the majority shows no progression at all. One of the assumptions underlying the use of means and standard deviations - descriptive parametric statistics that most clinicians are familiar with - is a normal distribution of the data. Since they are not normally distributed, progression scores should not be presented (only) as mean scores with standard deviations (SD). **Means and standard deviations** calculated in a set of radiographic scores are extremely sensitive to subtle changes at the upper extreme. A better way of presenting radiographic data is by medians (the value cutting off the 50 percentile), and 25- and 75 percentiles, or by **Box & Whisker plots**, that in addition present the 5- and 95-percentile, as well as the extreme values (figure 1). Some investigators present logarithmically transformed data, which may result in a dataset with a normal distribution, but these data are even more difficult to interpret. The most important disadvantage of percentiles like the median in comparison with means and SDs is that percentiles only relate to one observation in the distribution (e.g. the median observation), and neglect the majority of the variable's values. Means and SDs are so-called inferential statistics that include all variable's values, and describe the internal coherence of the data. Since the presentation of percentiles does not admit a proper judgement of the coherence of the data, this may easily conceal irregularities in the frequency distribution of radiographic scores. This may become important if cut-off levels for clinically important progression scores are chosen: a small change in the selected cut-off level may have a major effect on the results. Ordinary presentation of data (with percentiles only) that are not normally distributed thus gives rise to a significant loss of information as compared to the presentation of data derived from a normal distribution by means and SDs. Therefore there is a consensus that the minimum presentation of radiographic data should include both the mean and SDs and the median and IQR.

Figure 1. Change in radiographic damage - example box plot

How to present differences in scores between different observations and/or observers ?

Another issue is measurement error, the phenomenon that different observers score the same X-rays differently, or one observer who scores the same X-rays twice arrives at different scores. When comparing treatment groups, measurement error is equally divided across these groups as a consequence of randomisation and blinding of readings. In uncontrolled observational studies, or in analyses within one treatment group of a comparative trial, however, measurement error can become crucial. In order to gauge part of measurement error, there is some consensus that readings in clinical trials in RA should be performed by at least two readers, and that the average score obtained by all readers should be used in analyses. Inter-observer measurement error can be made visible by **Bland & Altman plots** (see extra information below), but this technique is difficult to understand to the uninvolved audience, and therefore often not published in medical journals.

Relatively new is the use of the **cumulative probability plot** as a means of presentation of radiographic progression scores. Probability plots can be used to help the reader of the article make a proper judgement about progression, but also about differences between different observations and/or observers.

How to construct and interpret cumulative probability plots ?

Radiographic data from the COBRA trial are used to illustrate how to construct and interpret cumulative probability plots. The COBRA trial is a one-year randomised clinical trial of 135 patients that compared the effects of a strategy with combination therapy (prednisolone, methotrexate and sulfasalazine) with monotherapy (sulfasalazine only).

Table 1 summarises all observed radiographic progression scores, which are defined as the difference between the total damage score at the end of the trial and that at the start of the trial. Data were summarised by change score in 3 different ways: 1) number of patients with a particular progression score; 2) cumulative number of patients with a progression score \leq that particular score (=cumulative frequency); and 3) cumulative percentage of patients with a progression score \leq that particular score (=cumulative probability). Cumulative probability is the cumulative frequency expressed as a percentage of the total number of patients. Note that every patient contributes for an equal part ($1/135 = 0.0074$ or 0.74%) to the cumulative probability.

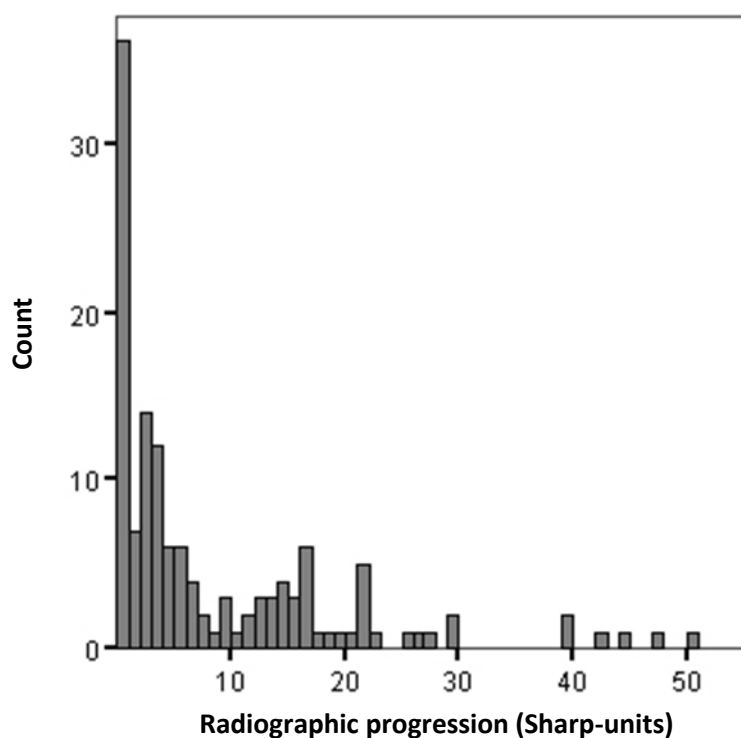
Table 1. Frequency distribution of radiographic progression scores of 135 patients who had participated in the COBRA trial

Progression score:	Number of patients with this score:	Patients with this score or below:	
		Cumulative frequency	Cumulative probability (%)
0	22	22	16.3
1	14	36	26.7
2	7	43	31.9
3	14	57	42.2
4	12	69	51.1
5	6	75	55.6
6	6	81	60.0
7	4	85	63.0
8	2	87	64.4
9	1	88	65.2
10	3	91	67.4
11	1	92	68.1
12	2	94	69.6
13	3	97	71.9
14	3	100	74.1
15	4	104	77.0
16	3	107	79.3
17	6	113	83.7
18	1	114	84.4
19	1	115	85.2
20	1	116	85.9
21	1	117	86.7
22	5	122	90.4
23	1	123	91.1
24	0	123	91.1

25	0	123	91.1
26	1	124	91.9
27	1	125	92.6
28	1	126	93.3
29	0	126	93.3
30	2	128	94.8
>30	7	135	100

If data such as in Table 1 (column 1 and 2) are plotted in a graph, a bar chart such as in Figure 2a can be created. **Bar charts** are useful to get an impression about the type of distribution of the data, e.g. to find out whether the data are normally distributed (bell-shaped curve). The pattern in Figure 1a is a typical example of a set of radiographic progression scores: since the change scores with the highest frequencies lie left as compared to the scores of the normal distribution, such a distribution is called skewed-to-the-left.

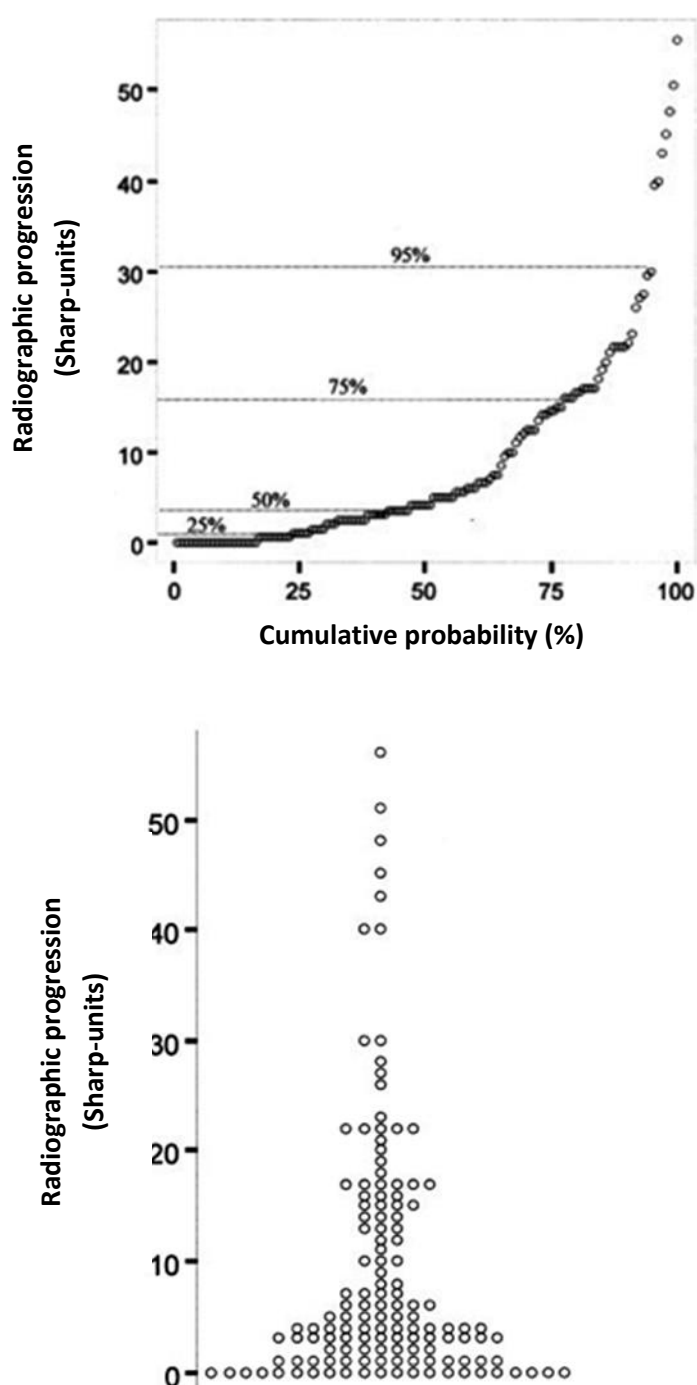
Figure 2a. Individual progression scores of 135 patients who participated in the COBRA trial. Data are visualised by histogram (Fig 2a), cumulative probability plot (Fig 2b), and dot plot (Fig 2c). See text for further explanation.



If all separate cumulative probability values (x-axis) are plotted against all separate scores (n=135) (y-axis), then a **probability plot** is created (Figure 2b). Every single change score (one score per patient) is now plotted in the graph, and represents a similar proportion of the cumulative probability (0.74%), so that the density of dots is similar along the entire range of the x-axis. The lowest scores are zero, and it is obvious from the figure that the lower range of progression scores (<10 Sharp-units) occur far more frequently than the higher range. It is easy to see which proportion of patients has a change score of zero. High and very high scores occur

sporadically, and hardly contribute to the cumulative frequency, but they importantly determine the curvature of the graph, as well as the mean and the standard deviation. The median and the 25/75 percentiles can easily be derived from the probability plot by drawing a straight line from the corresponding percentile on the x-axis through the curve (Fig 2b). The matching progression scores can be read from the y-axis. Figure 2c shows a dot plot of the same radiographic data. Dot plots also include all separate scores. Probability plots as well as dot plots allow an interpretation of the coherence of the data (irregularities, “jumps”), but it is impossible to directly interpret percentiles from a dot plot.

Figure 2b



How can cumulative probability plots be used to visualise inter-reader variability ?

Because of measurement error, readings of X-rays are usually performed by two or more readers. Cumulative probability plots can be used to visualise inter-reader variability, and to explore trends. Figure 3a shows the probability plot of change scores obtained by two independent readers who scored the same sets of X-rays of AS-patients from the OASIS cohort (2 years progression scores) according to the modified SASSS. At first glance, it is obvious that reader 1 scores somewhat higher than reader 2. Reader 1 sees some progression in a greater proportion than reader 2 (is more sensitive to change), but sees negative scores in a smaller proportion than reader 2 (sensitivity to change is not at the cost of specificity here). As compared to reader 2, the entire curve of reader 1 is translated to the left.

Extra information: Bland & Altman plot, another instrument to visualize inter- and intra-reader variability

Bland & Altman plots can be used to assess agreement between readers. These plots present the difference in progression scores between two readers on the y-axis against the average progression score of the readers on the x-axis. Figure 3b displays the same data as Figure 3a but now in the format of a Bland & Altman plot. Again, it is obvious that reader 1 scores a little bit higher (represented by a mean negative difference between the readers (dotted line), but additional information is difficult to deduct from this plot. What are the differences between probability plots and Bland & Altman plots? First, the actual progression scores can be easily and directly depicted from the probability plot. It requires additional inference if you want to get this information from a Bland & Altman plot. As an example, the dot designated with an arrow in Fig 3b (the mean score of 5 and the difference score of -4 comprises an actual score of $+3$ by reader 1, and of $+7$ by reader 2). Second, in probability plots, unlike Bland & Altman plots, the scores of two readers for a particular value of the x-axis do not necessarily belong to the same patient. Third, probability plots can simultaneously plot the scores of more than two readers, which is not possible with Bland & Altman plots. An advantage of probability plots is that these are appropriate for investigating the coherence of the data of the group, with presentation of the actual progression scores. It should be noted however, that probability plots are not appropriate to quantify measurement error, which can be done by using the data of the Bland & Altman plot. Therefore, both types of plots give complementary information, and it depends on the data and the study question to use either of them or both.

Figure 3. Cumulative probability plots (Fig 3a) and Bland & Altman plot (Fig 3b) of individual 2-years radiographic progression scores (in modified SASSS-units) in 109 patients with ankylosing spondylitis who had participated in the OASIS cohort. Every patient was scored twice by two different readers (open circles and open triangles), who both read with concealed time order.

Figure 3a

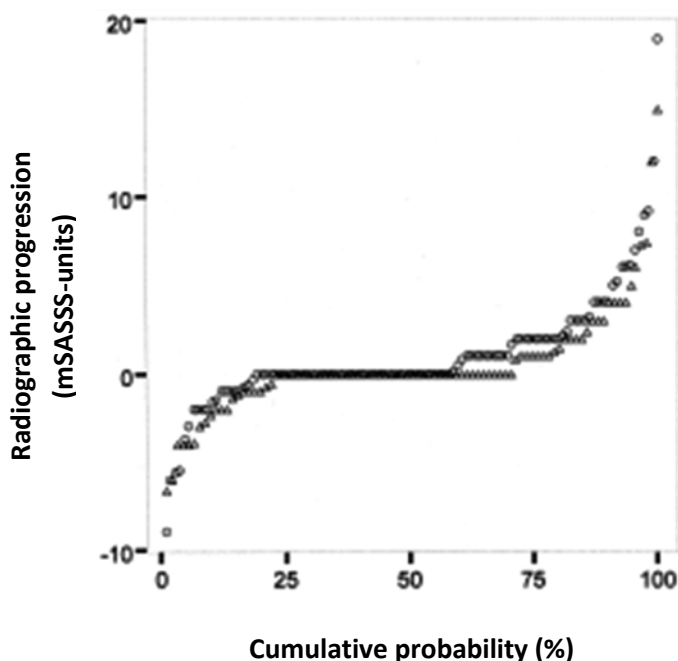
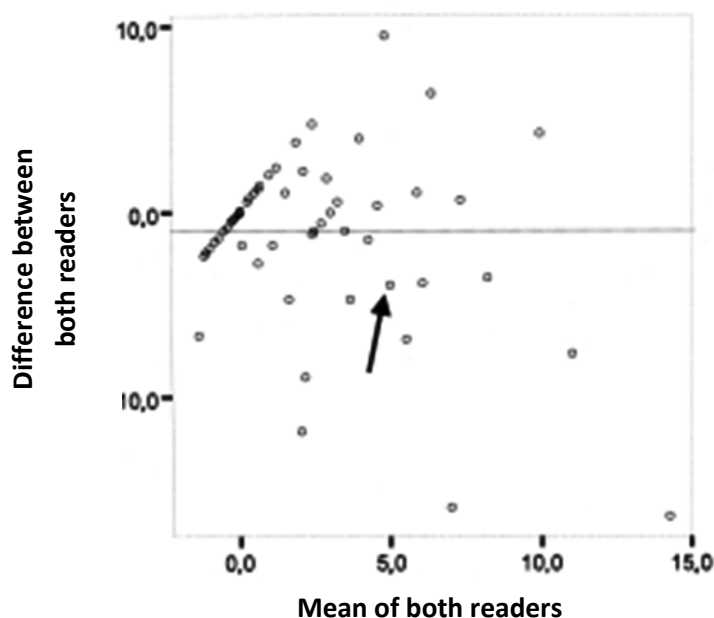


Figure 3b



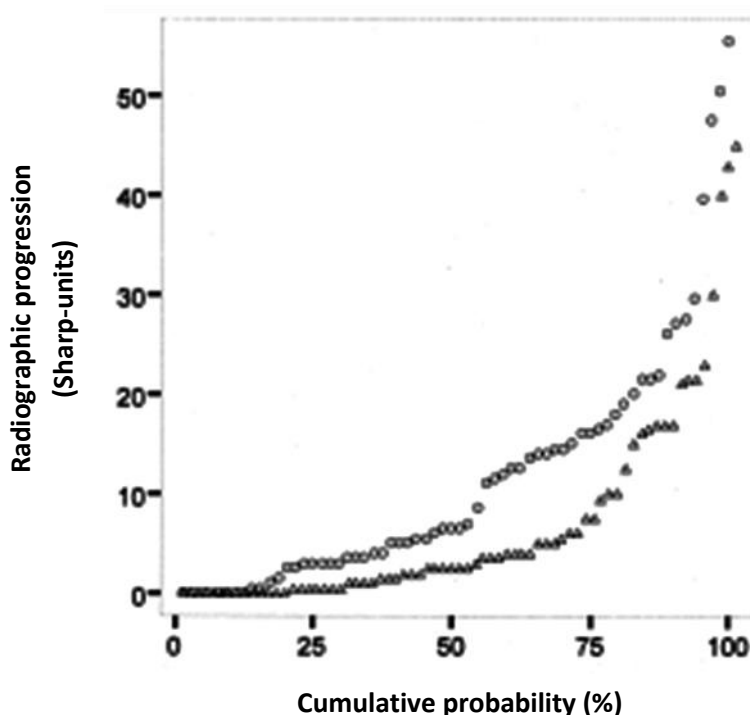
Note: a circle and a triangle with similar cumulative probability (Fig 3a) do not necessarily belong to the same patient. Every dot in the Bland & Altman plot (Fig 3b) refers to the same patient scored by two readers, but one symbol may comprise more than one patient.

(See text for the explanation of the arrow in the Bland & Altman plot)

How can cumulative probability plots be used to compare progression scores between treatment arms ?

Probability plots are also useful to visually compare the distributions of two (or more) treatment arms in a clinical trial. Figure 4 shows the probability plots of the two treatment arms of the COBRA trial. COBRA combination therapy was shown to be significantly better than SSZ monotherapy in slowing one-year progression. The plots immediately show that the treatment groups differ with respect to radiographic progression. In the COBRA trial the curve representing the combination therapy group lies closer to the X-axis than that representing the monotherapy group, along the entire range of change scores, except for the scores close to - or equal to - zero. It is also obvious that the distribution of the monotherapy group includes higher absolute change scores, as compared to the distribution of combination therapy group. At last, the cumulative probability curves are not entirely "smooth", and the space between both curves, which is an indication for the treatment contrast, varies along the axis of cumulative probability. This irregularity is important if one realises that binomial cut-off levels for radiographic progression are often used to "understandably" describe the magnitude of the treatment effect. The probability curves learn that the choice of the cut-off level is relevant for the magnitude of the treatment contrast. For example, if a cut-off level of 0 Sharp-units is selected (every patient with a score >0 is considered "progressive"), there is progression in 80% of the patients in the combination group compared to 87% in the monotherapy group, resulting in a between-group contrast of only 7%. The choice of a cut-off level of 5 Sharp-units, in contrast, would adjudicate progression to 31% and 58% in the combination group and monotherapy group, respectively, with a treatment contrast of 27%. As a consequence, an optimal cut-off level (read: that provides the highest contrast) can be constructed.

Figure 4. Cumulative probability plots of individual 1-year radiographic progression scores (in Sharp-units) in 135 patients with rheumatoid arthritis who had participated in the COBRA trial (67 patients in the monotherapy group (open circles), and 68 patients in the combination therapy group (open triangles)).



What can we conclude ?

The ordinary way of presenting radiographic progression by descriptive statistics such as medians and percentiles, combined with means and standard deviations, gives rise to a loss of potentially relevant information. Probability plots can be used to visualise the phenomenon of measurement error, or to explore treatment differences in clinical trials, and may learn a lot more about the course of radiographic progression. Likely the most important advantage of probability plots over conventional means of presentation is that probability plots, unlike percentiles or Box & Whisker plots, clarify whether or not there is coherence among the data. Demonstration of data coherence may add to the credibility of a group-result if this is presented as a median. Probability plots can also be used in other outcome areas to visualize data, especially if there is a skewed distribution.

Adapted from:

Landewé R, van der Heijde D. Radiographic progression depicted by probability plots: presenting data with optimal use of individual values. *Arthritis Rheum* 2004;50(3):699-706

Landewé R, van der Heijde D. Presentation and analysis of radiographic data in clinical trials and observational studies. *Ann Rheum Dis* 2005;64 suppl IV:i48-51

Landewé R, van der Heijde D. Radiographic progression in rheumatoid arthritis. *Clin Exp Rheum* 2005;23(suppl 39):S63-S68



8

module

EULAR on-line course on Rheumatic Diseases

Measuring disease activity and damage in inflammatory arthritis

Patrick Verschueren, Nathalie Berghen and Pedro Machado

A previous version was coauthored by Pernille Bøyesen, Pedro Machado, Désirée van der Heijde and Mikkel Østergaard



IN-DEPTH DISCUSSION II

**Magnetic resonance imaging of synovial and bone
inflammation: a clue to what drives erosive
progression in RA**

RA is a heterogeneous disease characterised by joint inflammation (1, 2). Persistent joint inflammation can cause local bone damage, which is related to functional disability during the course of the disease (3, 4). With the introduction of new therapeutic agents and knowledge about early treatment targeting inflammation, we have experienced a major improvement in RA patient care (5-7). Moreover, considerable research efforts have been made in search of prognostic markers that would be of benefit for clinical decision-making in individual patients (8). The prognostic role of magnetic resonance imaging (MRI) has been one of the research priorities. Synovitis is considered a hallmark finding for RA and inflamed synovium visualised by MRI has been shown to be associated with bone damage (9-11). More surprisingly, MRI detected inflammation within the bone (bone marrow oedema) is frequently observed in RA patients and also predicts subsequent bone damage (11-15). This has resulted in a discussion as to whether bone erosions are a result of synovitis or bone marrow oedema (16).

What is current hypothesis regarding the pathophysiology of bone erosions in Rheumatoid Arthritis ?

The rheumatoid synovial membrane is transformed into a hypertrophic inflammatory tissue caused by influx and proliferation of macrophages, fibroblasts, T cells and B cells (17). Bone erosions typically occur at the junction of the synovial membrane and the bone, suggesting that synovitis causes erosions. Jimenez-Boj et al showed in a histological study of bone from RA patients that inflammatory synovial tissue disrupts the cortical bone barrier, directly exposing the bone marrow to inflammatory infiltrates. They found that the subchondral bone was lined with osteoclasts, as opposed to the endosteum lined with osteoblasts. These findings support that erosions are triggered from the outside by synovial inflammation (18). A later study examining the histology of MRI bone marrow oedema found localised bone marrow inflammatory infiltrates, suggesting that the bone marrow plays an active role in the inflammatory process of RA (19). Further, McQueen et al confirmed these findings and proposed MRI bone marrow oedema as a pre-erosive lesion (20). These studies underline that bone marrow oedema can occur separately, but often in conjunction with synovitis and add to the understanding of how both synovitis and bone marrow oedema can cause bone damage.

How can MRI be helpful in elucidating the pathophysiology of bone erosions in Rheumatoid Arthritis ?

MRI has been demonstrated to be a suitable tool for the evaluation of inflammation in RA. Synovitis and bone marrow oedema are frequent MRI findings in RA (12, 21-24). MRI findings of synovitis have been found to represent inflamed synovium by mini-arthroscopy and histology (25, 26). MRI findings of bone marrow oedema in RA have contributed to our understanding of the involvement of the bone marrow in the disease process (19). MRI bone marrow oedema corresponds to histological inflammatory infiltrates of the subchondral bone (19, 20). A standardised and reliable semi-quantitative scoring system of MRI synovitis and MRI bone marrow oedema has been developed in the outcome measures in RA clinical trial (OMERACT) collaboration, as part of the RA MRI score (RAMRIS) (27-30). Several studies have examined how synovitis and

bone marrow oedema assessed by MRI are associated with subsequent development of erosions. Tanaka et al showed that CRP, RF and the sum score of MRI erosions and MRI synovitis independently predicted joint damage in 114 RA patients (31). The independent contribution of MRI synovitis based on this sum score is hard to elucidate. However, MRI measured synovitis has been associated with structural bone damage across several studies (3, 9, 11, 24, 32-34). The role of the bone marrow in the development of erosions was elucidated when MRI bone marrow oedema was found to be associated with both MRI and conventional radiology (CR) measures of bone damage (13, 35). Later, two separate studies have found that MRI bone marrow oedema is independently associated with joint damage (11, 14, 15).

So far we have seen evidence that both MRI synovitis and MRI bone marrow oedema are associated with subsequent joint damage, suggesting a temporal relationship. Other studies have examined how the cumulative impact of MRI measured inflammation influences subsequent joint damage (10, 11). Conaghan et al found in a randomised controlled trial of early RA patients that the cumulative presence of MRI measured synovitis was significantly correlated with MRI erosive change (correlation coefficient of 0.42), whereas Østergaard et al showed that both baseline and 1-year time-integrated MRI synovial membrane measurements were significantly correlated with radiographic joint damage in patients with established RA (3, 24). In 55 RA patients followed for 3-years, the cumulative presence of both MRI synovitis and MRI bone marrow oedema were independently associated with progression of joint damage in a dose-dependent order (11).

To what extent can we trust the current hypothesis about the pathophysiology of bone erosions in RA ?

Before accepting the hypothesis that synovitis or bone marrow oedema are causally related to the development of bone erosions, several methodological components need to be addressed. First of all study bias, confounding and random chance, which may lead to false explanations, should be ruled out. Further, the existence of a causal relation can be established by estimating the strength of the observed association, consistency and specificity of the findings, temporal and dose-response relationship, plausibility and coherence of the results (36). The methodology of the studies presented above is sound and based on the available histological evidence it appears plausible that both synovitis and bone marrow oedema can be at the origin of subsequent bone damage. Furthermore, results also suggest a temporal and dose-dependent relationship between synovitis and/or bone marrow oedema documented on MRI and joint damage. These findings suggest that causality exists between these measures of inflammation and subsequent bone damage.

What are the practical implications of using MRI for the evaluation of patients with Rheumatoid Arthritis ?

Even though MRI has several advantages in the management of RA patients, it also has limitations. MRI scans are time-consuming, expensive and have limited availability. In addition, the scanned joint area is limited by the MRI's field of view (FOV). The FOV of one scan can include one wrist or one wrist and MCPs 2-5.

In the CIMESTRA trial, MRI bone marrow oedema was shown to be an independent predictor of CR joint damage, based on MRI assessments of the wrist as well as MRI of wrist and MCPs (14). These results suggest that one joint area may sufficiently represent inflammation. Intra-venous administration of gadolinium is commonly used for enhanced assessment of synovitis (37). Even though complications are rare, reports of nephrogenic systemic fibrosis in patients with chronic renal failure after gadolinium administration needs to be taken into consideration when ordering an MRI scan (38).

What can we conclude ?

Synovitis has traditionally been considered to trigger development of erosions in RA. However, the finding of inflammatory infiltrates in the RA bone marrow preceding erosions has led to discussion on the pathogenic mechanism of erosions. The available MRI studies, presenting assessments of synovitis and bone marrow oedema, suggest that they both are of importance to the progression of erosions in RA. Nonetheless, the modest association between synovitis, bone marrow oedema and joint damage underlines the role of other components in the development of bone destruction in RA.

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Juvenile Idiopathic Arthritis

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LEARNING OUTCOMES

- Recognise the distinctive clinical patterns of juvenile idiopathic arthritis (JIA) and its key differential diagnoses
- Describe and explain the specific inflammatory mechanisms underlying different subgroups of JIA
- Use investigations appropriately to assist the differential diagnosis, subclassification and monitoring of JIA
- Be able to provide age-appropriate disease education and counselling for children with newly diagnosed JIA and their parents
- State the importance of a multidisciplinary team approach to the treatment of JIA
- Use a safe and effective approach to drug treatment in a child with JIA
- Describe and explain complications and prognosis of different subgroups of JIA
- Describe and explain the key elements for providing an effective transitional plan for young people with JIA transferring from paediatric to adult healthcare services

1 Introduction to juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is not a single disease but a diagnosis that applies to all forms of arthritis of unknown origin, with onset prior to the 16th birthday, lasting more than 6 weeks and where other causes of arthritis have been excluded (Martini A. 2012). JIA is one of the most common physically disabling conditions of childhood, with a prevalence that varies between 16 and 150 per 100,000; about 12 000 children are affected in the UK and about 62 000 in the USA (Prakken et al, 2011*). Reported annual incidence rates of chronic childhood arthritis have ranged from less than 1 per 100,000 in Japan to more than 20 per 100,000 in Norway (Cassidy and Petty, 2005*). Relative frequency of the various JIA subtypes vary substantially according to geographic and ethnic differences (Saurenmann RK et al. Arthritis Rheum 2007): oligoarthritis, by far the most common category in Western countries is, in fact, quite rare in countries such as Costa Rica, New Zealand and South Africa or India, where polyarthritis seems to be predominant.

JIA is a diagnosis of exclusion based on a careful history taking, a thorough physical examination, and laboratory tests meant to rule out other known causes of arthritis in childhood, as reported in box 1.

For the experienced paediatric rheumatologist, the patient with JIA often presents with an almost instantly recognisable pattern of symptoms and physical findings, even during the first few weeks of illness, and very few investigations may be required. An inexperienced clinician, however, may rely heavily on inappropriate investigations in an attempt to confirm or exclude JIA. The lack of timely detection of JIA and delay in treatment is likely to adversely affect the course and outcome of the disease.

Box 1 Differential diagnosis of juvenile idiopathic arthritis

A child presenting with a single inflamed joint

Septic arthritis or osteomyelitis: consider *Staphylococcus aureus*, *Haemophilus influenzae* in non-immunised individuals; *Mycobacterium tuberculosis*, *Salmonella* spp in sickle cell disease; *Pseudomonas* spp in puncture wounds of the foot

- Lyme disease in areas where the disease is endemic. Serology indicated if the history and clinical features are suggestive
- Reactive arthritis: secondary to extra-articular bacterial (eg, streptococcal, enteric bacteria) or viral infections (eg, hepatitis B, parvovirus, Epstein–Barr virus (EBV), varicella, rubella). ‘Irritable hip’ may be a form of reactive arthritis
- Haemarthrosis: secondary to trauma (including non-accidental) or bleeding diathesis
- Malignancy: acute lymphoblastic leukaemia is the most common
- Trauma
- Solid tumour

A child presenting with more than one inflamed joint

- Connective tissue diseases: systemic lupus erythematosus (SLE), juvenile dermatomyositis, sarcoidosis, Sjögren syndrome, mixed connective tissue disease (MCTD), Henoch–Schönlein purpura
- Reactive arthritis: secondary to bacterial or viral infections
- Lyme disease
- Malignancy: leukaemia or lymphoma should always be considered in a child who has suggestive clinical and laboratory features such as cytopenia
- Immunodeficiency-associated arthritis
- Inflammatory bowel disease-associated arthritis
- Other: chronic recurrent multifocal osteomyelitis, cryopyrin-associated periodic syndromes (CAPS), including chronic infantile neurological cutaneous and arthritis syndrome (CINCA), familial Mediterranean fever

A child presenting with prominent systemic features

- Connective tissue diseases: SLE, MCTD, Kawasaki disease, other systemic vasculitis syndromes
- Neoplasia: especially neuroblastoma in a young child
- Infection: bacterial (streptococcal, including acute rheumatic fever, tuberculosis, Gonococcus, Lyme disease, and Brucella), viral (EBV and hepatitis B) or parasitic (malaria)
- Inflammatory bowel disease
- Autoinflammatory disorders: these are characterised by recurrent attacks of fever and arthralgia or arthritis often accompanied by abdominal pains and rash. Many are the result of gene mutations and so present from birth or at a very early age. Specific genetic tests are indicated if the clinical features are suggestive. Examples are familial Mediterranean fever, hyper-IgD syndrome, CAPS including CINCA syndrome (CINCA/NOMID), tumour necrosis factor receptor associated syndromes (TRAPS) and pharyngitis fever arthritis periodic fever (PFAPA), familial Mediterranean fever

A child presenting with musculoskeletal pain in the absence of swelling

- Hip disease: Perthes disease or avascular necrosis of the femoral head, slipped upper femoral epiphysis
- Benign hypermobility syndrome
- Inherited metabolic diseases: Gaucher disease, Scheie disease
- Osteochondroses: Osgood–Schlatter disease, Scheuermann disease
- Idiopathic pain syndromes: nocturnal ‘growing’ pains, complex regional pain syndrome, fibromyalgia
- Solid tumours

JIA is an internationally accepted umbrella term that has replaced all previously used nomenclatures, including juvenile rheumatoid arthritis and juvenile chronic arthritis. JIA is an exclusion diagnosis that encompasses all

forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks and are of unknown origin (Box 2).

Box 2 Criteria for the diagnosis of juvenile idiopathic arthritis

All three conditions must be met

- Arthritis persisting for longer than 6 weeks
- Arthritis beginning before 16 years of age
- Exclusion of other conditions associated with or mimicking arthritis

This heterogeneous group of chronic arthritides has been classified on clinical and laboratory grounds to try to identify homogeneous, mutually exclusive categories primarily suitable for aetiopathogenic studies (box 3). By convention, classification is based on the symptoms presented during the first 6 months of disease (Petty et al, 2001*). This classification, which is an evolving process, has been recently criticised since there is evidence that while some categories identify quite definite disease entities, others represent heterogeneous conditions (Duffy et al, 2005*; Martini, 2012*).

Box 3 Second revision of the proposal for the development of classification criteria for juvenile idiopathic arthritis

Primary definition of juvenile idiopathic arthritis (JIA): definite arthritis of unknown aetiology that begins before the 16th birthday and persists for at least 6 weeks

Categories of JIA

1. Systemic arthritis
2. Oligoarthritis: - Persistent oligoarthritis
- Extended oligoarthritis
3. Polyarthritis (rheumatoid factor positive)
4. Polyarthritis (rheumatoid factor negative)
5. Psoriatic arthritis
6. Enthesitis-related arthritis
7. Undifferentiated arthritis

2 Clinical features of JIA

2.1 Symptoms of JIA

Many affected children present during their preschool or early school years, and often the patients have difficulty in describing their symptoms. The onset of arthritis in JIA is more often insidious than acute and pain is an inconsistently reported symptom of JIA. Parents are likely to note limping, particularly if the lower limb joints are affected, or joint swelling if one or more large peripheral joints are involved, such as the knee (the most commonly affected joint), ankle or wrist. It is more rare for children to present with isolated small joint (finger or toe) arthritis or axial joint involvement (i.e. involvement of the shoulder, hip or spine). Joint stiffness in the morning or gelling after prolonged rest occurs frequently in the active phase of the disease. Stiffness improves with movement, and is helped by a warm bath or shower. Duration of morning stiffness, limping and difficulty with function in the mornings and after naps provides a useful parameter for monitoring disease activity. The extra-articular features of JIA are mentioned in the description of the different JIA categories.

2.2 Physical findings in JIA

Joint involvement may be monoarticular, oligoarticular, polyarticular, symmetric or asymmetric depending on the specific JIA category. Though any joint can be affected, large joints such as the knee and the ankle are commonly involved in oligoarthritis and are responsible for the common complaint of limping; small joints of the hands and feet are usually involved in polyarticular-onset and systemic disease. The temporo-mandibular joint (TMJ) should be carefully examined, given the high prevalence of TMJ disease at the time of diagnosis. Early detection of TMJ inflammation is crucial to prevent severe mandibular growth abnormalities and condyle deformities. The clinical skills of paediatric musculoskeletal examination require knowledge of the development of the musculoskeletal system and of the joint excursion ranges in different ages. Examination of all children and adolescents should take place in an appropriately decorated, secure, sensitive and confidential environment. It is important to recognise that, particularly for young children, completing a thorough physical examination may require time and more than one attempt. Although it is time consuming, engaging the child in play may assist both initial and subsequent examinations. It is surprising how much functional musculoskeletal evaluation can be achieved by astute observation of the child at play (table 1).

Table 1 The functional musculoskeletal examination

Position	Musculoskeletal features examined
Sitting cross-legged	Hip abduction, external rotation and flexion, knee flexion
Rising to stand straight	Leg extension, back extension, lower limb muscle power
Bending forward	Anterior spinal curvature, scoliosis
Removing shoes/socks	Hip/knee flexion, hand and wrist function
Removing top	Shoulder and elbow range of movement
Walking normally	Gait phases: stance, push off, swing, heel strike
Tiptoe walking	Toe extension, ankle plantar flexion, muscle power
Heel walking	Ankle dorsiflexion, knee extension, pain at entheses
Hands pronated, arms extended	Elbow extension, shoulder power
Making a fist	Finger flexion
The 'hands praying' position	Wrist extension, elbow flexion, finger extension
Arms up above the head, reaching	Shoulder flexion
Looking over each shoulder	Cervical spine rotation

2.3 Normal variations in skeletal development

Children do not grow in a straight line, either in their skeletal alignment or their growth velocity. Minor degrees of asymmetry can often be detected on examination, most commonly in the size of the feet and length of the legs. It is important to be aware that babies are normally born with a varus knee angle which gradually straightens with age to neutral alignment between 18 months and 2 years of age. Further normal growth usually results in a progressive change in knee alignment to a valgus position, which is maximal between 5 and 7 years of age (up to 15°), resulting in an intermalleolar distance at the ankles of up to 5 cm. In this context, moderate degrees of knee varus (bow legs) or valgus (knock knee) are common and usually normal. Another common variation of normal is the posture of the foot. Most babies do not have an appreciable medial longitudinal foot arch, or a stable hindfoot position, at birth. This results in marked ankle valgus and a 'flat foot' (pes planus), which is obvious once the infant begins walking. If a child of about 10 years or over continues to have pes planus and ankle valgus (over pronation) in association with lower limb, back or generalised musculoskeletal pain, a diagnosis of hypermobility should be considered. In general, children are more flexible than adults, and the range of normal joint movement in children is measurably greater.

2.4 Effect of arthritis on the growing skeleton

An important source of damage in JIA is represented by effects of the inflammatory process and muscle atrophy, misalignment and muscle contracture on the development of bone and joint. In a growing skeleton, joint

contractures secondary to persistent synovitis may lead to deformity. For example joint contracture of the knee leads to a valgus deformity and, if the involvement is unilateral, to leg length discrepancy secondary to bone overgrowth in the affected side. These anomalies, that represented a major challenge in the past, can now be effectively prevented by intra-articular steroid injections that induce a rapid relief of inflammation, restore function and therefore interrupt the vicious circle leading to deformity .

Indeed, local growth disturbances occur at sites of inflammation, resulting in either overgrowth (possibly related to inflammation-induced increased vascularisation and growth factor release) or undergrowth (secondary to growth centre damage or premature fusion of epiphyseal plates) of the juxta-articular bone extremities. Other anomalies in growth and morphogenesis of skeletal segments include micrognathia and developmental anomalies of the hips. The management of JIA should therefore be aimed at treating progressive, erosive disease and also at preventing bone and joint deformities due to the effect of articular inflammation on the growing skeleton.

Chronic inflammation may affect linear growth, and stunted growth was one of the features described by GF Still in his initial description of systemic JIA (sJIA). However, especially in systemic onset JIA we should also consider growth retardation as a consequence of prolonged steroid therapy. Indeed, one of the main side effects of steroid therapy in paediatrics is the inhibition of growth. In every child, and more frequently in those receiving steroid therapy, growth and weight centiles have therefore to be checked periodically.

3 Clinical patterns of JIA

3.1 Systemic arthritis

sJIA is characterized by the presence of a quotidian, high spiking fever (figure 1) associated with systemic features such as an evanescent, non-fixed, erythematous rash (figure 2), hepatosplenomegaly, generalised lymphadenopathy and serositis. Myalgias and abdominal pain may be intense during fever peaks. Arthritis is more often symmetrical and polyarticular; it may be absent at the onset and develop during the disease course. Laboratory examinations show a prominent inflammatory response characterised by leucocytosis (with neutrophilia), high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration, hyperferritinaemia, very high serum levels of S100A8/S100A9 and S100A12 and thrombocytosis. A microcytic anaemia is common, as is ferritinaemia. The differential diagnosis of sJIA can be difficult, especially at presentation, and includes bacterial or viral infection, malignancy and other rheumatic diseases.

Figure 1 Temperature chart showing the characteristic quotidian fever of systemic arthritis.

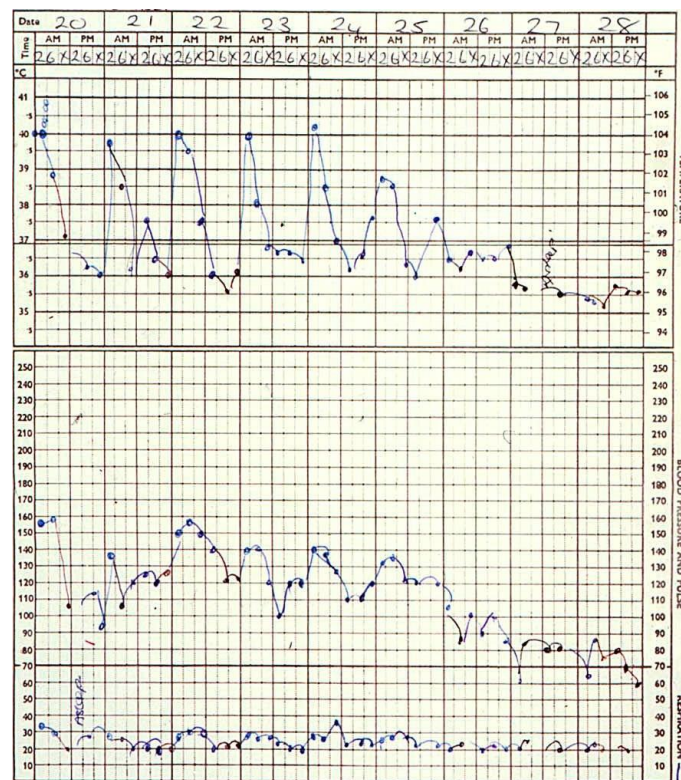


Figure 2 Typical, erythematous and evanescent rash of systemic arthritis.



The disease does not show a preferential age at onset and occurs as often in boys as in girls. It accounts for 10–15% of children with JIA and is considered the equivalent of ‘adult-onset Still's disease’.

The marked activation of the innate immune system has led to the suggestion that sJIA is a polygenic autoinflammatory disease. It probably represents a syndrome, the common endpoint of several different diseases all causing marked and persistent activation of the innate immune system (Martini A. 2012).

In about half of patients the disease is monocyclic or is characterised by relapses followed by intervals of remission. The long-term prognosis of these patients is usually good. In the other half of patients the disease follows an unremitting course; in many cases systemic symptoms eventually resolve, leaving chronic arthritis as the major long-term problem.

For unknown reasons, children with sJIA are particularly susceptible to developing a life-threatening complication, called macrophage activation syndrome (MAS), occurring in about 5–8% of patients. MAS is a form of reactive haemophagocytic lymphohistiocytosis and is characterised by the sudden onset of sustained fever, pancytopenia, hepatomegaly, liver insufficiency, a coagulopathy with haemorrhagic manifestations and neurological symptoms. Laboratory features include raised transaminases and triglycerides and markedly increased ferritin concentrations. Fibrin degradation products are present and hypofibrinogenaemia is induced by diffuse intravascular coagulation. The presence of phagocytosis of haematopoietic cells by macrophages in the bone marrow is common. MAS is a severe condition that can pursue a rapidly fatal course. Prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are, therefore imperative. Classification criteria for the timely diagnosis of MAS complicating sJIA have recently been produced. (Ravelli A 2016). The conventional therapeutic approach to MAS in sJIA is to administer intravenous methylprednisolone pulse therapy (in high divided doses) in association with cyclosporine. This approach is usually able to control this complication if the diagnosis is precocious and the treatment promptly instituted. Understanding the balance of cytokines in the cytokine storm of MAS is crucial to the effort of utilizing the available cytokine-targeted biologic therapies. The rapid and dramatic benefits seen with the use of (high dosed) anakinra, is generating substantial enthusiasm for treating sJIA associated MAS with IL-1 blockade.

3.2 Oligoarthritis

Oligoarthritis is defined as arthritis that affects four joints or fewer during the first 6 months of disease, in the absence of features (psoriasis, rheumatoid factor (RF) positivity, high spiking fever, etc) that qualify for other categories. In Western countries, where oligoarthritis represents up to 50% of all JIA cases, the large majority of patients belong to a well-defined disease entity seen only in children and characterised by several common features: an asymmetrical arthritis, an early onset (before 6 years of age), a female predilection, positive antinuclear antibodies (ANAs), a high risk for developing chronic iridocyclitis and consistent human leucocyte antigen (HLA) associations (HLA-DRB1*08, in particular).

The International League of Associations for Rheumatology (ILAR) classification distinguishes two categories: persistent oligoarthritis, in which the disease remains confined to four joints or fewer, and extended oligoarthritis, in which arthritis extend to more than four joints after the first 6 months of disease. It has been shown however that ANA-positive patients with persistent or with extended oligoarthritis share the same features, strongly suggesting that they represent the same disease differing just in the spread of arthritis.

Involvement of an upper limb joint and higher sedimentation rate at onset have been identified as predictors for evolution to the extended phenotype, which may occur in up to 50% of patients. Oligoarthritis is predominantly a disease of the lower limbs, with the knee joint being most commonly affected (figure 3), followed by the ankles. In about 30–50% of cases a single joint is involved at presentation. Acute phase reactants are usually normal or moderately increased; although in some instances ESR may be quite high.

While children with persistent oligoarthritis have in general a good long-term articular outcome, those with extended oligoarthritis may have a less favourable long-term prognosis. Both subtypes can however be complicated by (severe) anterior uveitis, a disease manifestation developing in about one-third of patients.

Figure 3 Persistent oligoarthritis in a 3-year-old girl.



JIA associated uveitis is a chronic, non-granulomatous, anterior uveitis that involves the iris and the ciliary body (iridocyclitis) and can cause severe visual impairment. In contrast with the painful, acute iridocyclitis that can be observed in enthesitis-related arthritis (ERA), it is asymptomatic. One or both eyes may be affected. In most cases it occurs at the time of diagnosis or shortly thereafter, although in a minority of patients (<10%) it can precede the onset of arthritis. Most children develop iridocyclitis within 5–7 years after onset of arthritis. The course of iridocyclitis may be relapsing or chronic and does not parallel the course of the arthritis. Children with iridocyclitis are at risk of developing serious complications, which include posterior synechiae, band keratopathy, cataract and glaucoma. The outcome of iridocyclitis relies very much on early diagnosis and treatment, therefore, since iridocyclitis is asymptomatic at onset, it is mandatory to screen children with oligoarthritis every 3 months by slit-lamp examination.

3.3 Polyarthritis (RF negative)

RF-negative polyarthritis is defined as an arthritis that affects five or more joints during the first 6 months of disease in the absence of RF (figure 4). Its frequency varies according to geographical origin: polyarthritis accounts for approximately 15-20% of JIA patients in British and Canadian studies while its percentage was significantly higher in other racial groups such as East Indian (61%) or native North American Indian (64%). It is a heterogeneous category. At least two distinct clinical phenotypes can be identified: (a) a form that is closely similar to adult-onset, RF-negative rheumatoid arthritis (RA) and is characterised by overt symmetrical synovitis of large and small joints, onset at school age, raised ESR, negative ANAs and variable outcome; (b) a second form that resembles ANA-positive, early-onset oligoarthritis in any respect (early age at onset, ANA positivity, asymmetrical arthritis, female predominance, increased incidence of chronic iridocyclitis, association with HLA-DRB1*08) except the number of joints involved during the first 6 months of disease. The strong similarities between this second subset and ANA-positive, early-onset oligoarthritis led to the suggestion that they are the same disease, the former representing a rapid arthritis spread in the latter. In keeping with this hypothesis, gene expression studies in oligoarticular and polyarticular JIA have shown that patients with early-onset arthritis (≤ 6 years) are characterised by a B cell signature independently of the number of joints involved. The long-term prognosis of ANA-positive, early-onset, RF-negative polyarthritis is worse than that of persistent oligoarthritis and similar to that of extended oligoarthritis. ANA-positive patients carry a high risk of chronic iridocyclitis and have to be checked every 3 months by slit-lamp examination.

Figure 4 Symmetrical arthritis in a young child with polyarthritis (rheumatoid factor negative). Parental/guardian consent obtained.



3.4 Polyarthritis (RF positive)

RF positive polyarthritis is defined as the involvement of five or more joints during the first 6 months of disease and by the presence of positive rheumatoid factor (RF) on two occasions at least three months apart during the first 6 months of disease. It is considered the paediatric counterpart of adult RF-positive rheumatoid arthritis (RA) and shares a similar clinical phenotype, serology and immunogenetic profile. The shared epitope (SE) present in some HLA-DR4, DR1 and DR14 alleles is associated with an increased risk for both adult RA and RF positive JIA. In Europe it accounts for a small ($\leq 5\%$) percentage of patients with JIA. It primarily affects girls and usually presents in late childhood or adolescence with a symmetric polyarthritis affecting principally wrists and the small joints of the hands and feet. It can be rapidly progressive and destructive. Rheumatoid nodules have been reported in about a third of patients in the first year of disease. Nodules which are firm, mobile and non-tender, often occur on bony prominences and pressure points such as distal to the olecranon, on flexor tendon sheaths and on the soles of the feet. ESR and C-reactive protein are elevated and a moderate normochromic and normocytic anaemia is often associated. It is the only JIA category in which antibodies to cyclic citrullinated peptides (anti-CCP) are found. Aggressive medical treatment of RF-positive polyarthritis is warranted because of its almost uniformly poor prognosis. Patients with RF-positive polyarthritis, in fact, have the lowest remission rate off-medication among children with chronic arthritis monitored for 10 years (Wallace CA et al. 2005). Radiological changes occur earlier and more frequently in RF-positive polyarthritis than in the other JIA categories and are observed particularly in the hands and feet.

3.5 Psoriatic arthritis (JPsA)

The diagnosis of juvenile psoriatic arthritis (PsA) by ILAR criteria requires the simultaneous presence of arthritis and a typical psoriatic rash or, if the latter is absent, the presence of arthritis and any two of the following: family history of psoriasis in a first-degree relative (figure 5); dactylitis (swelling of one or more digits that extends beyond the joint margins) and nail pitting.

Figure 5: Psoriatic arthritis.



Psoriatic arthritis is another heterogeneous JIA category representing about 5–10% of all JIA cases. Younger children, most commonly female and with positive ANA test, tend to develop asymmetric oligoarthritis and have a high risk of chronic iridocyclitis. This subgroup appears very similar to the early-onset oligoarticular JIA, the main difference being that patients with JPsA tend in some series to develop more frequently a polyarticular course. By contrast, older-onset JPsA patients exhibit a gender ratio closer to 1:1, with a tendency to enthesitis and to develop sacroiliitis during follow-up, similar to several adult patients with psoriatic arthritis who share features with spondyloarthropathies. The ILAR classification criteria for PsA, in which patients with enthesitis are by definition excluded, limit the identification of those patients who have a form of PsA similar to that seen in adults.

In children with JPsA, dactylitis is observed in 20% to 40% of patients, its swelling is typically uniform, giving the appearance of a "sausage digit". Ultrasound (US) examination shows tenosynovitis of the digit flexor tendons as a dominant finding, with or without synovitis in the adjacent joints. Subperiosteal new bone growth can also increase the thickness of the digit. Overt psoriasis occurs in 40% to 60% of patients with JPsA usually as the classic vulgaris form. As in other JIA subsets, young patients with ANA positivity are at highest risk of chronic uveitis, and periodic screening with slit-lamp should be performed. The long term prognosis of PsA is not well defined, due to its heterogeneity and the lack of available information.

3.6 Enthesitis-related arthritis

Enthesitis-related arthritis accounts for about 5–10% of JIA cases and is an undifferentiated spondyloarthritis. It typically begins after the age of 6 years and affects boys more often than girls. Most patients are HLA-B27 positive. Arthritis commonly affects the joints of the lower extremities and is usually associated to enthesitis (inflammation of the point where a tendon, ligament or fascia inserts into the bone). The most common sites of enthesitis are the calcaneal insertions of the Achilles tendon, plantar fascia, and tarsal area. In contrast to the other JIA categories, hip involvement is frequent at disease presentation. Symptoms of sacroiliitis and spine involvement are uncommon at presentation. Although it may be a precursor to ankylosing spondylitis, it is not known how many children with ERA progress to ankylosing spondylitis during their adult years. Uveitis may also affect these JIA patients, but in ERA it tends to be symptomatic, presenting with red eyes, photophobia and pain. A family history of similarly affected relatives is often positive.

3.7 Undifferentiated arthritis

Undifferentiated arthritis is not a defined entity, but a category that includes patients who do not fulfil inclusion criteria for any category, or fulfil the criteria for more than one category. About 10–15% of all JIA cases are included in this category.

4 Investigations in children with arthritis

Laboratory Examination

JIA is a diagnosis of exclusion and a wide range of differential diagnosis need to be ruled out. Laboratory investigations may be useful for the exclusion of other disorders (Table 2), to aid categorization of the JIA subsets, and to monitor the extent of inflammation. Immunological markers such as antinuclear antibodies (ANA) and rheumatoid factor (RF) are not specific for JIA. They, in fact, may be transiently positive after a viral illness, and may be also present in other connective tissue disorders and even in healthy children. Tests for RF, antibodies to cyclic citrullinated peptides (anti-CCP) and ANAs should be considered only after the diagnosis of JIA has been made: RF to help sub classify children with polyarthritis, and ANAs to identify a group of patients who carry a high risk of developing iridocyclitis and require a periodic slit-lamp examination. As mentioned above, ANA positivity allows to identify early-onset, ANA-positive arthritis, which represents a well-defined entity that is seen only in childhood and which is currently misclassified into several different JIA subtypes (oligoarthritis, RF-negative polyarthritis, PsA).

Hematologic abnormalities such as leukocytosis (polymorphonuclear leukocytes predominate) and thrombocytosis usually reflex the extent of the inflammatory disease. On the other hand, isolated raised lactate dehydrogenase associated to hematologic abnormalities such as leukopenia and thrombocytopenia should alert the physician to the possibility of acute lymphoblastic leukaemia.

Acute phase reactants help in monitoring disease activity and monitoring the therapeutic efficacy. It is important however to highlight that JIA patients, especially those with oligoarthritis, may have normal values at the disease onset. In the systemic and polyarticular categories, ESR and CRP are usually raised, often along with neutrophilic leucocytosis, thrombocytosis and a microcytic anaemia. Anaemia, usually secondary to chronic inflammation, can occur in all forms of JIA but is more pronounced in systemic JIA. It is characterised by a striking defect in the iron supply for erythropoiesis, while growth of erythroid colonies is normal and erythropoietin production is appropriate. These findings are consistent with the effect of IL-6 on erythropoiesis. A sudden drop of leucocyte count and platelets occurs during MAS as well as a sudden increase of transaminases and ferritin levels. Liver function tests should always be performed as a baseline screening before starting non-steroidal anti-inflammatory drugs (NSAIDs) or methotrexate and then to monitor drug-related side effects. Increases in serum levels of the immunoglobulins reflect the acute-phase response, whereas selective IgA deficiency occurred in 4% of the children.

Antistreptolysin O titres and anti-DNase B titres should be acquired to exclude acute rheumatic fever or post-streptococcal arthritis. To exclude other forms of reactive arthritis, stool cultures or serology for yersinia, salmonella, shigella, campylobacter or viral serology (Parvovirus B 19, hepatitis B, influenza, Coxsackie virus, Epstein–Barr virus, cytomegalovirus, varicella, endemic viruses) should be performed based on the clinical

history. *Borrelia burgdorferi* or brucellosis serology should be acquired to rule out Lyme disease or brucellosis if there is a history of travel in endemic areas and/or clinical suspicion.

Synovial biopsy is not indicated for the diagnosis of JIA, but may have a role in the exclusion of rare causes of joint swelling, such as neoplasia, sarcoidosis or pigmented villonodular synovitis. The inflammatory synovitis in JIA does not have specific features; macroscopically and microscopically it is similar to that seen in adult RA while the findings seen in enthesitis-related arthritis overlap with those reported in adult spondyloarthritis.

Radiologic Examination

Imaging evaluation of the child with clinical features of rheumatic disorder has an important role in excluding a wide range of differential diagnosis. Conventional radiographs (CR) is the first-step imaging modality which should be performed to exclude other causes of joint pain and swelling, such as fracture, osteocondroses, bone tumours, skeletal dysplasias, slipped upper femoral epiphysis, avascular necrosis etc. MR imaging (MRI) and musculoskeletal ultrasound (US) are encountering expanding application in the assessment of patients with chronic inflammatory arthritis. EULAR/PRES point to consider for the use of imaging in the diagnosis and management of JIA in clinical practice have been recently published. US (figure 6) and MRI are more sensitive than clinical examination in the evaluation of joint inflammation; these techniques should therefore be considered for more accurate detection of inflammation, both in diagnosis and assessing extent of joint involvement.

Figure 6 Ultrasound longitudinal scan of the hip joint of a girl aged 2 years. FH, femoral head; FN, femoral neck; GP, growth plate; JE, joint effusion; SH, synovial hypertrophy.



US has a great potential amongst the paediatric rheumatologists; it is non-invasive, well tolerated and it can be applied directly in the clinic. Over the last decades a great deal of effort has been done to define the normal sonographic anatomy throughout paediatric age groups, to standardize a US scanning approach (i.e., patient

position, transducer placement, and joint positioning) and provide definitions and grading of joint pathological findings. These steps are essential to consider US as a valuable imaging tool for diagnosis and monitoring of disease course and treatment efficacy.

Since no specific MRI signature for JIA has yet been described, MRI is not recommended as a first line investigation in every patient suffering from recent-onset arthritis, but should be used when there is clinical diagnostic doubt to rule out other intra-articular pathologies mimicking JIA, such as pigmented villo-nodular synovitis, synovial haemangioma or lipoma arborescens, which all have recognisable features on MR imaging. In JIA MR imaging may be of particular benefit over routine clinical evaluation when assessing disease activity is highly challenging as for TMJ or axial skeleton. MRI has proven to be the most sensitive and specific imaging method to detect early and/or subtle sacroiliitis and for diagnosis cervical spine involvement. It allows the detection of synovial pannus at the C1-2 joints which, if persistent, potentially lead to posterior laxity of the ligamentous complex resulting in atlo axial instability and consequent risk of upper spinal cord.

More information concerning the use of imaging in the assessment of JIA have been reported in a separate chapter (see in-depth discussion I).

Table 2 Laboratory and imaging investigations in juvenile idiopathic arthritis and differential diagnosis

Investigation		Justification for investigation				
		Differential diagnosis	JIA sub-classification	JIA monitoring	Drug adverse event monitoring	
Haematology	Full blood count	Leukaemia, SLE			Several DMARDs and biological agents	
	Bone marrow examination	Leukaemia				
	ESR	Macrophage activation syndrome Core outcome variable				
Biochemistry	Liver function	Macrophage activation syndrome			NSAID and MTX	
	Muscle enzymes	JDM, overlap syndromes				
	Renal function including urine analysis	SLE with nephritis			NSAID	
	Urinary catecholamines	Neuroblastoma				
	Urinary amino and organic acids, etc.	Inherited metabolic diseases				
	ANA	SLE, JDM, overlap, other autoimmunity		Associated with risk of chronic anterior uveitis		

Immunology	RF Antibodies to CCP HLA-B27	Overlap	In RF-positive patients In enthesitis-related arthritis
	Immunoglobulins	Immune deficiency	
	<ul style="list-style-type: none"> Bacterial and viral serologies 	Reactive arthritis	Varicella titres before beginning DMARDs, biological agents
Microbiology	Skin test for TB Quantiferon		Before beginning DMARDs, biological agents or steroids
	Synovial fluid microscopy and culture	Septic arthritis	

ANA, antinuclear antibodies; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RF, rheumatoid factor; SLE, systemic lupus erythematosus; TB, tuberculosis.

5 Treatment of JIA

5.1 General principles of JIA treatment

The past decade has witnessed major advances in the treatment of JIA and remission has now become a realistic goal. The main aims of these medications is to achieve complete control of the disease with normalization of physical findings and laboratory markers of inflammation, to preserve the physical and psychological integrity of the child, and to prevent any long-term consequences related to the disease or its therapy. Evidence has been provided that early diagnosis and a prompt control of inflammation improves the outcome and can prevent long-term sequelae. Whenever possible, the care of a child with JIA should be provided by an efficient operating, multidisciplinary team (boxes 4 and 5). It should be led by one or more paediatric rheumatologists working in tandem with a team of clinical experts in paediatric rehabilitation, disease education, clinical and drug monitoring, school advocacy, nutrition, family and social support, and psychology, if appropriate. In addition, the need for ready access to other paediatric specialties, such as ophthalmology, orthopaedics, maxillofacial surgery, nephrology, infectious disease and dermatology, underlines the complexity of optimal management required for these children.

Box 4 Healthcare professionals involved in the treatment of juvenile idiopathic arthritis (JIA)**Members of the paediatric rheumatology care team**

- Paediatric rheumatologist
- Paediatric nurse clinician
- Occupational therapist
- Social worker
- Psychologist, nutritionist

Members of the extended specialist team for JIA

- Ophthalmologist: detection and monitoring of uveitis
- Paediatric physiotherapist: to keep JIA patients active, promote regular exercise and a healthy lifestyle
- Orthopaedic surgeon: surgical interventions to aid rehabilitation, correction of local growth deformity
- Dentist: for diagnosis and management of TMJ involvement
- Orthotist/podiatrist: correction of pes planus and other foot deformities

NSAIDs and intra-articular steroids

Oral non-steroidal anti-inflammatory drugs (NSAIDs) represent the initial treatment for the majority of JIA patients. In contrast to adults, just a few NSAIDs are approved for use in children. The most common include naproxen, ibuprofen, indomethacin and meloxicam, an inhibitor of both cyclo-oxygenase 1 (COX1) and COX2.

Salicylates have been replaced by NSAIDs in paediatric practice because of the association of aspirin with Reye syndrome and greater frequency of liver function abnormalities. NSAIDs are used in higher doses, relative to body weight, than in adults because children have increased rates of metabolism and renal excretion. NSAID are generally well tolerated and unlike adults fewer side-effects are reported. They include abdominal pain (usually minimised by taking the NSAID with food), and, rarely, bronchospasm (mild asthma is not a contraindication to the use of NSAIDs in children). Naproxen has the additional risk of inducing pseudo-porphyrria. However, most patients need better control of inflammation than can be accomplished with NSAIDs alone. Intra-articular steroid injections are commonly indicated at disease onset or during disease course since their quick effectiveness is pivotal in the prevention of deformities-e.g. valgus knee secondary to joint contractures, which represents an important source of damage in JIA. The long-acting steroid triamcinolone hexacetonide is used worldwide since its induced remission lasts much longer compared to other steroids. To inject smaller joints and those not easily reached, it is advised however to use a more soluble corticosteroid preparation such as methylprednisolone acetate. The procedure can be performed in an ambulatory care setting using local anaesthesia, with or without conscious sedation. Younger children, or those candidate to multiple injections, require general anaesthesia/sedation. Ultrasound guidance allows an accurate placement of the needle within the joint space thus reducing the risk of side effects and maximizing the efficacy of the procedure. The most common adverse effect is subcutaneous atrophy at the site of injection, which is caused by the delivery of the

steroid preparation out of the joint space. This complication, that can usually be avoided with a careful injection technique, may resolve with time although it can persist in some patients.

DMARDS

Patients who do not respond effectively to these approaches need systemic therapy with second line agents. Methotrexate (MTX) is considered the second-line agent of choice for persistent active arthritis, due to its effectiveness and acceptable level of toxicity. Since its efficacy begins to show usually only after one to three months, a *short* course of low-dose prednisone (0.2-0.5 mg/kg/day) might be considered as a bridging agent until MTX is effective, especially in patients with severe polyarthritis.

The most common adverse events associated with methotrexate are nausea, followed by mouth sores. Other side effects include abdominal pain, raised liver enzymes, and rarely, hair loss and bone marrow suppression. Patients taking methotrexate must have monthly blood monitoring to screen for abnormal liver function and bone marrow suppression. To reduce the risk of the side effects supplementation with folic or folinic acid should be concomitant. Furthermore adolescents must refrain from drinking alcohol. It is important to realize that up to 30-40% of patients develop signs of 'intolerance' (malaise, nausea, vomiting not only shortly after taking MTX, but often already starting hours *prior* to the intake of the weekly dose) after prolonged use of MTX. This can be difficult to manage, and can result in change of the DMARD or even to escalation of the therapy to biologics in a subset of patients.

Although recent trials have shown the efficacy of leflunomide in polyarticular JIA, clinical experience of treatment with leflunomide in JIA is still limited. This drug may be an alternative for MTX, particularly for patients who develop intolerance or major side effects to MTX.

Overall MTX is effective in about 70% of children with polyarthritis. For those unresponsive or intolerant to conventional antirheumatic agents, the introduction of biological medications should be considered.

Biologicals

The soluble TNF α receptor, etanercept, was the first biologic to be registered for the treatment of children (more than 2 years old) with polyarticular JIA based on a randomized, double-blind withdrawal study comparing Etanercept to placebo (Lovell et al, 2003*). In the open label phase, sustained effectiveness and long term safety of Etanercept were demonstrated. A synergic effect between Etanercept and Methotrexate has also been suggested. Etanercept is indicated for patients with polyarthritis/extended oligoarthritis whose disease is not adequately controlled with methotrexate or who are intolerant to it. Etanercept binds to circulating TNF- α , preventing its interaction with the cell surface receptor and the subsequent inflammatory response. It is administrated at the dose of 0.8 mg/kg/week or 0.4 mg/kg twice weekly subcutaneously (max = 50 mg/week), and its initial clinical effect usually manifests in two-three weeks. Regular (1–3 months) monitoring of blood

counts and chemistry studies are recommended. Long-term follow-up registries for use of etanercept in JIA show tolerable side effects (Shakoor et al, 2002). Since cases of reactivated tuberculosis have been reported during treatment with TNF inhibitors, all children must be negative for tuberculosis tests before starting TNF α blocking agents.

Subsequently, others biological agents have been registered for the use in JIA. In a randomised double-blinded, placebo-controlled withdrawal study, adalimumab, a fully humanised monoclonal antibody to TNF α , showed a good efficacy in children with polyarticular JIA in combination with methotrexate or alone (Lovell DJ et al N Engl J Med 2008). Adalimumab was approved by FDA for treatment of polyarticular subtype (children equal or more than 4 years old, recently modified to > 2 years of age) in 2008. Adalimumab is a fully humanized monoclonal IgG1 antibody against TNF- α that acts binding both soluble and membrane bound TNF- α . It is administered subcutaneously at a dose of 24 mg/m² every other week. Also for Adalimumab, association with Methotrexate seems to result in increased efficacy. As with other biological agents, the occurrence of (neutralising) anti-Adalimumab antibodies is described and can be considered an early marker associated to a poor clinical response. In contrast to Etanercept, Adalimumab appears to be efficacious for the treatment of JIA-related uveitis, and shows a better efficacy in maintaining remission in chronic anterior JIA-associated uveitis.

Infliximab is a chimeric monoclonal antibody directed against TNF- α in its soluble and membrane-bound forms, leading to TNF- α neutralisation and to antibody-dependent cytotoxicity of TNF- α producing cells. In 2007, a multicentre randomized double-blind placebo-controlled trial suggested efficacy of Infliximab (3mg/Kg) in polyarticular subtype, but primary end point was not significantly different from placebo, so Infliximab was not approved by FDA for JIA. The author's explanation in the publication was that probably children clear the drug more rapidly than adults, making the dosage of 3 mg/kg insufficient. Currently, doses of 6 mg/kg are suggested in children. Tolerability of Infliximab infusion is a major concern, because there is a relevant risk of infusion-related reactions, development of antinuclear antibodies (ANA) and of neutralising human anti-chimeric antibodies (HACA). Concurrent administration of MTX can help to prevent development of HACAs that may cause a higher clearance of Infliximab. HACAs seem also to be related with a higher rate of infusion-related reactions. Finally, evidence has been provided on the efficacy of Infliximab in treating JIA-related uveitis.

Golimumab is a fully humanized monoclonal antibody to soluble and transmembranous TNF- α . A phase III multicentre, open-label trial, with the purpose of evaluating the pharmacokinetics of Golimumab administered intravenously in polyarticular JIA is ongoing currently.

Certolizumab pegol is a pegylated anti-TNF- α inhibitor. Pegylation enhances the half-life of the drug and allows a 2–4-week dosing schedule. There is a clinical trial underway for the use of certolizumab in children with JIA.

T-cells play a central role in starting the inflammatory process in JIA. Several studies on monoclonal T cell-depleting antibodies were disappointing, failing to prove sustained clinical improvement or showing severe side

effects. Also interactions between molecules expressed on the surface of T cells and on antigen-presenting cells are involved in the immune response. Targeting lymphocyte activation and cellular functions may be an alternative approach for the management of JIA, in particular refractory polyarticular subtype that shows inadequate response to other therapies, including one or more anti-TNF agents. Abatacept, CTLA-4 Ig, is a soluble fusion protein that selectively modulates the CD80/CD86:CD28 co-stimulatory signal for T-cell activation during antigen presentation. Its efficacy in the treatment of children with polyarticular JIA subtype has been demonstrated in a randomized controlled trial. Abatacept is an approved therapeutic option for patients with polyarthritis who are resistant to TNF α -inhibitors. It is administered via 30 minute intravenous infusion at a dose of 10 mg/kg every 28 days.

As outlined, JIA is clearly not a single disease, and therefore different therapeutic approaches should be followed for the different subtypes. This holds particularly true for systemic JIA vs other JIA subtypes. Data from literature have demonstrated that for example anti-TNF α therapy is less effective in patients with sJIA. These clinical observations, along with increased insight in the last 15 years on the pathophysiological mechanisms, underscoring a major pathogenic role for the IL-1 and IL-6 pathways in sJIA, have subsequently directed biologic therapy for sJIA.

IL-1 is a pro-inflammatory cytokine and is produced by monocytes, macrophages and dendritic cells. IL-1 activity is physiologically controlled by the soluble IL-1 receptor antagonist (IL-1RA). In patients with chronic inflammatory arthritis, IL-1 stimulates production of inflammatory mediators by synoviocytes and chondrocytes, leading to cartilage destruction and bone erosions.

The discovery of the important role of IL-1 came from the rather serendipitous observation of the efficacy of anakinra, an IL-1 inhibitor which is the recombinant version of the naturally occurring soluble IL-1 receptor antagonist (IL-1 Ra) (Pascual V et al 2005). Anakinra binds to the IL-1 receptor on cell surfaces preventing its interaction with IL-1 and subsequent cell signalling. Due to his short half-life, Anakinra is administered in daily subcutaneous injection (1-2 mg/kg/day, max = 100 mg). Since the first description of its efficacy in sJIA, it has become apparent that the response to IL-1 blockade can be variable. In fact, two subsets of sJIA can be identified ,according to patient response to anakinra (Gattorno M Arthritis Rheum 2008). One (accounting for about 50% of patients) with a dramatic, complete response to IL-1 blockade (similar to that observed in cryopyrin-associated autoinflammatory syndromes) with complete normalization of clinical as well as laboratory features in a few days. The other resistant to treatment or with an intermediate response; in general in these patients systemic features respond well to therapy while synovitis persists. Compared to patients who had an incomplete response or no response, complete responders had a lower number of active joints and an increased absolute neutrophil count. There is increasing evidence that the early use of anakinra in sJIA is associated with a higher response rate (Vastert et al, Arthritis Rheum, 2014).

More recently canakinumab, a monoclonal antibody against IL-1, has been approved for the treatment of sJIA. Canakinumab is a fully human anti-IL-1 β monoclonal antibody that blocks selectively IL-1 β . The long half-life of Canakinumab justifies the subcutaneous administration every 4 weeks in sJIA (4 mg/kg, max 300 mg). Two randomized, placebo controlled trials have demonstrated efficacy of Canakinumab in children with sJIA and active systemic features (Ruperto N et al. N Engl J Med 2012).

In the 1990s, several laboratory studies led to the hypothesis that systemic JIA is an IL-6 driven disease (De Benedetti et al, 1994). This hypothesis was confirmed ten years later by a double-blind controlled study with a withdrawal design which showed the efficacy of tocilizumab, a monoclonal antibody against the IL-6 soluble receptor (sIL-6R), in 56 patients with sJIA (Yokota et al, 2005). More recently a multicentre double-blind placebo-controlled trial (De Benedetti et al, N Engl J Med, 2012) has confirmed the marked efficacy of tocilizumab which has been approved by the Food and Drug Administration and European Medicines Agency for patients > 2 years with persistently active sJIA. Tocilizumab is administered at a dose of 8 mg/kg (children < 30 kg: 12 mg/Kg) every 2 weeks, via intravenous infusion. In addition to its efficacy in sJIA, the efficacy and safety of the interleukin-6 receptor inhibitor (given intravenously every 4 weeks) for the treatment of patients with polyarticular-course JIA has been recently demonstrated in a randomised, double blind withdrawal trial (Brunner et al, Ann Rheum Dis 2015).

Box 5 Drug treatment

Non-steroidal anti-inflammatory drugs

- Ibuprofen 10 mg/kg/dose four times a day
- Naproxen 10-15 mg/kg/dose twice a day

Intra-articular steroids

Triamcinolone hexacetonide

- 1 mg/kg/joint for large joints
- 0.5 mg/kg/joint for medium joints

Methotrexate

- 10–15 mg/m²/dose once weekly orally or subcutaneously

Parenteral steroids

- Methylprednisolone 10–30 mg/kg/dose daily over 1–3 days
- Prednisolone 0.2–2 mg/kg/dose once a day

TNF α drugs

Etanercept

- Given by subcutaneous injection of 0.8 mg/kg once weekly or 0.4 mg/kg twice weekly
- Outcome best when combined with weekly methotrexate

Adalimumab

- 24 mg/m²/dose every 2 weeks (max 40 mg) subcutaneously
- Outcome best when combined with weekly methotrexate

T-cell costimulation modulator

Abatacept

- Given by intravenous infusion of 10 mg/kg every 28 days
- Outcome best when combined with weekly methotrexate

IL-1 drugs**Anakinra**

- Daily subcutaneous injection of 1–2 mg/kg/dose

Canakinumab

- 2–4 mg/kg/ every 4 weeks (max 150 mg) subcutaneously

IL-6 drugs**Tocilizumab**

- <30 kg, 12 mg/kg; >30 kg, 8 mg/kg every 2 weeks intravenously

Management of Chronic iridocyclitis

Anterior uveitis, that involves the iris and the ciliary body (iridocyclitis), is a characteristic complication of JIA and occurs with much higher frequency in ANA positive patients. The onset is insidious and often entirely asymptomatic. The course may be relapsing or chronic and does not parallel the clinical course of arthritis. Topical steroids associated with mydriatics are sufficient to control inflammation in a substantial part of the patients. In cases where inflammation does not respond to topical therapy, periocular subtenon injection of steroids can be indicated. Systemic steroids (prednisone at an induction dose is 1-2 mg/kg body weight) are usually prescribed in case of vision-threatening ocular inflammation. Limited response to topical (or systemic) corticosteroids requires initiation of a second-line therapy, most commonly methotrexate. From the biologic agents, both adalimumab and infliximab have been reported to be beneficial for treating JIA-associated uveitis, whereas etanercept has been associated with the newly development of uveitis in JIA patients. For patients who have failed therapy with TNF inhibitors there is minimal data to guide subsequent management. There have been successful case reports with mycophenolate mofetil, Abatacept, and Rituximab. The efficacy of Tocilizumab for severe JIA-Associated uveitis refractory to anti-TNF therapy has been recently demonstrated in a (small) multicentre study (Calvo-Rio et al, Arthritis Rheum 2016).

Tolerability and Safety of biological agents

Skin reactions at the injection site with subcutaneously administered agents are common, in particular with anakinra. Acute infusion reactions occur especially with Infliximab and are less frequent observed with Tocilizumab and Abatacept.

Cytopenias are occasionally reported upon treatment with anti TNF- α , whereas neutropenia is a concern in patients treated with Tocilizumab. All the biologic therapies potentially increase the risk of infection, tuberculosis in particular. Screening for latent tuberculosis should be performed before the introduction of a biologic agent because the increased risk of reactivation. A potential link between anti TNF- α medication and demyelinating disorders have been suggested but not proven. A major concern with the anti TNF agents in particular is the possible increase in risk of malignancy. In 2009 a FDA reported 48 cases of malignancies in children treated with an anti-TNF agents. A large part of these patients was diagnosed with an inflammatory

bowel disease and 88% were received another immunosuppressive treatment. To date a causal relationship between malignancy and biologic therapy has not been proven.

Finally the use of biologic treatment in clinical practice has raised questions on long-term safety of these drugs. For these reason, registries for long term monitoring of patients under biologic therapies are crucial. The largest international registry for biologics in JIA is Pharmachild.

7 Prognosis and Outcome

The term JIA encompasses an heterogeneous group of disorders. Its spectrum varies from mild to severe, smouldering to rapidly progressive disease. The outcome of JIA is variable and it is difficult at the onset of the disease to predict which children will remit and which will go on to have unremitting, rapidly erosive disease with subsequent high risk of functional impairment. Although several indicators of a poor outcome have been identified, including polyarticular onset of JIA, early wrist or hip involvement, the presence of RF, persistent active disease and early radiographic changes, the prediction of disease outcome in any individual patient remains unsatisfactory.

A pronounced improvement in functional outcome has been documented in the past decades, with the proportion of patients with serious functional disability and who need of assistance or aids to manage their daily routines ranging from 2.5% to 10 %. A number of studies have shown however that adolescents with chronic disease, compared with their peers, are twice as likely to be unemployed, have lower health status and be more socially isolated. Although there is a large variability among studies, around 30-40% of children with JIA seem to enter adult age with active disease and will need to participate in adult healthcare services, usually in rheumatology clinics (Szer et al, 2006*). The remission rate varies considerably with the JIA subtype, being the best for persistent oligoarthritis (Foster et al, 2003*). It should be emphasized, however, that most of the long-term outcome studies refer to an era in which biological agents were not available (David et al, 1994). Recent advances in therapeutics are expected to dramatically change the long-term outcome of children with JIA and significantly decrease the risk of permanent structural damage.

8 Adolescence and transition

The process of transition in healthcare is defined as a multifaceted, active process that attends to the medical, psychosocial and educational needs of adolescents as they move from child-oriented to adult-oriented lifestyles and systems. The evolution of the disease during adolescence also has an impact on the young person and requires more research. There is little doubt that the important tasks of adolescence can be delayed or curtailed by JIA and other chronic illnesses, including consolidation of identity, establishment of relationships outside the family and independence from the family, and successful vocational attainment. It is of concern that almost one-third of adolescents report frustration as being amongst their biggest problems. Adolescents with JIA are faced

with symptoms that can be difficult to relieve, activities they cannot perform and the uncertainty of daily fluctuations and long-term prognosis. Establishing realistic expectations and emotional responses is an important step in self-management. There are seven components of self-management: (1) minimising or overcoming disability (eg, through exercise, nutrition or rest); (2) establishing realistic expectations and emotional responses to the changes of circumstances caused by the disease; (3) interpreting and managing symptoms; (4) learning how to judge the effects of drugs and manage their use; (5) learning to become a good problem-solver; (6) communicating with health professionals and (7) using social resources. Special transition programmes and trained rheumatologists are needed in the field of adolescent rheumatology to deal specifically with the needs of adolescent patients and to consider the specific aspects in the pathology of JIA during further treatment since most adult rheumatologists are not familiar with the clinical differences of the distinct subgroups of JIA. A professional transitional programme should include individual transition plans, collaboration between paediatric and adult rheumatologists, primary care, paediatric and adult healthcare providers, administrative support and direct involvement of the young people themselves.

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SUMMARY POINTS

- The diagnosis of juvenile idiopathic arthritis (JIA) relies on detecting typical clinical patterns, which are characterised by persistent swelling of one or more joints, beginning before the age of 16 years, without any clear cause being identified.
- A wide range of diseases may mimic the clinical features of JIA, the most serious of which include septic arthritis, osteomyelitis, neoplasia such as acute lymphoblastic leukaemia, neuroblastoma and lymphoma, and non-accidental injury.
- There are different clinical subtypes of JIA, including oligoarthritis, extended oligoarthritis, enthesitis-related arthritis, psoriatic arthritis, polyarthritis (rheumatoid factor (RF) negative), polyarthritis (RF positive) and systemic arthritis.
- Laboratory investigations may be helpful to exclude differential diagnoses which may mimic JIA, to subclassify JIA and to monitor the disease, but there are no pathognomonic investigations for the diagnosis of JIA itself.
- The provision of disease education on JIA—ancillary, age-appropriate written material, web resources and support and contact groups—is an essential component of treating the child with JIA and their family.
- Every child with JIA deserves access to a paediatric multidisciplinary team of healthcare professionals who are experienced in the management of JIA, in addition to appropriately trained paediatric rheumatologists. The multidisciplinary team should include nursing staff, physiotherapists, occupational therapists and psychologists. Extensive liaison with the child's school is an essential component of the management of the illness.
- Drug treatment for JIA usually proceeds in a stepwise escalating approach, beginning with non-steroidal anti-inflammatory drugs and intra-articular corticosteroids, with the early use of methotrexate for higher-risk JIA subgroups. Biological therapies, such as blockade of the proinflammatory cytokines, tumour necrosis factor, interleukin (IL)-1 and IL-6, are valuable for the treatment of JIA, which cannot be treated effectively with methotrexate.
- The child with JIA is at risk of a number of complications, including chronic anterior uveitis, dental decay, significant anaemia, osteoporosis and growth disturbance. Rare but life-threatening complications or adverse effects of treatment include sepsis, macrophage activation syndrome, Reye syndrome and amyloidosis.
- The young person who has, or develops, JIA during their adolescent years is particularly at risk of poor therapeutic adherence, an inability to complete the tasks of adolescence (identity, independence and vocation) and disenfranchisement from the medical system.
- Successful transitional programmes for young people with JIA include individualised transition plans, collaboration between paediatric and adult rheumatologists, primary care, paediatric and adult healthcare providers, administrative support and direct involvement of the young people themselves.

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EULAR on-line course on Rheumatic Diseases

Juvenile Idiopathic Arthritis

Clara Malattia, Bas Vastert, Ellen Schatorje and Alberto Martini

Previous versions were coauthored by Seza Özen, Taunton Southwood, Patricia Woo, Dirk Holzinger and Johannes Roth

IN-DEPTH DISCUSSION I

Imaging in the assessment of juvenile idiopathic arthritis

MR imaging and musculoskeletal ultrasound are encountering expanding application in the assessment of patients with chronic inflammatory arthritis [1]. These imaging techniques, by providing additional and more sensitive information over clinical examination and conventional radiographs (CR), are promising tools for the diagnosis, prognosis and assessment of treatment efficacy in patients with juvenile idiopathic arthritis (JIA) [2].

This discussion aims at providing the current evidence to support the use of imaging in the assessment of JIA. Furthermore peculiar aspects relevant to the evaluation of growing skeleton will be discussed.

Conventional radiography

JIA is a diagnosis of exclusion and a wide range of differential diagnosis, many of which have recognisable features on imaging, need to be ruled out. CR is the first-step imaging modality which should be performed to exclude other causes of joint pain and swelling, such as trauma, osteochondroses, osteoid tumours, skeletal dysplasias, etc.

In patients with established JIA, CR remains the gold standard for the demonstration of cumulative structural damage to joints resulting from uncontrolled inflammation over time. Traditionally, the presence and extent of joint changes are assessed by visual inspection of CR to detect joint-space narrowing, bone erosions, and bone growth abnormalities. However, it is difficult to reliably determine cartilage loss in children, due to growing joint changes (i.e. cartilage thickness varies with age, ossification is incomplete etc.). Additionally, advancement of bone maturation secondary to hyperaemia, or the premature fusion of epiphyses due to damage, and the occurrence of unique radiographic abnormalities, such as disturbance of bone growth, are other factors that contribute to make the assessment of radiographic damage in JIA a real challenge.

In the past decade, a great deal of effort has been put into devising radiographic scores targeted to paediatric age group and also in the adaptation of adults methods to be used in JIA. Some of these measures have proved to be reliable and valid for capturing structural damage progression in JIA, thus supporting their use in standard clinical practice as well as their inclusion in therapeutic trials for testing the disease-modifying potential of new antirheumatic drugs [3].

Magnetic resonance

The major limit of CR is that it visualizes late and often irreversible erosive damage and it is insensitive in detecting soft tissue inflammation. MR by providing multiplanar tomographic imaging allows to simultaneously evaluate all joint components. Contrast-enhanced MR is the most sensitive imaging modality for the detection of synovial inflammation and allows a reliable differentiation of active hyper vascular pannus from the inactive fibrotic pannus. Standardised and validated scales for evaluating MR findings in JIA are now available [4]. The OMERACT rheumatoid arthritis (RA) MR synovitis score, has proven to be a promising imaging biomarker for

measuring the therapeutic response in patients with JIA. In a recent study only the ACR Pedi 90 responders showed a significant decrease in synovitis and the halting of structural damage, enhancing the need to move towards higher levels of clinical response to assess drug efficacy, and suggesting the potential of MR as a primary efficacy outcome [5]. In this perspective quantitative measurements of synovitis appear particularly promising in evaluating treatment efficacy. Dynamic contrast-enhanced MR, which analyses the time course of signal changes following gadolinium administration, and computerized measurements of synovial volumes have proved to be reliable methods to quantitatively assess disease activity, monitor treatment efficacy and predict joint destruction in JIA [6].

Although sustained synovitis was recently documented by MR in a sizable proportion of JIA patients who satisfied clinically-defined remission criteria [7], no longitudinal studies have thus far investigated whether MR detectable subclinical inflammation may end up in further joint damage and functional disability, as reported in adults with RA.

Early detection of patients who will develop erosive damage is of outstanding value to reduce the chance of further disability. MR is the only imaging modality able to visualize bone marrow oedema (BMO), a key predictor of erosive joint damage and functional impairment in adults with RA. Caution is however needed before considering BMO as a prognostic indicator in JIA, since longitudinal studies investigating whether the presence of BMO predates the development of bone erosions are still lacking. Furthermore, signal changes resembling BMO have been recently described in the carpal bones of healthy children. The same was not revealed from similar studies in healthy adults thus highlighting the peculiarities of the growing skeleton and the need to include age-matched healthy subjects in MR studies on JIA.

The availability of normative data is also pivotal for an accurate assessment of bone erosions. Evidence that MR is more sensitive in detecting early erosive damage compare to the others imaging modalities has been provided. However the detection of bony depressions mimicking erosive changes in the carpal bones of healthy children has raised some concern that the higher sensitivity of MR may be to the cost of a reduced specificity [8]. A sound knowledge of growth-related changes is essential prior to use MR to select aggressive phenotype and tailor treatment according to disease severity.

Articular cartilage is a major target of erosive process in JIA. The capability of MR to reliably visualize damage to cartilage in JIA patients has been so far documented only in larger joints. Advancement in imaging technologies has recently allowed to investigate biophysical properties and molecular changes in the composition of cartilage matrix. In particular, T2-relaxation mapping, by providing information on the integrity of type II collagen-based fibrillar network allows to identify very early, and potentially reversible, cartilage molecular abnormalities in JIA.

Musculoskeletal Ultrasound (MSUS)

MSUS has several advantages over other imaging modalities, as it does not entail ionization, allows a safe and multiplane assessment of several joints at one time, and is fairly inexpensive. Joint effusion and synovial hypertrophy are the most common abnormalities detected by grey-scale MSUS. MSUS has proven to be more sensitive than clinical examination in detecting joint inflammation. Since the current ILAR classification is based on the number of affected joints, this issue may be particularly relevant in JIA. The detection of subclinical inflammation by MSUS, in fact, may potentially lead to both reclassifying patients and shifting to a more aggressive treatment [9].

The advent of Doppler modalities has allowed the identification of intra-synovial vascular signals which are of particular benefit in differentiating active synovitis from inactive disease. However, the interpretation of juxta-articular Doppler signal is challenging in children, as it can be a sign of the increased synovial vascularization indicating inflammation, or expression of the physiologically enhanced blood flow of the well-vascularized epiphyseal cartilage of the growing skeleton. Unlike adults, the prognostic meaning of MSUS findings in JIA is still being debated, as abnormalities, including Doppler signal, in children with clinically inactive disease, have been documented not to predict a disease flare [10]. This shortcoming further highlights the need of defining the normal sonographic anatomy throughout paediatric age groups before addressing the role of MSUS in children with JIA.

Tendons are frequently involved throughout JIA course and isolated tenosynovitis may be responsible for joint swelling in children with JIA. The advantage of US over clinical examination in ascertaining whether joint swelling is due to synovitis, tenosynovitis or both, has been largely documented in complex joints with numerous adjacent tendons, such as the ankle or the wrist.

Guidance to local injection therapy represents an important application of MSUS in routine care. US allows the operator to place the needle tip into the joint cavity, tendon sheaths or other peri-articular structures, minimizing the rate of side effects due to delivery of the steroid preparation out of the joint space and maximizing the efficacy of the procedure.

The capability to evaluate joints dynamically and in different spatial planes makes MSUS suitable for capturing bone erosions in sonographically accessible areas. However, the assessment of erosive changes of growing children is challenging as some physiological bone irregularities can be misinterpreted as cortical erosions leading to both an over- or under-estimation of structural damage in children with JIA.

US is well suited for the cartilage assessment in the immature skeleton as it visualizes the cartilage of unossified epiphyses and detects the ossific nuclei several weeks before they become visible by CR. Damage usually appears as cartilage loss with thinning or blurring of its anechoic structure. Recent studies have

documented an acceptable inter- and intra-observer reliability and a good agreement between MSUS and MRI for the measurement of cartilage thickness in several joints; furthermore age- and sex-related normal standards for cartilage thickness for several joints have been established [11].

In childhood, US diagnosis of enthesitis, which is a common feature of the enthesitis-related arthritis (ERA) category of JIA, may be somewhat difficult to make. MSUS evaluation of enthesal inflammation, in fact, requires a thorough knowledge of the age-related anatomic changes as physiological vascularization of the ossification centres next to the entheses can be difficultly discriminated from pathological inflammatory blood flow. In addition the irregular shape of some ossification centres may be misinterpreted as a sign of enthesitis rather than as a normal age-related feature.

Conclusions

Imaging approach to JIA has been radically changing over the last decade and modern imaging modalities such as MR and US are increasingly flanking CR for diagnosis of JIA, assessing its severity, monitoring disease course and treatment efficacy. A thorough knowledge of the relative value of the currently available imaging modalities is necessary to optimize the management of JIA.

MR and US are still in their infancy and further research focusing on the validation and standardization of these techniques is warranted before considering their use in clinical practice. Due to the peculiarities of the growing skeleton, studies aiming to establish normative data for healthy children are of high priority.

Figure 1 Plain radiography of the wrist from a JIA patient with unilateral wrist disease showing advancement of skeletal maturation in the affected side (arrow) secondary to hyperaemia.



Figure 2 A. Contrast-enhanced coronal FFE 3D fat-saturated T1-weighted image in a patient with JIA and active wrist involvement showing synovitis in the radioulnar, radiocarpal and intercarpal joint recesses. B. Coronal TSE fat-saturated T2-weighted image in a second patient with JIA showing diffuse bone marrow oedema involving the scaphoid, the capitate, the hamate, the trapezoid and the lunate. C. Coronal TSE T1-weighted MRI of the carpus in a third patient with JIA showing multiple bone erosions visible in the lunate, scaphoid and capitate. FFE: fast field echo; TSE, turbo spin echo.

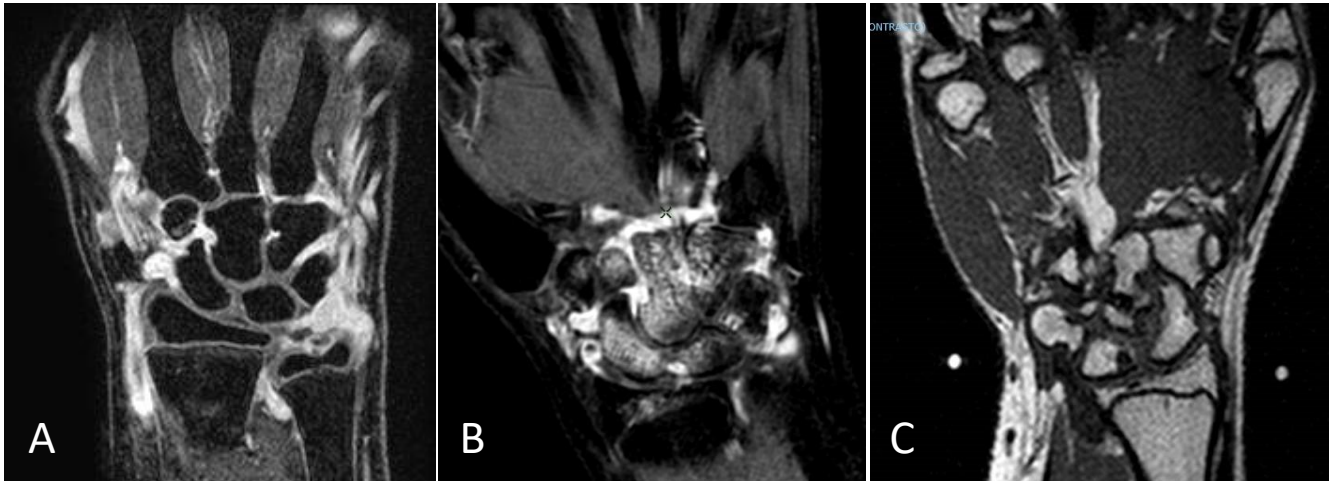
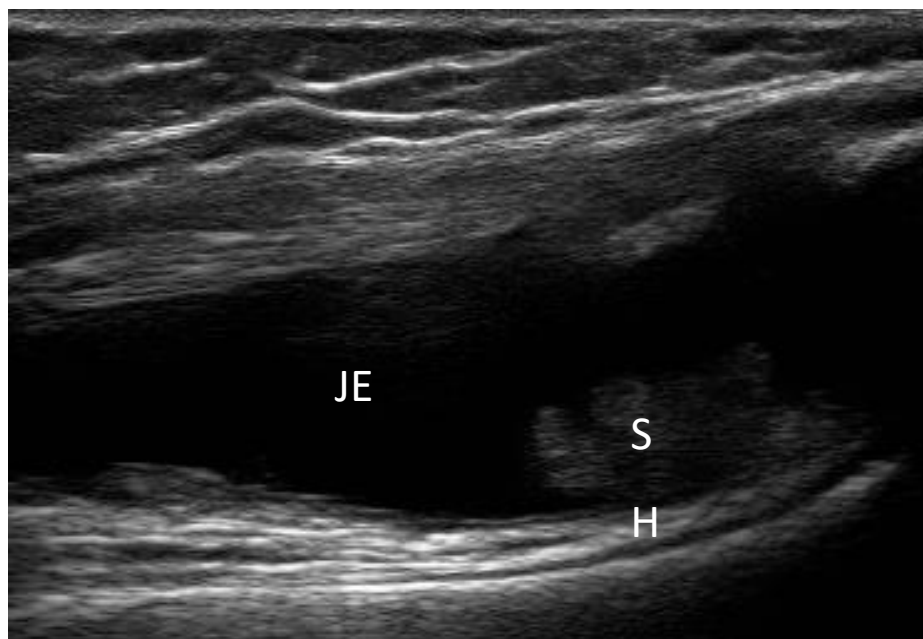


Figure 3 Longitudinal ultrasound scan of the supra-patellar pouch of the knee from a patient with JIA showing joint effusion (JE) and synovial hypertrophy (SH).



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EULAR on-line course on Rheumatic Diseases

Juvenile Idiopathic Arthritis

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IN-DEPTH DISCUSSION II

**Measuring disease activity, physical function and damage
in JIA current clinical practice**

The complexity in the assessment of JIA is mainly related to the absence of a single gold standard measure to support clinical decision making. JIA is a multifaceted disorder and therefore measurement of multiple outcomes, including disease activity, disability and joint damage, is relevant to its management. Most of the currently available outcome measurements are complex, time requiring and have been developed to be used to test assess the effectiveness of antirheumatic drugs in clinical trials or in research setting.

Computational difficulties and data score interpretation further hinder their use in a busy regular clinical setting [1].

A compelling argument is available to suggest that the incorporation of quantitative measures of disease status in standard practice, and adjustments of therapy accordingly (treat-to-target approach), may improve the quality of patient care and disease outcomes on the longer run.

This discussion will focus on the disease assessment indices specifically devised for routine clinical care and on the description of disease status such as inactive disease, minimal disease activity etc., which represent suitable therapeutic targets.

Measures of disease activity

Evaluation of disease activity is a fundamental component of the clinical assessment of children with JIA because persistently active disease is the major determinant of joint damage and physical functional disability. A variety of clinical instruments are available for measuring disease activity, including joint count, global assessment scales, inflammatory serum biomarkers, parent/patient self-reported disease activity. However, due to high disease heterogeneity, no single measure can reliably capture disease activity in all patients. Conversely, evaluation of all measures individually is associated with methodological and statistical problems, especially when these measures are used as clinical endpoints in clinical trials.

Definition of improvement

Measurement of the level of disease activity over time is important to assess the effectiveness of anti-rheumatic drugs in clinical trials and to monitor the patient course in daily care. Response to treatment is currently assessed using validated outcome measures and is calculated as the percentage of change of a core set of clinical variables which consist of; 1) physician global assessment of overall disease activity (PGA); 2) parent/patient global assessment of overall well-being; 3) functional ability; 4) number of joints with active arthritis; 5) number of joints with limited range of motion; 6) erythrocyte sedimentation rate. Using this core set of disease activity measures, response criteria have been created. The American College of Rheumatology paediatric (ACRp) 30 definition of improvement (at least 30% improvement in at least 3 core set variables, with no more than one of the remaining variables deteriorating by more than 30%) has been accepted by

regulatory agencies for drug registration as primary outcome measure in clinical trials in JIA [2]. To provide for more demanding levels of response, ACRp 50, 70, 90 and 100 levels of response have been recently assessed in clinical trials. For ACRp50, ACRp70 or ACRp90, improvement had to be at least 50%, 70% or 90% respectively, with no more than one of the core outcome variables deteriorating by 30% or more. The ACR p response criteria emphasise change in disease state, however, the nature of their calculation does not enable the measurement of actual disease activity and the comparison of one patient's absolute response with that of another. Furthermore, they do not allow discernment of whether one group of patients has more active disease than the other. In this perspective pooling individual measures of disease activity into composite scores appear more effective in order to increase the validity and precision of its evaluation.

Composite scores in JIA

Juvenile Arthritis Disease Activity Score (JADAS) is the first composite disease activity score which aims to quantify the absolute level of disease activity on a continuous scale. JADAS is calculated as the arithmetic sum of the scores of its 4 components: 1) physician global assessment of overall disease activity (PGA), measured on a 0-10 cm visual analogue scale (VAS); 2) parent/patient global assessment of overall well-being, measured on a 0-10 cm VAS; 3) count of joint with active disease assessed in 71 (JADAS-71), 27 (JADAS-27) or 10 (JADAS-10) joints; 4) ESR, normalized to a 0-10 scale (according to the following formula: $[\text{ESR (mm/hour)} - 20]/10$; before making the calculation, ESR values <20 mm/hour were converted to 0 and ESR values >120 mm/hour were converted to 120) [3]. Alternatively, the ESR parameter can be substituted by CRP with High correlation with the original JADAS [1]. Moreover, also the 'clinical JADAS', or cJADAS, which is the JADAS score without CRP or ESR has shown high correlation with the original JADAS scores [1].

The variables included in JADAS are also part of the core set outcome variables included in the ACR Pedi criteria. Restricted joint count and functional assessment were not suited for inclusion in the JADAS because these are affected by disease damage. In validation analysis, JADAS was found to have good metrologic properties, including the ability to predict disease outcome.

JADAS calculation is simple and quick; being a measure with absolute value, it is suitable to determine the disease activity status and course thus increasing the consistency of its assessment across physicians. Moreover, by providing a single number, allows patient/parent to better understand the meaning of disease activity and its course with relevant impact on therapeutic compliance.

Recently JADAS cut-offs values of high and low levels of disease activity have been established, enabling the physicians to have a tighter therapeutic control of disease [4, 5]. Table 1 summarizes these scores for oligo-arthritis and poly-arthritis.

Table 1: cut-offs for disease activity states in oligo and poly-JIA [1].

	JADAS10/71	JADAS27	cJADAS10
Oligoarthritis			
Inactive disease	≤1	≤1	≤1
Low disease activity	1.1 – 2	1.1 – 2	1.1 – 1.5
Moderate disease activity	2.1 – 4.2	2.1 – 4.2	1.51 – 4
High disease activity	>4.2	>4.2	>4
Polyarthritis			
Inactive disease	≤1	≤1	≤1
Low disease activity	1.1 – 3.8	1.1 – 3.8	1.1 – 2.5
Moderate disease activity	3.9 – 10.5	3.9 – 8.5	2.51 – 8.5
High disease activity	>10.5	>8.5	>8.5

Current limitations of JADAS are the Lack of quantification of extra-articular manifestations such as fever and rash (relevant to systemic JIA assessment) and the omission of ocular disease assessment.

Inactive disease, clinical remission and minimal disease activity

Therapeutic advances have increased the expectations of treatment benefits, with disease remission now becoming a realistic goal of any therapeutic intervention in JIA. Preliminary criteria for inactive disease have been established through an international collaborative effort. Accordingly, a patient is classified as having inactive disease at a specific point in time when he/she has no joints with active disease, no systemic manifestations attributable to JIA, no active uveitis, normal values of acute phase reactants, and a PGA indicating no disease activity [6]. Recently, the criteria were modified by adding duration of morning stiffness ≤ 15 minutes. When these criteria are satisfied for at least 6 consecutive months while the patient is receiving anti-rheumatic drugs, the patient is classified as being in state of clinical remission on medication. Disease remission off medication was defined as at least 12 months of inactive disease after discontinuation of all medications [7].

The achievement of complete absence of any signs or symptoms of active disease is however not always possible, particularly among patients with polyarticular or systemic disease. Therefore, a more attainable goal could be to achieve and maintain a state of minimal disease activity which is an intermediate state between high disease activity and remission, though very close to remission. The state of minimal disease activity is defined as the presence of all of the following: PGA of ≤3.5, parent's global rating of well-being of ≤2.5, and swollen joint count of ≤1 in patients with polyarthritis, and PGA of ≤2.5 and swollen joint count of 0 in patients with oligoarthritis. Children with systemic arthritis, RF-positive polyarthritis, RF-negative polyarthritis, or extended oligoarthritis were included in the polyarthritis group. [8]

Evidence has been provided that achievement of disease quiescence helps prevent functional impairment, structural damage and may enhance quality of life and thus is regarded as ideal therapeutic target.

Physical function assessment

The assessment of physical function is a fundamental component of the clinical evaluation of children with JIA. The Childhood Health Assessment Questionnaire (CHAQ) is the most widely used questionnaire on self-estimated functional ability in children with JIA. It assesses functional ability in 8 domains of physical function (dressing, arising, eating, walking, hygiene, reach, grip, activities). The mean score of the eight domains finally makes up the disability index and ranges from 0 (no disability) to 3 (disabled). Utilization of assistance and or aids in a domain sets the score to a minimum of 2 for that domain. The CHAQ is supplemented with two VAS: one for pain, and one for global assessment of overall well-being. The original version has been validated in several languages and different cultures [9]

Although the CHAQ has proved to be valid, reliable, and sensitive to change over time, it is however not routinely incorporated in daily care, due to its complexity, including the requirement of a calculator to compute the score. Studies aiming to set up a functional measure more feasible than CHAQ for routine use in standard clinical care of children with JIA, are therefore warranted.

Assessment of disease damage

So far, in JIA outcome studies, the long-term morbidity has been evaluated in terms of functional disability, as assessed by the C-HAQ. However, despite its widespread use, the C-HAQ may not capture information on several possible forms of damage that may develop in JIA patients over time, such as micrognathia, height retardation, localized growth disturbances, pubertal delay, or visceral organ failure. Permanent changes may also develop in extra articular organs/systems, such as the eye (as a complication of chronic anterior uveitis) or the kidney (due to systemic amyloidosis), or may result from side effects of medications. This morbidity may have a relevant impact on the quality of life of patients and their families

The JADI is intended to rate the extent of damage, defined as persistent changes in anatomy, physiologic status, pathologic processes, or function, that is the result of prior active disease, complications of therapy, or comorbid conditions, that is not due to currently active arthritis, and that is present for at least 6 months despite previous therapies.

The index is composed of 2 parts, one to assess articular damage (JADI-A) and one to address extra-articular damage (JADI-E). In the JADI-A limited ROM, deformity, and previous surgical interventions such as prosthetic replacement, arthrodesis, arthroplasty, or fusion are evaluated in 36 joints and scored in each joint on a 2 point scale (1: partial damage, 2: severe damage, ankylosis, or prosthesis). The maximum total score is 72. The JADI-E explores the presence of damage in 5 different organs/systems. Damage is evaluated using a binary scale (0: absent, 1: present) on 13 items. Due to the relevant impact of ocular damage on the child's health, it

was decided to give a score of 2 for each eye when the patient has had ocular surgery, and a score of 3 when the patient has developed legal blindness. The maximum total score is 17 [10].

Damage is often irreversible and cumulative, and thus, damage scores are most frequently expected to increase or remain stable over time. However, because some forms of damage may improve in paediatric patients, scores may decline in some cases.

The Juvenile Arthritis Damage Index (JADI) is a feasible and easy-to-apply clinical index; it takes only 5–15 minutes for each patient, depending on the amount of damage, making it practical for use in the busy clinical setting. The definitions for scoring each item are concise and simple, in order to make the method accessible even to inexperienced assessors. The JADI represent a promising tool to investigate the full range of factors that can promote long-term morbidity and disability in JIA.

Conclusions

In conclusion a new generation of instruments have been developed in line with current insights about the importance of close monitoring of patients. A tight control strategy, including measurement of disease activity, target setting, and planned adjustment of antirheumatic medication, allows us to improve long term disease outcome and improve the quality of care in patients with chronic inflammatory arthritis.

For applying tight control principle in practice simple tools to quantify multiple outcomes, such as those above illustrated, are relevant for clinicians to know and to apply in daily clinical practice.

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EULAR on-line course on Rheumatic Diseases

Miscellaneous inflammatory arthritides:

Adult Still's disease, Sarcoidosis,
Palindromic rheumatism,
Paraneoplastic arthritis,
Hypertrophic osteoarthropathy



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1. Adult Still's disease

LEARNING OUTCOMES

- Outline the epidemiology of adult Still's disease (ASD)
- Describe associations found in the pathogenesis of ASD in terms of genetics, environmental factors and cytokines
- Describe the clinical manifestations of ASD in terms of fever pattern, and dermatological, musculoskeletal, cardiopulmonary and haematological manifestations
- Describe and evaluate the sensitivity and specificity of laboratory and radiographic findings in ASD
- Describe different sets of classification criteria for ASD, and evaluate their sensitivity and specificity
- Describe the clinical course of ASD in terms of disease patterns and evaluate their prognosis
- Describe treatment options in ASD, and evaluate their level of evidence, efficacy and side effects

1.1 Introduction

Adult onset Still's disease (AOSD) is a rare inflammatory disorder characterised by the classical clinical triad of a daily high spiking fever, arthritis and an evanescent rash. In 1897, Sir George Frederick Still described 22 children with symptoms consistent with the current systemic onset of juvenile idiopathic arthritis (SOJIA) (Still 1990). The first case of an adult exhibiting the same symptoms was reported the year prior in the Lancet (Gerfaud-Valentin, Jamilloux et al. 2014). Following this, numerous cases of patients suffering from high spiking fever, polyarthritis, lymphadenopathy, evanescent rash, sore throat and a striking leucocytosis of unknown origin were described and grouped in Europe under the 'Wissler Fanconi syndrome'. In 1971, Eric Bywaters described the first series of 14 adults with the same symptoms as those seen in paediatric Still's disease, thus defining adult onset Still's disease (Bywaters 1971).

Today the diagnosis AOSD is based on a constellation of symptoms, and Yamaguchi's criteria are one of the most well-known classification criteria (Gerfaud-Valentin, Jamilloux et al. 2014). According to the existing literature, this disease is relatively benign and not usually fatal. However, it can cause macrophage activation syndrome

(MAS) and disseminated intravascular coagulation (DIC), both of which can be life-threatening (Efthimiou, Kadavath et al. 2014, Sakata, Shimizu et al. 2016).

Amongst the group of immune mediated inflammatory disorders managed by rheumatologists, AOSD is often referred to as an 'auto-inflammatory' disorder, signifying the dominant role of the innate immune system in disease pathogenesis, and the notable lack of any associated autoantibodies.

This module will describe in detail the epidemiology, pathogenesis, clinical features, laboratory and radiographic findings, classification criteria, course and treatment options of AOSD.

1.2 Epidemiology

Based on reviews from the 1980s, it appears that AOSD occurs worldwide with estimated annual incidence at 0.16 per 100,000 persons in France, 0.22 in Japan and 0.4 in Norway. (Magadur-Joly, Billaud et al. 1995, Wakai, Ohta et al. 1997, Evensen and Nossent 2006). The disease characteristically affects young adults with equal sex distribution (Efthimiou, Paik et al. 2006, Gerfaud-Valentin, Maucourt-Boulch et al. 2014), although Japanese and Chinese studies report a slight female dominance. (Sakata, Shimizu et al. 2016). A retrospective observational study of 62 patients from France demonstrates a bimodal peak at disease onset at ages 15-25 years and 36-46 years (Magadur-Joly, Billaud et al. 1995). A Dutch retrospective review of 45 patients demonstrated the median age of onset at 25 years (range 16–65), with 27% of the patients showing the first symptom after the age of 35 (Wouters and van de Putte 1986). Interestingly, a large retrospective study of 513 patients from Japan demonstrated a later onset of disease with about half of the patients greater than 55 years old and approximately 16 % were ≥ 75 years old (Sakata, Shimizu et al. 2016). This may be explained by an aging population and regional differences in presentation across ethnicities.

When onset of AOSD occurs before 16 years old, the disease is called Systemic onset Juvenile Idiopathic Arthritis (SoJIA). Whether AOSD and SOJIA are the same disease remains controversial. SOJIA is considered a subtype of juvenile idiopathic arthritis (JIA), however evidence suggests it should be considered apart from JIA because of clear differences in epidemiology, clinical manifestations, pathophysiology and response to treatment. It is more likely to belong to the auto inflammatory diseases along the same continuum as AOSD.

1.3 Pathogenesis

1.3.1 Genetics

Although no familial trend has been reported, some studies have reported some associations with HLA antigens. HLA-Bw35 was the first identified as a susceptibility antigen and associated with a mild self-limited pattern of disease (Terkeltaub, Esdaile et al. 1981). HLA DR4 was found more prevalent in 29 AOSD cases versus healthy controls and HLA DRw6 was associated with the occurrence of proximal arthralgia (Wouters, Reekers et al. 1986). In a retrospective review on 55 patients from Canada, a strong association was seen with HLA-B17, -B18,

-B35 and -DR2, however other studies failed to confirm these findings (Pouchot, Sampalis et al. 1991). The lack of consistent results may reflect an absence of associated or wide heterogeneity of such associations between different ethnic groups (Gerfaud-Valentin, Jamilloux et al. 2014).

Interestingly, no mutation in genes involved in hereditary autoinflammatory disease has been associated with AOSD. Polymorphisms have been described in genes encoding innate immunity-associated factors and cytokines, and include IL-6, IL-1a, IL1-RN, Macrophage inhibitory factors (MIF) in patients with SOJIA and IL-18 or MIF in patients with AOSD. These polymorphisms are anecdotal and likely to have very low penetrance suggesting that a polygenic pattern of inheritance is likely (Gerfaud-Valentin, Jamilloux et al. 2014, Jamilloux, Gerfaud-Valentin et al. 2015).

1.3.2 Environmental factors

A number of epidemiological aspects of AOSD support the hypothesis that the disease is triggered by an environmental source, including clinical features (frequent onset of pharyngitis in prodrome) and seasonality. As in SoJIA, a number of viruses and bacterial have been isolated in AOSD patients (Jamilloux, Gerfaud-Valentin et al. 2015) (table 1). The observation that many different infectious agents may act as disease triggers, suggests a similarity with reactive arthritis. Overall, AOSD does not seem to be an infectious disease but rather an autoinflammatory disease in which infections or environmental agents may trigger a flare up.

Table 1: Viruses and bacteria isolated in AOSD patient (Efthimiou, Paik et al. 2006).

Viruses	Bacteria
Rubella and Mumps, Echovirus 7, Cytomegalovirus, Epstein-Barr virus, Parainfluenza, Coxsackievirus B4, Adenovirus, Influenza A, Human herpes virus 6, Parvovirus B19, Hepatitis B and C	<i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> , <i>Yersinia enterocolitica</i> 3 and 9, <i>Brucella abortus</i> , <i>Borrelia burgdoferi</i>

1.3.3 Immunopathogenesis

Immune dysregulation including cytokine mediated inflammation and dysregulated apoptosis is implicated in the development of AOSD (Kadavath and Efthimiou 2015). A hallmark of the condition is activation of the innate immune pathway with prominent neutrophil and macrophage involvement.

A proposed pathophysiological model suggests that environmental triggers, termed danger signals, activate a dysregulated NLRP3 inflammasome, which in turn triggers the activation and secretion of pro-inflammatory cytokines (IL-1 β and IL-18) and Th1 polarisation of CD4 T cells. At the same time, these danger signals activate toll-like receptors 7 which cause dendritic cells to induce Th17 response. Th17 cells secrete IL-17 which stimulates the production of chemokines and neutrophil recruitment (Gerfaud-Valentin, Jamilloux et al. 2014, Jamilloux, Gerfaud-Valentin et al. 2015).

IL-1 β can induce its own production through IL-1 receptor in an autocrine process. IL-18 is also processed through the inflammasome machinery. It induces production of Th1 cytokines. It also triggers a natural killer (NK) cell mediated IFN γ production, which in turn increases macrophage activation. These NK cells are abnormal with decreased cytotoxic function. Serum concentrations of IL-1 β and IL-18 are significantly higher in AOSD patients than in controls (Gerfaud-Valentin, Jamilloux et al. 2014, Jamilloux, Gerfaud-Valentin et al. 2015).

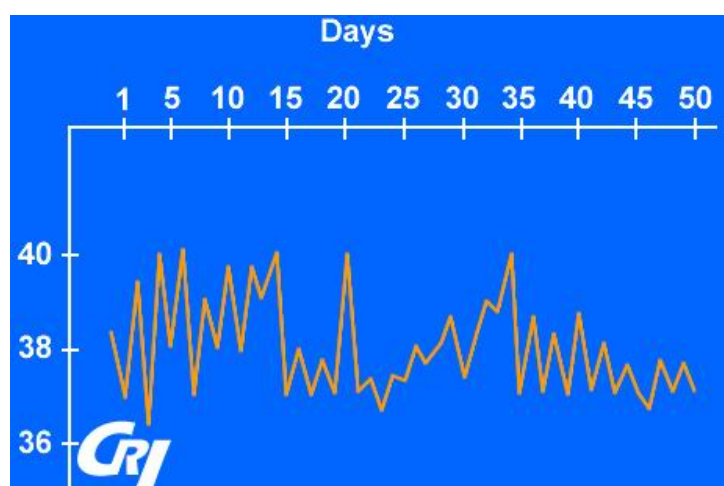
Downstream of IL-1 β several other cytokines have important roles including IL-6, TNF α and IL-8. IL-6 is responsible for some of the clinical features (fever, rash) and the liver synthesis and fast release of ferritin. Its levels are correlated with disease activity. Additionally, many chemokines are involved in the inflammatory reaction including CXCL8, a major neutrophil inducer and CXCL1 (Gerfaud-Valentin, Jamilloux et al. 2014, Jamilloux, Gerfaud-Valentin et al. 2015).

1.4 Clinical manifestations

1.4.1 Fever

This is often the initial symptom preceding other manifestations. The fever is usually of sudden onset and generally exceeds 39°C. It is transient and is most commonly quotidian or double quotidian in pattern, with the highest temperatures seen in the late afternoon or early evening (Larson 1985) (figure 1). It is present in almost all patients. (Pouchot, Sampalis et al. 1991, Efthimiou, Paik et al. 2006, Gerfaud-Valentin, Jamilloux et al. 2014).

Figure 1 Body temperature curve in adult Still's disease. (Source: CRI (Club Rhumatismes et Inflammation) <http://www.cri-net.com>)



1.4.2 Rash

The typical skin rash is classically described as evanescent, salmon-pink, macular or maculopapular erythema (figure 2). It appears or becomes more prominent with the onset of fever. It is found predominantly on the trunk and proximal extremities (Kadavath and Efthimiou 2015). It can be mildly pruritic and associated with a burning sensation. A Koebner's phenomenon has been described (Pouchot, Sampalis et al. 1991) Histology shows perivascular inflammation of the superficial dermis with invasion of lymphocytes and histiocytes, and immunohistochemistry is sometimes positive for complement and immunoglobulin (Pouchot, Sampalis et al. 1991, Efthimiou, Paik et al. 2006). Overall, the incidence of the rash in AOSD is from 51% to 87% (Efthimiou, Paik et al. 2006)

Figure 2 Transient, salmon-pink, maculopapular erythema, on the trunk. (Source: CRI (Club Rhumatismes et Inflammation), <http://www.cri-net.com>)



1.4.3 Sore throat

Sore throat is an early manifestation in approximately 70% of cases AOSD and can precede fevers and other symptoms. It is also commonly observed during occurrence of subsequent disease flares. It has been linked to a viral infection, although imaging studies have suggested inflammation of the crico-arythenoid joints, plus perichondritis of cricothyroid cartilage that may be the cause of symptoms (Nguyen and Weisman 1997, Chen, Lan et al. 2007).

1.4.4 Musculoskeletal disease

Arthralgia and arthritis are found in the majority of patients with AOSD, with incidences ranging from 64% to 100% (Efthimiou, Paik et al. 2006). Joint involvement is typically oligoarticular with pain associated with fever spikes. Symptoms are transient, resolving as the fever diminishes (Efthimiou, Paik et al. 2006). However, joint disease can evolve over months into a more destructive form. The joints affected most frequently are the knees, wrists and ankles, although involvement of the elbows, shoulders, proximal and distal interphalangeal joints,

metacarpophalangeal and metatarsophalangeal joints, temporomandibular joints, and hips have been described as well (Bywaters 1971, Elkon, Hughes et al. 1982, Pouchot, Sampalis et al. 1991, Masson, Le Loet et al. 1995). Of note, AOSD arthritis has a predilection for the carpal and pericarpitate bones. Changes in the wrist typically present 6 months after disease onset, with progressive joint space narrowing, with ankylosis developing after 1.5–3 years (Medsger and Christy 1976).

Generalised myalgia is common, with an incidence of 56-84%. Myalgia may coincide with the fever spike. It may be severe and debilitating, but an inflammatory myopathy is rarely found (Efthimiou, Paik et al. 2006) (Masson, Le Loet et al. 1995).

1.4.5 Liver disease

Hepatomegaly and modest liver biochemistry abnormalities occur in 50-75% of patients. Acute hepatitis or hepatic failure is extremely rare, and most of the reported cases occurred during treatment with hepatotoxic drugs or in the setting of macrophage activation syndrome (Reginato, Schumacher et al. 1987) (Mylona, Golfinopoulou et al. 2008).

1.4.6 Lymphadenopathy and splenomegaly

Tender cervical lymphadenopathy and splenomegaly occur in 50% of patients. Lymph node biopsy findings may resemble lymphoma on light microscopy, but immunohistochemistry demonstrates benign polyclonal B cell hyperplasia (Quaini, Manganelli et al. 1991).

1.4.7 Cardiopulmonary disease

Cardiopulmonary manifestations include pleuritis, pericarditis and transient pulmonary infiltrates occurring in 30-40%. These improve rapidly after treatment (Gerfaud-Valentin, Jamilloux et al. 2014). Pericarditis is mild in nature but in rare cases has been reported to lead to tamponade (Reginato, Schumacher et al. 1987). Rarely, pulmonary disease may become severe, progressing to ARDS. Chronic interstitial lung disease and pulmonary hypertension are rare (Campos and Schiopu 2012) (Cheema and Quismorio 1999).

1.4.8 Haematological manifestations

Macrophage activation syndrome (MAS) or reactive haemophagocytic syndrome (RHS) is a life threatening complication of AOSD with a reported mortality between 10-22% (Efthimiou, Kadavath et al. 2014). Despite a very rare condition, MAS in AOSD has likely been underdiagnosed and is in fact more common than previously recognized (Arlet, Le et al. 2006).

Clinical and biological features of MAS closely resemble reactive haemophagocytic lymphohistiocytosis (HLH) and the disease is in fact considered as secondary subclass of HLH (Davi, Consolaro et al. 2011). MAS is characterised by an uncontrollable activation and non-malignant proliferation of T lymphocytes and

macrophages which lead to phagocytosis of haematopoietic cells in various organs. The underlying physiopathology is not well understood. There is impairment of cytotoxic function with a reduced number or defective activity of CD8⁺ lymphocytes and NK cells. The perceived failure of complete pathogen destruction results in persistent lymphocyte and macrophage activation. Macrophage activation subsequently results in tissue infiltration, production of ferritin and high levels of cytokines (TNF α and IL-6, IL-18, IL-8) (Grom 2003).

MAS most commonly occurs early on during the course of AOSD (Lenert and Yao 2016). MAS and AOSD share several clinical and laboratory features which may explain the difficulty in recognizing the condition when it complicates a flare of AOSD. Some red flag clinical features including renal insufficiency, lung involvement with hypoxia, hypotension, and DIC, should raise concern for the impending development of MAS (Lenert and Yao 2016). Laboratory findings include pancytopenia with lymphopenia in particular and high serum levels of ferritin, triglycerides, and liver enzymes, whilst paradoxically demonstrating a normal erythrocyte sedimentation rate, due to increased fibrinogen consumption (Sawhney, Woo et al. 2001, Lenert and Yao 2016). It is important to acknowledge that hyperferritinaemia is a classical laboratory finding in AOSD even without overt MAS, but extreme ferritin elevation (>10,000 ng/mL) in the context of cytopenias should prompt urgent evaluation for MAS.

Gold standard diagnostic criteria for MAS in AOSD are lacking. The presence of haemophagocytosis on bone marrow examination has been regarded as a standard criterion for diagnosis. However, this finding may be absent in up to 40% of patients. The HLH 2004 criteria have been traditionally used for identifying MAS in patients with autoimmune diseases (Kumakura, Ishikura et al. 2004, Henter, Horne et al. 2007) (Box 1). The Ravelli criteria have been refined to increase post-test probability for earlier identification of MAS in SOJIA (Ravelli, Magni-Manzoni et al. 2005) (Box 2). As MAS is becoming better studied and defined, novel associations and tests are being used. Soluble IL-2 receptor α (sCD25), reflective of T cell activation, and soluble CD163, related to activation of phagocytic macrophages/histiocytes, might be useful as diagnostic markers of MAS and helpful in monitoring disease activity and response to treatment.

Box 1. Haemophagocytic lymphohistiocytosis (HLH) criteria 2004 (Henter, Horne et al. 2007)

The diagnosis *non-familial HLH* is established with the presence of five criteria or more

- fever
- splenomegaly,
- peripheral blood cytopenias affecting at least 2 of 3 cell lineages
- hypertriglyceridemia or hypofibrinogenaemia
- microscopic evidence of haemophagocytosis in the bone marrow, spleen, or lymph nodes,
- low or absent natural killer (NK) cell activity,
- elevated ferritin levels
- elevated soluble CD25 (sCD25; IL-2 receptor) levels

Adapted from (Henter, Horne et al. 2007)

Box 2 Preliminary guidelines for MAS complicating SoJIA (Ravelli, Magni-Manzoni et al. 2005)*Presence of ≥ 2 laboratory criteria or ≥ 2 clinical and/or laboratory criteria***- Laboratory criteria include**

- platelet count $\leq 262 \times 10^9/\text{litre}$,
- aspartate aminotransferase level > 59 units/litre
- white blood cell count $\leq 4.0 \times 10^9/\text{liter}$ ~~litre~~ blood cell count $\leq 4.0 \times 10^9/\text{litre}$

- Clinical criteria include

- hepatomegaly,
- haemorrhagic manifestations,
- central nervous system (CNS) dysfunction

- Demonstration of macrophage haemophagocytosis on bone marrow aspirate only in doubtful cases.*Adapted from Ravelli, Magni-Manzoni et al. 2005*

Other haematological complications in AOSD are rare. Pure red cell aplasia, thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome have been described. (Bagnari, Colina et al. 2010)

1.5 Laboratory and radiographic findings

1.5.1 Laboratory findings

The laboratory findings in AOSD reflect the systemic inflammation and cytokine cascade present, and none of the findings are specific for AOSD. This is no association with antinuclear antibodies or rheumatoid factors. Erythrocyte sedimentation rate and C-reactive protein are raised in virtually all patients.

1.5.1.1 Haematological studies

Neutrophilic leukocytosis remains as the most common haematological abnormality (98%) and may allow differentiation from other fevers of 'unknown origin'. Most patients have a normocytic, normochromic anaemia (anaemia of chronic disease) especially during active disease, and a reactive thrombocytosis is common. (Efthimiou, Paik et al. 2006, Gerfaud-Valentin, Jamilloux et al. 2014). Disseminated intravascular coagulation may occur.

1.5.1.2 Liver function studies

Liver abnormalities are common with raised serum aminotransferase, lactate dehydrogenase, γ -glutamyltransferase and bilirubin are seen in 75% of patient with AOSD. The pathophysiology of liver involvement is not known; cytokine production and sustained macrophage activation are implicated. Liver biopsy findings are non-specific (Pouchot, Sampalis et al. 1991, Efthimiou, Kadavath et al. 2014) (Kong, Xu et al. 2010).

1.5.1.3 Serum ferritin

AOSD is associated with marked increase in ferritinaemia, higher than seen in other inflammatory disease. Ferritin is an acute phase reactant, produced by the histiocytic / macrophage systems under the influence of IL-1 β , IL-18, TNF α and also released by damage hepatocytes. There is increasing evidence that ferritin not only reflects the acute phase response but may play critical pro-inflammatory functions.

It has been suggested that rare conditions such as AOSD, reactive HLH and catastrophic anti-phospholipid syndrome should be group together due to their exceptionally high serum ferritin levels and subsequent cytokine storms by the term 'hyperferritinaemic syndrome' (Narula, Narula et al. 2015). Extreme ferritin elevations have also been reported in other settings such as HIV seroconversion (Babiker, Wingfield et al. 2015).

A Chinese series found 99% of patients with AOSD had elevated ferritin levels with 51% having levels of 1000–1500 ng/ml, and 32% having more than 1500 ng/ml (Kong, Xu et al. 2010). Levels ranging between 4000 ng/ml and 30,000 ng/ml are not infrequent, although levels >10,000 ng/ml are often associated with MAS (Arlet, Le et al. 2006). A threshold five times the normal value (ie 1000-1500 ng/ml) is suggestive of AOSD (Ota, Higashi et al. 1987). However the specificity remains poor as similar levels may be seen during infection, neoplastic conditions, haemochromatosis or storage disease such as Gaucher. Serum levels seem to correlate with disease activity, normalising when the disease goes into remission.

1.5.1.4 Glycosylated ferritin

A more specific marker may be to consider with the drop in glycosylated ferritin, as an isoform of ferritin. In healthy subjects 50-80% of ferritin is observed in its glycosylated isoform. In inflammatory disease this level drops to 20-50%, and in AOSD it is noted at less than 20%. It remains low in both the active phase of the disease and in remission (Fautrel, Le Moel et al. 2001).

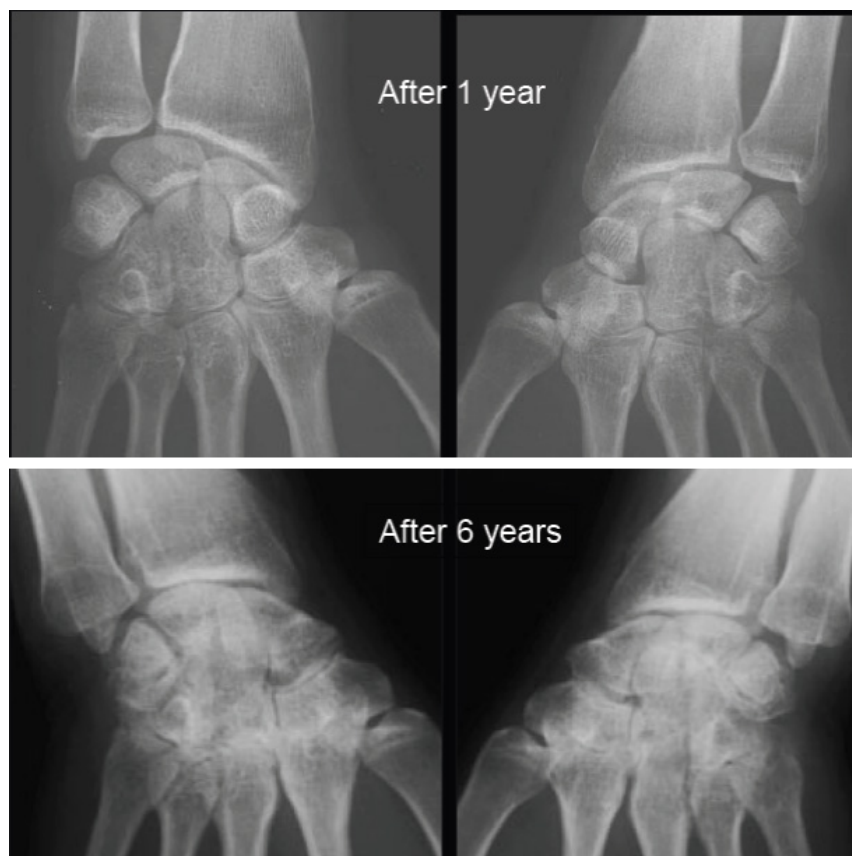
1.5.2 Radiographic findings

No radiographic findings are specific for AOSD and changes vary from normal to soft-tissue swelling, joint effusion, or mild periarticular demineralisation. A classical pattern is non erosive intercarpal and carpometacarpal joint space narrowing of the wrist reported in 41%, which was bilateral in 69%, presenting 6 months after disease onset and developing to ankyloses in 25% in 3 years (Pouchot, Sampalis et al. 1991) (Medsger and Christy 1976) (Figure 3 and 4). Ankylosis of other joints is less common. An unusual complication of AOSD is the rapid destruction of the hip and, less commonly, the knee, which can require total joint arthroplasty (Cabane, Michon et al. 1990).

Figure 3 Isolated carpal disease with fusion in the course of adult Still's disease. (Source: CRI (Club Rhumatismes et Inflammation), <http://www.cri-net.com>)



Figure 4 Isolated carpal disease with fusion in the course of adult Still's disease.



1.6 Classification criteria

There are no specific diagnostic tests for AOSD and the diagnosis is made upon the presence of characteristic clinical and laboratory features in the absence of another condition that may cause similar findings; infections, neoplasm and other autoimmune diseases. Several classification criteria have been proposed. The Yamaguchi's criteria are the most widely cited and provide the highest sensitivity (93%) (Yamaguchi, Ohta et al. 1992), although within these criteria the exclusion of other diseases is required (Box 3). In 2002, Fautrel et al. proposed a new set of criteria which contained serum ferritin and glycosylated ferritin and did not contain exclusion criteria (Box 4). The sensitivity and specificity of Fautrel criteria were 80.6% and 98.5%, respectively (Fautrel, Zing et al. 2002). This classification criteria has been recently validated in a cohort independent of that used for the original publication (Lebrun, Mestrallet et al. 2017).

Box 3. Yamaguchi criteria

The diagnosis ASD is established with the presence of five criteria or more, with at least two major criteria present and no exclusion criteria (96% sensitivity; 92% specificity) (Yamaguchi et al, 1992).

Major criteria

- Fever of at least 39°C, intermittent, lasting ≥ 1 week
- Arthralgias or arthritis, lasting ≥ 2 weeks
- Typical rash
- Leucocytosis ($\geq 10\,000/\mu\text{L}$), with $\geq 80\%$ granulocytes

Minor criteria

- Sore throat
- Recent development of significant lymphadenopathy
- Hepatomegaly or splenomegaly
- Abnormal liver function studies, particularly aminotransferases and lactate dehydrogenase
- Negative tests for antinuclear antibody and rheumatoid factor

Exclusion criteria

- Infections
- Malignancies
- Other rheumatic diseases

Adapted from Yamaguchi et al, J Rheumatol 1992;19:424–30.

Box 4. Fautrel criteria

Four major criteria or three major and two minor criteria.

Major criteria

- Spiking fever ($\geq 39^\circ\text{C}$)
- Arthralgias
- Transient erythematous rash
- Sore throat
- Polymorphonuclear cells $\geq 80\%$
- Glycosylated ferritin $\leq 20\%$

Minor criteria

- Maculopapular rash
- Leucocytosis ($\geq 10\,000/\mu\text{L}$)

Adapted from Fautrel et al, Medicine (Baltimore) 2002;81:194–200.*

1.7 Course

1.7.1 Monophasic, polycyclic systemic and chronic articular

The outcome of AOSD is unpredictable and the disease is conventionally divided into three different subtypes based on disease evolution; 1) self-limited or monophasic, 2) intermittent or polycyclic systemic; and 3) chronic articular. Both monocyclic and polycyclic patterns are more common than the chronic articular pattern (Wouters and van de Putte 1986). The self-limited monophasic pattern is characterized by a single disease episode with systemic symptoms typically involving fever, rash, serositis, and organomegaly. Remission is achieved in most within 1 year, with a median duration of 9 months. The polycyclic systemic pattern is characterised by recurrent disease flares interspersed with complete remissions which can last from 2 weeks to 2 years. Subsequent flares tend to be shorter and less severe and may be years apart (Pouchot, Sampalis et al. 1991, Kadavath and Efthimiou 2015). The chronic articular pattern is characterised by persistent active disease, predominantly articular manifestations with joint destruction, which can mimic other chronic inflammatory arthritides. Involvement of shoulder and hip at disease onset with cutaneous involvement is associated with a worse prognosis than those with only systemic involvement (Pouchot, Sampalis et al. 1991, Kadavath and Efthimiou 2015).

1.7.2 Dichotomous view on clinical expressions and cytokine profile

A new conception of AOSD divided into two distinctive phenotypes is currently emerging based on clinical observations and on studies investigating cytokine profiles and responses to specific biologic treatments. These two subtypes are distinguished according to the dominant clinical expression; those patients that exhibit primarily systemic symptoms with multi-organ involvement, increased levels of inflammatory markers and ferritin and the risk of MAS, more in keeping with an autoinflammatory group of disorders; and those patients that exhibit chronic polyarthritis and a lower inflammatory state in keeping with a seronegative rheumatic disease (Maria, Le Quellec et al. 2014). Some patients may present with systemic flares at the onset of their disease but progressively evolve into a chronic erosive polyarthritis.

1.8 Treatment

Evidence for treatment in AOSD remains largely empirical, derived from single case reports, small case series or retrospective cohort studies. The rarity of AOSD makes it difficult to carry out controlled clinical trials and none has been conducted in adults (Pouchot and Arlet 2012).

1.8.1 Nonsteroidal anti-inflammatory drugs and corticosteroids

Historically, patients with AOSD have been treated along similar regimen as children having the SoJIA with high-dose aspirin or other NSAIDs. However more than 80% of AOSD patients did not achieve remission with this treatment and in the majority corticosteroids are necessary. Nevertheless, temporary use of NSAIDs can be considered during diagnostic workup or for early relapse of the disease (Franchini, Dagna et al. 2010, Jamilloux, Gerfaud-Valentin et al. 2015). Often high therapeutic levels of salicylates are required (Pouchot and Arlet 2012).

Corticosteroids remain the first-line treatment for AOSD regardless of clinical presentation. The usual dose is 0.5-1 mg/kg/day, and pulses of methylprednisolone have been used for severe disease refractory to oral corticosteroids. There are however conflicting reports regarding the impact of the dose or route of administration on therapeutic response (Kong, Xu et al. 2010, Gerfaud-Valentin, Maucourt-Boulch et al. 2014). Several case series report greater efficacy of corticosteroids in those with systemic symptoms compared to those with articular disease. In a series of 45 patients, prednisone monotherapy achieved satisfactory control of disease in more than 79% of the trials administered to those with systemic symptoms, but only 35% of the trials in the articular disease group. Furthermore, 80% of patients whose arthritis did not respond to prednisone within the first 3 months would proceed on a chronic disease course, compared with only 18% of the corticosteroids responders.(Franchini, Dagna et al. 2010). Corticosteroids dependence in AOSD is high, reported at 45%, more prevalent in the polycyclic and chronic forms (Gerfaud-Valentin, Maucourt-Boulch et al. 2014).

1.8.2 Disease modifying anti Rheumatic drugs

In case of corticosteroid failure or dependence, immunosuppressive drugs can be used. Methotrexate remains the first-line corticosteroid-sparing drug in AOSD, although benefits have been reported with cyclosporine A (Mitamura, Tada et al. 2009), azathioprine, leflunomide, hydroxychloroquine (Franchini, Dagna et al. 2010), and tacrolimus (Nakamura, Odani et al. 2014).

1.8.2.1 Methotrexate

In a retrospective cohort of 26 patients with AOSD, 23 (88%) responded to low dose methotrexate (mean dose 11.5 mg/week) with 18/23 (78%) achieving complete remission and 11/26 (42%) able to discontinue their corticosteroids (Fautrel, Borget et al. 1999). Methotrexate seems especially effective for the treatment of polyarthritis. Methotrexate induced hepatotoxicity does not seem to occur more frequently in AOSD than in adult rheumatoid arthritis.

1.8.2.2 Intravenous immunoglobulin IVIG

Data concerning on IVIg in AOSD is more controversial. In 2 open-label studies, IVIg was shown to be effective early in the disease course but other studies have found this treatment had no consequence on the course or the prognosis of AOSD (Permal, Wechsler et al. 1995, Vignes, Wechsler et al. 1998). It is however well tolerated and may be useful in life-threatening situations or in cases of AOSD flare-up during pregnancy.

1.8.3 Targeted biologic therapies

Although dramatic responses have been reported in SoJIA when given as first-line treatment, targeted biologic agents are actually reserved for refractory AOSD. Resistance to corticosteroids and DMARDs defines refractory AOSD, which mostly includes the polycyclic or chronic patterns of the disease. Anti-IL1 is generally used as the first line biologic and anti-IL6 is generally considered the second line biologic, although may be used first line in severe disease, especially in light of the efficacy data in systemic onset JIA that have emerged (De Benedetti, Brunner et al. 2012). Anti-TNF was historically the first line biologic, although is now reserved when other options fail.

1.8.3.1 IL-1 antagonists

Three IL-1 antagonists are presently available, a recombinant antagonist of the IL-1 receptor (IL-1Ra, anakinra), a human monoclonal antibody directed against IL-1 β (canakinumab), and a soluble IL-1 trap fusion protein (rilonacept). Anakinra has been more frequently reported in the treatment of AOSD. The rationale of IL-1 inhibition in AOSD lies in the demonstration of elevated IL-1 levels in active untreated disease and empirical evidence from the successful treatment of the auto-inflammatory syndromes with IL-1 inhibition (Kontzias and Efthimiou 2012). Compiled data from a recent comprehensive literature review on each anti-IL-1 agent, reported similar rates of full or partial remission. Primary treatment failures were rare, but efficacy was lost over time in some cases (Junge, Mason et al. 2017).

1.8.3.1.1 Anakinra

Despite the lack of randomised controlled trials in AOSD, anakinra seems to have an impressive rapid and sustained efficacy, associated with a corticosteroid-sparing effect in most patients (Pouchot and Arlet 2012). Its effect seems to be greater in patients with highly active systemic disease than in patients with isolated chronic arthritis (Jamilloux, Gerfaud-Valentin et al. 2015). The first use of anakinra was an open-label study on 4 patients with disease refractory to methotrexate, of which 2 had disease refractory to etanercept. Treatment resulted in a rapid and complete resolution of both systemic and articular manifestations, sustained during a 6–14 month follow-up period (Fitzgerald, Leclercq et al. 2005). Single case reports have reiterated this remarkable effect, sometimes in those with life-threatening manifestations (Vasques Godinho, Parreira Santos et al. 2005, Debiais, Maillot et al. 2008) and benefit was reported in 1 prospective, randomized, open-label trial (Nordstrom, Knight

et al. 2012). Lequerré et al in a retrospective survey of anakinra therapy in 35 patients (20 with SoJIA and 15 with AOSD) demonstrated similar results. All 15 patients with AOSD had disease refractory to methotrexate, and 10 had also failed anti-TNF α therapy. A total of 11 AOSD patients achieved rapid and major improvement with at least a 50% improvement for all disease markers (Lequerre, Quartier et al. 2008). The largest retrospective observational study evaluated the efficacy and safety of Anakinra in 140 AOSD patients. Treatment was effective in improving all clinical and serological manifestations, with a good response noted at 3 months after therapy onset. Skin reaction were the main causes for discontinuation (Colafrancesco, Priori et al. 2017). Other data regarding anakinra efficacy is available from studies in SoJIA (Swart, Barug et al. 2010). Nigrovic et al. observed rapid resolution of systemic symptoms in more than 95% of cases with an additional preventive effect on refractory arthritis in almost 90% with anakinra as s first-line treatment. Nigrovic postulated that there could be a “window of opportunity” for IL-1 blockade very early in the course of the disease in SoJIA (Nigrovic, Mannion et al. 2011).

Anakinra is given as 100mg subcutaneously daily, due to its short half-life of 4–6 hours. Injection site reactions have been reported. Other side effects are uncommon (Lequerre, Quartier et al. 2008, Pouchot and Arlet 2012).

1.8.3.1.2 Canakinumab

Canakinumab has a longer half-life of 26 days, and thus is administered every 8 weeks. It was reported to be successful in two case of AOSD who were resistant to short-acting IL-1 blockade with anakinra (Kontzias and Efthimiou 2012). However, the high cost of this drug currently precludes widespread use in most healthcare settings.

1.8.3.1.3 Rilonacept

Rilonacept is a soluble dimeric fusion protein that binds to both IL-1 β and IL-1 α and prevents its interaction with cell surface receptors. It is also longer-acting with a half-life of 8.6 days, administered as a weekly subcutaneous injection (220 mg loading dose and 160 mg maintenance dose). Small cohort and case series have reported successful use in patients with refractory AOSD (Petryna, Cush et al. 2012). One study reported high levels of IL-18 at baseline as a predictor of a successful response (Henderson and 10.1002/art.29596 2010;)

1.8.3.2 Inhibitors of IL-6

IL-6 is another pro-inflammatory cytokine through to play an important role in the pathogenesis of AOSD. Serum levels of IL-6 are commonly markedly elevated in active disease and as such it is considered as a suitable target for the treatment.

1.8.3.2.1 Tocilizumab

Tocilizumab is a humanised anti-IL-6 receptor antibody that recognises both the membrane-bound and the soluble form of IL-6 receptor, blocking the actions of IL-6. Tocilizumab is used less widely in treating AOSD and should be used only if anti-IL-1 treatments fail to control the disease or if relapses occur during weaning of anti-IL-1 (Jamilloux, Gerfaud-Valentin et al. 2015). The safety profile seems identical to that reported in rheumatoid arthritis (Pouchot and Arlet 2012).

A small case series on three patients with AOSD who were refractory to standard treatment and cytokine blockade with anakinra and TNF α blockers demonstrated complete remission with tocilizumab therapy (Rech, Ronneberger et al. 2011). A Japanese survey reported a favourable response in both systemic and articular symptoms in 11 patients treated with tocilizumab after failure with TNF α blocker or anakinra. The tocilizumab treatment group had the highest continuation rate, with a tendency for large corticosteroids-sparing effects (Suematsu, Ohta et al. 2012).

In a French review of 14 patients with refractory AOSD treated with tocilizumab, at 6 months a EULAR remission (DAS < 2.6) was achieved in 57% of the patients, and resolution of systemic manifestations was observed in 86%. In most patients, response to tocilizumab was rapid and sustained (Puechal, DeBandt et al. 2011). A recent systematic review identified 35 patients with AOSD treated with tocilizumab for AOSD of which 94% had unsuccessfully tried other immunosuppressive agents including TNF α blocker and anakinra. They reported a prompt articular improvement in 86% and disappearance of systemic symptoms in 96% (de Boysson, Fevrier et al. 2013). Similar findings were reported in a retrospective open label study rapid although joint manifestations appeared more refractory to treatment compared with systemic manifestations. (Ortiz-Sanjuan, Blanco et al. 2014)

1.8.3.3 Anti-Tumour Necrosis Factor α

Historically anti-TNF α drugs were the first biologics used to treat refractory AOSD with supporting data from case reports, retrospective case series, and one open-label trial. TNF α inhibitors were used along the same regimen as adopted for treatment of rheumatoid arthritis. Results were retrospective and rather heterogeneous, although responses appeared more favourable in the setting of chronic polyarticular disease (Gerfaud-Valentin, Maucourt-Boulch et al. 2014).

1.8.3.3.1 Infliximab

Infliximab was the first TNF α blocker to be used in AOSD. In a small case series of six patients there was a rapid and sustained effect in both systemic and articular manifestations (Kraetsch, Antoni et al. 2001). In two other small case series with seven patients with disease resistant to MTX, the addition of infliximab was effective in

all but one patient (Cavagna, Caporali et al. 2001, Kokkinos, Iliopoulos et al. 2004). However, less effective results were noted in a retrospective study conducted by the French 'Club Rhumatismes et Inflammation' group on all prescriptions of anti-TNF α (infliximab and etanercept) in twenty patients with chronic AOSD resistant to conventional DMARDs. A complete response (complete resolution of all clinical and laboratory features) was seen in 4 out of 15 (27%) and a partial response (persistence of one or several AOSD related manifestations) in 9 out of 15 (60%). Ten out of the 15 patients treated with infliximab discontinued treatment after a mean duration of 9 months due to lack of efficacy or side effects (Fautrel, Sibilia et al. 2005). Side effects reported included infusion reactions, cutaneous eruptions, recurrent bronchitis and pneumonia, pneumonitis, heart failure, visual disturbance and fulminant hepatitis in a patient with concomitant hepatitis B (Efthimiou, Paik et al. 2006).

1.8.3.3.2 Etanercept

Etanercept was used in a prospective open-label study in 12 AOSD patients with chronic polyarthritis resistant to conventional therapy. At 6 months, 7 of 12 patients achieved an ACR-20, of which 4 achieved ACR-50 and 2 an ACR-70. Three patients had concomitant systemic manifestations and only one of them improved (Husni, Maier et al. 2002). Other positive case reports have been published, but it is important to acknowledge the inherent publication bias that arises in the case report literature. A further retrospective study again from the French 'Club Rhumatismes et Inflammation' group, reported that out of 10 patients treated with etanercept, only one achieved a complete response and seven a partial response (Fautrel, Sibilia et al. 2005). Side effects associated with etanercept use in AOSD include injections site reactions, paradoxical disease flares, cutaneous eruptions, infection complications and diarrhoea (Efthimiou, Paik et al. 2006).

1.8.3.3.3 Adalimumab

Adalimumab has been used and was effective in fewer than 10 patients (Pouchot and Arlet 2012).

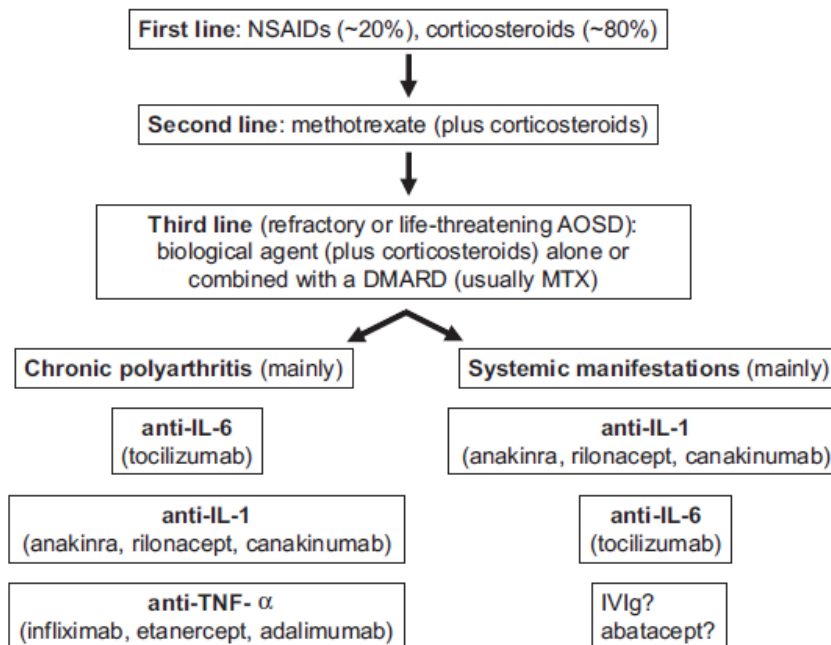
1.8.3.4 Other biological agents

Emerging data on other cytokine pathway blockers continues to emerge. This include recent positive phase 2 trial results of il-18 inhibition in patients with refractory AOSD (Gabay, Fautrel et al. 2017). Abatacept been used in four patients with AOSD and was reported to be effective in two. Rituximab has been tried in four patients but was not effective (Pouchot and Arlet 2012).

1.8.3.5 Therapeutic Strategies

A therapeutic strategy in management is outlined below (figure 5)

Figure 5. Therapeutic strategies in adult-onset Still's disease (AOSD) (adapted by Pouchot et al, best Practice & research Clinical Rheumatology)



Legends: IL: interleukin; IVIg: intravenous immunoglobulins; TNF: tumour necrosis factor

1.8.4 Management Macrophage activation syndrome

Empiric treatment of MAS traditionally consisted of the following agents alone or in combination: intravenous pulse corticosteroids, immune gamma globulin (IVIg), and cyclosporine A (CyA). Corticosteroids therapy has a well-established key role. Cyclosporine was found to be dramatically efficacious in patients whose disease was refractory to high-dose intravenous corticosteroids in the mid-1990s. It is also used in treating HLH (Ravelli, De Benedetti et al. 1996).

There are several reports of the use of IL-1 inhibitors in the management of MAS in SoJIA (Bruck, Suttrop et al. 2011). TNFα inhibitors are considered ineffective or even harmful, and there are several cases of MAS following the use of etanercept in patients with AOSD (Stern, Riley et al. 2001, Gianella, Schaer et al. 2008). A multinational, multicentre study of treatment and outcome of MAS complicating SoJIA reported nearly all patients were treated with corticosteroids with 61% receiving cyclosporine. Biologic medications were given to 15% of the patients, with anakinra being the most frequently selected. Etoposide, which is a central medication in HLH therapeutic protocols was used in 11% of cases. It is argued that this may be too aggressive for use as first-line therapy in systemic JIA-associated MAS (Minoia, Davi et al. 2014).

SUMMARY POINTS

- Adult Still's disease (ASD) is a systemic inflammatory disorder of unknown aetiology, typically characterised by daily spiking high fevers, evanescent rash, arthritis and sore throat.
- ASD is a rare disorder with an incidence of approximately 0.2 per 100 000 people, with a bimodal peak at ages 15–25 and 36–46, and equal sex distribution.
- The aetiology of ASD is unknown. Some observations support a genetic predisposition, while various infectious triggers and alterations in cytokine production and innate immunity deficiency have also been suggested.
- Clinical manifestations of ASD include daily high spiking fever, evanescent salmon-pink macular rash, arthritis, sore throat, lymphadenopathy, hepatosplenomegaly, pleuritis, pericarditis, transient pulmonary infiltrates and haematological manifestations.
- The laboratory findings in ASD reflect the systemic inflammation and cytokine cascade present, and no finding is specific for ASD.
- ASD has been associated with marked elevations in serum ferritin concentrations with a low glycosylated fraction of ferritin ($\leq 20\%$).
- No radiographic finding is specific for ASD. The classic radiographic finding is bilateral non-erosive intercarpal and carpometacarpal joint space narrowing, progressing to bony ankylosis.
- Different sets of classification criteria can be used to establish a diagnosis of ASD. Most of these rely on the exclusion of other diseases.
- The clinical course of ASD can be divided into three main patterns with different prognoses: self-limiting or monophasic pattern, intermittent or polycyclic systemic pattern, and a chronic articular pattern with poor prognosis.
- There are no randomised, controlled, clinical trials assessing efficacy of treatment in ASD.
- The majority of patients with ASD will require glucocorticoids. In the presence of glucocorticoids resistance or dependence, a disease-modifying antirheumatic drug should be used and methotrexate is the preferred treatment.
- In patients with refractory or life-threatening ASD, biological agents should be considered off-label.
- Interleukin (IL)-1 and IL-6 blockers seem to be more effective than anti-tumour necrosis factor α agents (anti-TNF α). TNF α blockers and anti-IL-6 may be more useful in chronic polyarthritis. Anti-IL-1 and anti-IL-6 may be more effective in the presence of systemic manifestations.

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2. Sarcoidosis

LEARNING OUTCOMES

- Outline the epidemiology of sarcoidosis
- Outline cellular and histological aspects of the pathogenesis of sarcoidosis
- Outline associations found in the aetiology of sarcoidosis in terms of environmental factors, genetics, cellular aspects and cytokines
- Describe the clinical manifestations of sarcoidosis in terms of pulmonary and extra pulmonary disease, especially musculoskeletal manifestations
- Describe and evaluate laboratory findings and imaging studies in sarcoidosis
- Describe how to achieve a diagnosis of sarcoidosis, initial evaluation and subsequent diagnostic procedures
- Describe the clinical course of sarcoidosis
- Describe treatment options in sarcoidosis, their indications and level of evidence

2.1 Introduction

Sarcoidosis is systemic inflammatory disease, characterised by non-caseating granulomas. Although primarily affecting the lungs, the disease is known for its myriad of presentations, frequently crossing the specialist boundaries of medicine. The earliest descriptions of sarcoidosis originate from Hutchinson, a 19th century London clinician with practices in internal medicine, dermatology, venereal disease, ophthalmology and surgery. In January 1858 Hutchinson encountered a 58-year-old coal wharf employee who presented with purple symmetrical skin plaques on his legs and hands that had developed gradually over the preceding 2 years. (Hutchinson 1877) To the best of our knowledge, this was the index case report of sarcoidosis in the medical literature.

This section will describe in detail the epidemiology, pathogenesis, aetiology, clinical manifestations, laboratory findings, imaging studies, diagnosis, course and treatment options of sarcoidosis.

2.2 Epidemiology

The exact prevalence and annual incidence of sarcoidosis are unknown, with studies reporting significant heterogeneity in incidence, prevalence, disease presentation and severity among different ethnic racial groups. Across Europe there is a greater incidence at higher latitudes (Sawahata and Sugiyama 2016), with Nordic countries reporting much higher incidence rates than other European countries (Hosoda, Sasagawa et al. 2002). Epidemiological studies from Africa are sparse and under-represented in the literature (Benatar 1977). The disease is more common in blacks than whites. In the United States the annual age adjusted incidence was 10.9 per 100 000 for white Americans and 35.5 per 100 000 for African-Americans (Rybicki, Major et al. 1997). It is rare among Asians (Morimoto, Azuma et al. 2008). Furthermore, the phenotypic expression and prognosis of the disease may vary by race. For example, blacks tend to present with more acute and severe disease, with eye, skin and bone marrow involvement, while white people may present with chronic disease and a higher prevalence of hypercalcemia (Ungprasert, Crowson et al. 2016).

Sarcoidosis occurs more frequently in adults younger than 40 years of age, with incidence peaking between 20 and 29 years (Gary W. Hunninghake 1999), although in recent decades, evidence has emerged of an upward shift in age at diagnosis (Sawahata and Sugiyama 2016). Several epidemiological studies have reported a second peak seen in women over the age of 50 (Hosoda, Sasagawa et al. 2002).

Familial clustering of sarcoidosis has repeatedly been reported since the 1920s. The prevalence of familial sarcoidosis (the rate of index having another member affected) ranges from 1.7% in the UK, 9.6% in Ireland and up to as high as 14%. (Hosoda, Sasagawa et al. 2002) In a case-control etiologic study of sarcoidosis the relative risk of sarcoidosis was estimated using first- and second-degree relatives. Cases were almost 5 times more likely than controls to report a first degree relative with sarcoidosis, although the absolute risk for having a relative with sarcoidosis was low. (Rybicki, Iannuzzi et al. 2001)

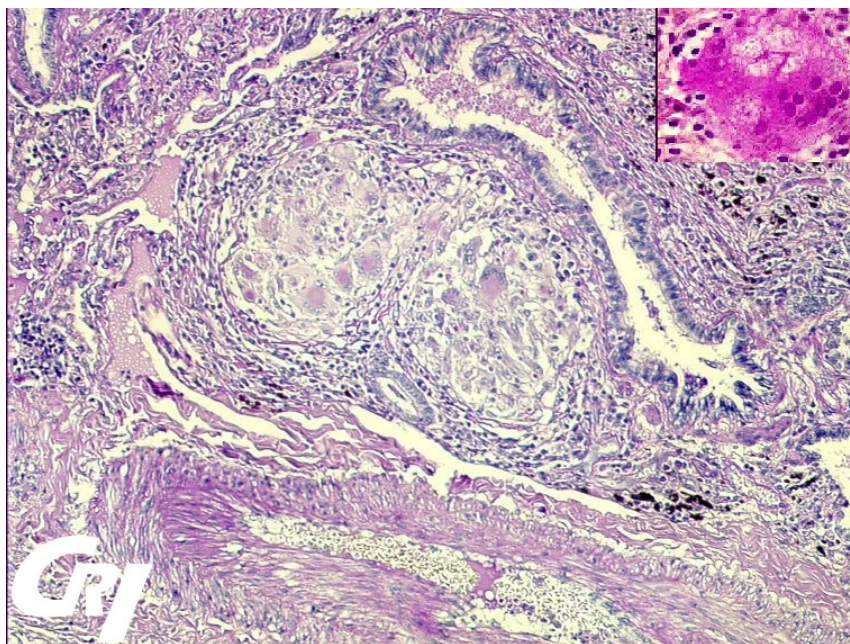
2.3 Pathogenesis

The immunopathogenesis of sarcoidosis is not completely understood, but likely represents disordered immune regulation in genetically predisposed individuals exposed to environmental triggers. The disease is characterised by the formation of epithelioid non-caseating granulomas which can affect any tissue in the body (figure 1). Humans generate granulomata whenever an antigen cannot be degraded and completely eliminated by its macrophages.

2.3.1 Granuloma

In sarcoidosis, an antigen is internalized by macrophages which process and present peptides to CD4 T cells via class II MHC molecules. Antigen presentation leads to CD4 T-cell activation. T cells and macrophages release cytokines or chemokines (IL-2, IL-12, IL-18, IFN- γ and TNF α) that amplify the Th1 response, leading to proliferation and recruitment. (Iannuzzi and Fontana 2011) The cytokine cascade induces cell–cell fusion between macrophages and monocytes/dendritic cells giving rise to multinucleated giant cells which organise into a cluster to form immature granuloma. (Hernandez-Pando, Bornstein et al. 2000, Sakthivel and Bruder 2016) (Agostini, Adami et al. 2000). As the granuloma develops, central areas become tightly packed with macrophages, epithelioid cells and multinucleated giant cells surrounded by a peripheral rim consisting of T cells, mast cells and fibroblasts. Epithelial cells are activated monocytes-macrophages which produce TNF α that mediates T cell activation and recruitment. Caseation is absent, although occasionally fibroid necrosis may be seen where several granuloma have coalesced (Van Gundy and Sharma 1987).

Figure 1 Sarcoid granuloma along a bronchiole (periodic acid–Schiff stain, $\times 100$) with inset (haematoxylin–phloxin–safran stain, $\times 1000$). (Source: CRI (Club Rhumatismes et Inflammation), <http://www.cri-net.com>)



2.3.2 Persistent Granuloma

In most cases granuloma resolve spontaneously, but in 20% to 25% of patients obliterative fibrosis may evolve with persistent granulomatous inflammation (Prasse, Pechkovsky et al. 2006, Zissel, Prasse et al. 2010). In these patients Th2 lymphocytes become the predominant type in the granuloma; they participate in inducing fibrous changes that begin at the periphery and migrate to the centre of the granuloma, ending with fibrosis and/or hyalinization.

The immunologic determinants of clinical remission versus chronic, unremitting sarcoidosis remain unknown. Several studies suggest that persistent inflammation results from inadequate regulatory T-cell function that is

deficient in suppressing TNF α or IFN- γ expression, whilst other studies have proposed an “exhausted” T-cell phenotype from repeated stimulation by pathogenic tissue antigens. (Chen and Moller 2015)

2.3.3 T cells populations

Within the granuloma the majority of lymphocytes are T helper (Th1) CD4+ T cells. The periphery of the granuloma is composed of CD4+ and T suppressor CD8+ T cells. Bronchoalveolar lavage (BAL) reflects this strong increase in cellularity with lymphocytic pleocytosis and predominance CD4+ T cells. In contrast peripheral blood demonstrates a T cell lymphopenia, a decrease number CD4+ T cell and a decreased CD4+:CD8+ T cell ratio, leading to decrease cell mediated immunity, and B cell hyperactivity. Significant lymphopenia has been correlated with disease severity. (Semenzato, Pezzutto et al. 1982, Forrester, Wang et al. 1994, Sweiss, Salloum et al. 2010)

The discovery of regulatory T cell classes has resulted in further evaluation of T cell phenotypes in sarcoid. Regulatory T cell (Treg) populations are elevated in BAL samples, but functionally defective. Th17 lymphocytes are a distinct subset of CD4+ cell that produce IL-17. These cells are present in both the early stage and in the progression towards the fibrotic phase of disease. A significant imbalance between these cell populations, an increase Th17:Treg ratio may contribute to the development of sarcoidosis. (Miyara, Amoura et al. 2006, Facco, Cabrelle et al. 2011)

2.3.4 Cytokines

Understanding the cytokine profiles of different diseases can help pinpoint aetiology and predict both biomarkers and also efficacious therapies. Sarcoidosis is associated with a highly polarised Th1 profile, reflected by increased levels of Th1 associated cytokines, chemokines and cytokine receptors and low Th2 associated cytokines in blood, BAL and sputum. TNF- α and IFN γ are fundamental to granulomatous inflammation and levels of both are elevated in sarcoid tissues. However multiple other cytokines also are important. These cytokines profiles would suggest that sarcoid is a T cell driven disease.

- IL-2 facilitates the expansion of the activated lymphocytes population. CD4+T cells possess IL-2 receptors. (Roth, Huchon et al. 1981, Girgis, Basha et al. 1995)
- IL-12 and IL-18 produced by macrophages act synergistically to stimulate CD4 T cells to produce IFN γ
- IL-6 stimulates T and B cell proliferation. IL-8 produced by macrophages is a strong neutrophil chemotactic factor. Elevated IL-6 and IL-8 levels in BAL fluid is associated with a BAL neutrophilia and a poor prognosis in sarcoidosis.(Shigehara, Shijubo et al. 2001)
- IL-15 produced by macrophages, co-acts with IL-2 in stimulating T and B cell proliferation, acting through the IL-2 receptor system. (Agostini, Trentin et al. 1996)

2.4 Aetiology

The reason why people develop sarcoid is unknown though both environmental and genetic factors are involved.

2.4.1 Genetics

Sarcoidosis can cluster in families, suggestive of a genetic contribution to its aetiology. A Scandinavian registry study of 210 twin pairs identified a higher risk for developing sarcoidosis in the co-twin of affected monozygotic (80-fold) and dizygotic (7-fold) twin siblings compared to the general population (Sverrild, Backer et al. 2008). Genetic associations with risk of developing sarcoidosis are frequently associated with the major histocompatibility complex. The first reported association was the with class I HLA-B8. (Brewerton, Cockburn et al. 1977) Since this, HLA class II antigens, HLA-DRB1 and DQB1 alleles have been more frequently associated (Iannuzzi, Maliarik et al. 2003, Rossman, Thompson et al. 2003), and subsequently specific pockets of HLA-DQ and HLA-DR have been reported as the most important regions involved. (Voorter, Amicosante et al. 2007, Chen and Moller 2015). These associations vary depending on the ethnic and racial makeup of the population studied and some associations are relatively weak, whilst not all have been validated. These findings suggest that the genetic background of an individual with sarcoidosis may account in part for the clinical heterogeneity seen in sarcoidosis.

2.4.2 Environmental risk factors

A number of environmental exposures, including infectious and inorganic, have been associated with the development of sarcoid.

2.4.2.1 Infection

The immunopathogenesis of sarcoidosis support an infectious aetiological hypothesis, and various probably inhaled micro-organism have been suspected but the evidence for specific pathogens varies significantly.

Löfgren's

Seasonal variation in the onset of sarcoidosis has been reported in both hemispheres with the highest prevalence in the cool summer or mild winter zones (Hosoda, Sasagawa et al. 2002). This is often cited as evidence for an infectious cause. Cases diagnosed during the springtime often present with Löfgren's Syndrome, with an acute onset, presence of erythema nodosum and often a favourable outcome.

Mycobacterium Tuberculosis (MTB)

The considerable histological and clinical similarities between sarcoidosis and mycobacterial disease, has led to extensive evaluation of MTB as an aetiological factor (Mangiapan and Hance 1995). A number of studies have

identified mycobacterial DNA within the sarcoid granuloma.(Mitchell, Turk et al. 1992, Saboor, Johnson et al. 1992). However this finding could not be confirmed in other reports (Wilsher, Menzies et al. 1998, Ishige, Usui et al. 1999, Matsui, Ohsumi et al. 2006). Interestingly the incidence and prevalence of sarcoidosis has not been reduced in countries where BCG vaccination is used.

Propionibacterium acnes

Propionibacterium acnes, a commensal bacterium, is capable of inducing a granulomatous reaction in experimental models. A multicentre study of lymph node samples detected *Propionibacterium* DNA by PCR analysis in 106 of 108 lymph nodes from patients with sarcoidosis. However, a significant number of controls also harboured propionibacteria DNA but in lower copy numbers. (Ishige, Usui et al. 1999). An antibody response to a *P. acnes* protein has been demonstrated in sarcoidosis BAL samples; however, the organism is also found in subjects without sarcoid. (Hiramatsu, Kataoka et al. 2003, Ishige, Eishi et al. 2005).

Viruses

Several different viruses, particularly herpes viruses, have been implicated as an inciting factor in sarcoidosis on the basis of serologic evidence. However, other studies have failed to confirm these findings. (Saidha, Sotirchos et al. 2012).

2.4.2.2 Environmental exposures

The association with specific occupations (agricultural workers and fire/rescue workers) has identified a link with environment factors. Studies have largely failed to identify other external exposures(Newman, Rose et al. 2004). Only beryllium is shown to produce granulomata similar to that seen in sarcoidosis.

Beryllium,

An immunological sensitization to beryllium salts manifest long after the cessation of chronic exposure to the inorganic metal. Beryllium causes chronic beryllium disease (CBD). This is defined by granulomatous inflammation in the lung, histologically indistinguishable from sarcoidosis, and the presence of mild to moderate thoracic lymph node enlargement.(Mayer, Hamzeh et al. 2014) (Müller-Quernheim, Gaede et al. 2006) Unlike sarcoidosis, systemic and extra-pulmonary manifestations are not characteristic. CBD is like a perfect phenocopy of sarcoidosis. With no widely accepted animal model of sarcoidosis some authors propose studying CBD to gain insights about the pathobiology of sarcoidosis.(Chen and Moller 2015).

September 11th World Trade Centre (WTC) collapse

There are reports of an increased incidence of sarcoidosis-like granulomatous pulmonary disease during the five years following the September 11th World Trade Centre (WTC) collapse. A case series reported 26 patients with

pathological evidence of new onset sarcoidosis following exposure to dust during the rescue and recovery (Izbicki, Chavko et al. 2007). A subsequent study in 2011 described post-9/11 sarcoidosis in 43 individuals from WTC health registry, noting musculoskeletal manifestations in over half of subjects (Jordan, Stellman et al. 2011). More than 400 substances were identified in airborne and settled samples of WTC. Potential agent(s) in this complex exposure could have triggered a sarcoidosis-like immune response.

Silicone breast implants

Lofgren syndrome and neurosarcoidosis have been reported in the context of silicone gel breast implants, sometimes years after insertion (Yoshida, Tanaka et al. 1996, Barzo and Tamasi 1998). Cutaneous inflammation and regional lymphadenopathy characterized by granuloma that contain silicone if examined appropriately (Vaamonde, Cabrera et al. 1997).

2.4.3 Kveim test

The Kveim test is an historic procedure that was considered diagnostic of sarcoidosis. An extract of sarcoid involved spleen from a donor was injected intradermally into a patient with suspected sarcoidosis. A raised papule would develop which was biopsied 6 week later with histological confirmation of sarcoid like granuloma. The test was considered confirmatory for the disease, demonstrating that a given individual was susceptible to granulomatous reactions when exposed to the appropriate antigen. However, subsequent studies of components of the reagent have not identified a responsible antigen (Siltzbach 1961). The Kveim test was used up until the 1990s when concerns about transmission of blood borne diseases led to its withdrawal.

2.5 Clinical manifestations

2.5.1 Pulmonary sarcoid

Pulmonary involvement is present in 90% of cases (Box 1). Patients may be asymptomatic and sarcoidosis can be detected incidentally on routine chest radiography.

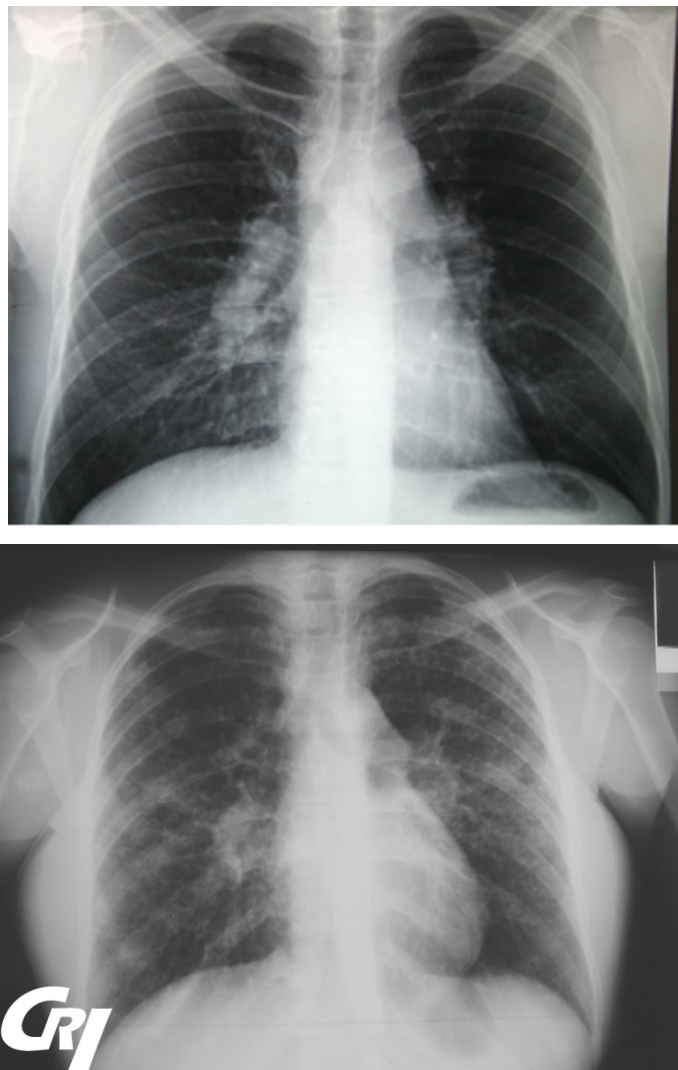
Box 1. Pulmonary sarcoid - classification

Based on chest radiography findings, several stages of pulmonary involvement are distinguishable (Abril and Cohen 2004)

- **Stage 0: Normal radiograph**
- **Stage I: Bilateral hilar adenopathy without parenchymal involvement (figure 2(A))**
 - 50% present with bilateral hilar adenopathy as first expression of sarcoidosis.
 - Regression of hilar nodes occurs within 1-3 years occurs in 75%, whilst 10% will develop chronic enlargement that may persist for 10 years or more
- **Stage II: Bilateral hilar adenopathy with parenchymal involvement (figure 2(B))**
 - 5% present with these findings at initial diagnosis.
 - Two-thirds undergo spontaneous resolution, while in the remainder, the disease progresses or remains unchanged.

- **Stage III: Parenchymal involvement (reticular opacities) with shrinking hilar nodes**
 - Seen in 10%. Of these, approximately 14% have spontaneous remission
- **Stage IV: Pulmonary fibrosis**
 - reticular opacities with evidence of volume loss, predominantly in upper lung zones
 - traction bronchiectasis, calcification and cavitation or cyst formation may also be seen

Figure 2 (A) Stage I sarcoidosis with bilateral hilar adenopathy without parenchymal involvement in a 40-year-old man with Löfgren's syndrome. (B) Stage II sarcoidosis with bilateral interbronchial and laterotracheal adenopathy, diffuse micronodules with a predominance in the median region of the lung, sometimes confluent forming macronodules. (Source: CRI) <http://www.cri-net.com>



The most common pulmonary symptoms are cough and dyspnoea. Pulmonary sarcoid can affect the upper and/or lower airways. Upper respiratory tract involvement of sinuses, pharyngeal, vocal cord, tracheal and upper bronchus is less common, with an overall incidence of about 5%. (Baughman, Lower et al. 2010, Panselinas, Halstead et al. 2010) Lower bronchiole airflow obstruction occurs in a significant number of patients with sarcoidosis (Sharma and Johnson 1988, Baughman, Teirstein et al. 2001)

Adenopathy alone (or with parenchymal disease) is found in 50% of patients at diagnosis. (Baughman, Teirstein et al. 2001) It rarely leads to symptoms; however it may cause compression of a pulmonary artery or bronchial airway. Chest pain is common in pulmonary sarcoidosis, however there is no correlation between pain and adenopathy or pleural disease (Baughman, Lower et al. 2012)

Parenchymal disease occurs in a significant number of patients with sarcoidosis, with dyspnoea the most common symptom. (Baughman, Lower et al. 2012).

2.5.2 Extra pulmonary sarcoid

Sarcoidosis can involve all organ systems; 30% of patients have extra pulmonary disease. It may manifest in the musculoskeletal system, skin, eyes, reticuloendothelial system, exocrine and endocrine glands, heart, kidney and central nervous system. The frequency of extra-pulmonary manifestation varies with gender, age at presentation and ethnicity (Baughman, Teirstein et al. 2001)

2.5.3 Musculoskeletal manifestations

Musculoskeletal manifestations occur in up to 40% of patients with sarcoidosis, and include arthropathy, bone lesions, muscular disease and vasculitis

2.5.3.1 Acute arthritis (Löfgren's syndrome)

The most frequent musculoskeletal manifestation of sarcoidosis is an acute arthritis that occurs as part of Löfgren's syndrome. In 1953 Löfgren described 113 patients with the triad of symmetric hilar adenopathy, joint pain and erythema nodosum (Löfgren 1953).

The ankles are the most frequently involved joint, reported by Visser et al in 98% of patients with Löfgren's syndrome. It is bilateral in the majority (Visser, Vos et al. 2002). Joint involvement can extend to other sites including knees, wrist and elbows and metacarpophalangeal joints. On ultrasound imaging, joint swelling is usually attributable to periarticular soft tissue swelling and tenosynovitis. True joint synovitis or effusions are rare, and if present are usually minor and without power Doppler activity (Kellner, Spathling et al. 1992, Le Bras, Ehrenstein et al. 2014). Synovial fluid analysis reveals a mild inflammatory reaction with a predominance of mononuclear cells. Histopathological examination of the synovium typically does not demonstrate a granulomatous reaction (Pettersson 2000).

Chest radiographs reveal bilateral hilar adenopathy in 90% of patients, which is usually asymptomatic (Visser, Vos et al. 2002). Erythema nodosum is not universal, occurring in approximately 40%, reported more frequently

in Caucasians and women (Mana, Gomez-Vaquero et al. 1999, Grunewald and Eklund 2009). Fever and other constitutional symptoms may be present.

The natural course of Löfgren's syndrome is complete resolution, settling over a few months. In a minority of cases the duration until complete resolution is longer (18-24 months)(Mana, Gomez-Vaquero et al. 1999). Only a very small proportion experience relapse of the disease after resolution(Gran and Bohmer 1996, Mana, Gomez-Vaquero et al. 1999). Joint destruction in Löfgren's syndrome is extremely rare(Gran and Bohmer 1996).

2.5.3.2 Chronic arthritis

Chronic sarcoidosis related arthritis is uncommon (figure 3) and usually occurs with other complications of sarcoidosis, particularly skin involvement (Pettersson 1998, Abril and Cohen 2004, Chatham 2010, Sweiss, Patterson et al. 2010). The typical pattern is a symmetric medium to large joint oligoarthritis (Spilberg, Siltzbach et al. 1969, Visser, Vos et al. 2002). It is important to distinguish true synovitis from tenosynovitis, the latter being more frequently observed. Symmetric involvement of the extensor tendon compartment of the wrists should prompt suspicion of musculoskeletal sarcoidosis (Merle, Bour et al. 1986, González del Pino, Ulloa et al. 1997). Destructive arthritis is less frequently described(Sokoloff and Bunim 1959). Synovial fluid analysis reveals a milder inflammatory reaction compared to other arthritides, with a predominance of lymphocytes(Palmer and Schumacher 1984). Synovial biopsy may demonstrate non-caseating granulomas but is non-specific and other causes of synovial granuloma must be considered (e.g. mycobacterial infection).

Figure 3 Chronic arthritis in a young woman with sarcoidosis. (Source: CRI <http://www.cri-net.com>)



2.5.3.3 Jaccoud's

Jaccoud's arthropathy is characterized by the presence of a deforming, non-erosive arthritis. It is classically described in connective tissue disease, specifically systemic lupus erythematosus. Jaccoud's arthritis in sarcoidosis has been described in case reports (Sukenik, Hendler et al. 1991, Lima, Ribeiro et al. 2013). It usually presents in the context of extensive internal organ involvement, later in the course of the disease. Biopsy reveals fibrosis of the tendons with granulomas of epithelioid cells in the muscles and tendon sheets.

2.5.3.4 Axial disease

Spinal involvement in sarcoidosis is often asymptomatic and thus true prevalence is unknown. Vertebral lesions may be the initial presenting symptom, or can be identified incidentally when patients undergo isotope imaging for other reasons (e.g. to assess lung disease activity)(Rua-Figueroa, Gantes et al. 2002, Boyaci, Hornicek et al. 2012). Spinal lesions may appear lytic, sclerotic or both(Boyaci, Hornicek et al. 2012) and can involve any segment of spine(Rua-Figueroa, Gantes et al. 2002). Sacroiliitis in sarcoid is described in several case reports(Kötter, Dürk et al. 1995). While the prevalence in the general population of spondyloarthritis ranges from 1% to 1.9%, Erb et al. reported a 6% prevalence of spondyloarthritis in patients with sarcoidosis, suggesting a possible association between the two conditions(Erb, Cushley et al. 2005). Involvement may be unilateral and biopsy would typically confirm granulomatous disease(Kobak, Sever et al. 2014).

2.5.3.5 Dactylitis

Dactylitis is one of the most familiar appearances of musculoskeletal involvement in sarcoid. It is well documented in text books and most clinicians are familiar with this pattern of disease. However, it is actually quite uncommon. Dactylitis is almost exclusively associated with chronic systemic disease. It has been described in coexistence with lupus pernio and other forms of chronic cutaneous sarcoidosis. It typically develops in a symmetrical pattern, most often affecting the second and third phalanges, preserving the metacarpophalangeal joints(Awada, Abi-Karam et al.). Dactylitis is associated with swelling and erythema and similar in appearance to that in psoriatic arthritis(Rothschild, Pingitore et al. 1998). It is more common in Black-Americans. Histology confirms tenosynovitis and soft tissue granulomas. Radiographs tend to reveal cystic bone lesions, with a characteristic lattice like appearance(Pitt, Hamilton et al. 1983). Joint line erosions are not characteristic, although the cystic lesions can lead to articular collapse.

2.5.3.6 Myopathy

Skeletal muscle involvement has been estimated to occur in as many as half of all sarcoid patients(Silverstein and Siltzbach 1969), but is symptomatic in fewer than 3%(Wolfe, Pinals et al. 1987, Prayson 1999). Patients with

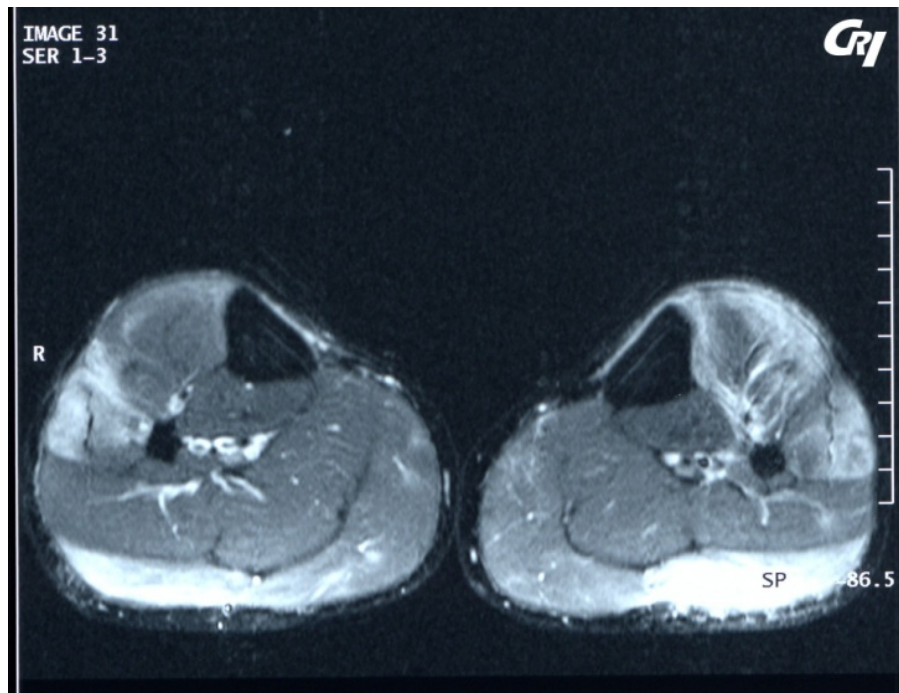
sarcoidosis frequently report generalized weakness, fatigue and reduced exercise capacity. Assessing the extent that such symptoms are attributable to respiratory disease versus muscle disease is often challenging (Marcellis, Lenssen et al. 2011). Sarcoid patients report myalgia more commonly than healthy controls (Hinz, Fleischer et al. 2011).

Three distinct clinical patterns of muscle involvement in sarcoidosis are recognized: chronic myopathy, nodular myopathy, acute myopathy. The chronic myopathy is the most common form, mainly reported in female patients between the age of 50 and 60 years. Clinically it manifests with insidious onset of symmetrical proximal muscle weakness; trunk and neck muscles can also be involved (Maeshima, Koike et al. 2015). Patients often have normal levels of muscle enzymes, whilst neurophysiology demonstrates myopathic changes comparable to other inflammatory muscle disorders (Wolfe, Pinals et al. 1987, Scola, Werneck et al. 2001). Muscle biopsy when performed, typically shows granulomatous change, alongside cellular infiltration with lymphocytes and macrophages with endomysial and perivascular inflammation (Prayson 1999, Le Roux, Streichenberger et al. 2007). Muscle tissue may be abnormal in patients without muscle symptoms, and represents a potential site for biopsy when other involved organs are less accessible to tissue diagnosis (figure 4). MRI may reveal muscle atrophy with fatty degeneration (Moore, Teirstein et al. 2005, Han, Jang et al. 2013). It is notable that some of the earlier MRI studies did not include fat suppression or STIR sequences, which have since been shown to be more sensitive to abnormalities. In more recent years FDG PET/CT has emerged as the most sensitive imaging technique for muscle involvement (Braun, Kessler et al. 2008, Cremers, Van Kroonenburgh et al. 2014).

The nodular form of sarcoid myopathy is characterized by the presence of single or multiple nodules in the muscles affected (Koyama, Ueda et al. 2004). Patients with this form of myopathy typically have symmetrical lower limb involvement (Fayad, Liote et al. 2006, Le Roux, Streichenberger et al. 2007). The nodules are often painful and over time can lead to muscle contractures. Serum levels of muscle enzymes and neurophysiology studies are within normal range. Macroscopic histological analysis demonstrates the location of the granulomatous lesions between the muscle bundles without direct involvement of the muscle fibres (Jamal, Cilursu et al. 1988, Fujimoto, Ikeda et al. 2002). MRI is a useful modality for localizing this pattern of myopathy (Aptel, Lecocq-Teixeira et al. 2015).

Acute myopathy is the least common form of sarcoid myopathy. It tends to occur early in the course of sarcoidosis and in patients younger than 40 years old (Le Roux, Streichenberger et al. 2007). The clinical presentation it's similar to other inflammatory myopathies with rapid onset of proximal weakness and myalgia associated with elevated creatinine kinase levels. Muscle biopsy confirms non-caseating granulomas with pronounced lymphocytic infiltration (Fujita, Ishimatsu et al. 2011).

Figure 4 Muscular localisation of sarcoidosis; MRI aspect. (Source: CRI <http://www.cri-net.com>)



2.5.3.7 Bone

Bone involvement is usually asymptomatic and often identified following imaging for other reasons (Neville, Carstairs et al. 1977). It is estimated to occur in 1-15% of patients with sarcoidosis (Neville, Carstairs et al. 1977). Bone involvement is seen in all ethnicities, although there is a suggestion of a racial predilection for the site of involvement, with bone cysts of the hands and feet more common in black people (Wilcox, Bharadwaj et al. 2000). Bone involvement is often accompanied by overlying skin disease. Soft tissue swelling and skin involvement predates bone abnormalities, observed up to four years prior to detectable radiologic changes (JAMES 1959). Three patterns of bone lesion are described in the literature: Permeative “moth-eaten” appearance, involving the cortex of the phalanges and accompanied by soft tissue swelling; Lytic lesions, also called bone cysts, which appear as cortical defect in the phalangeal heads or round punch out lesions; Sclerotic lesions, which are described in the spine and are similar to those seen in metastatic disease (Wilcox, Bharadwaj et al. 2000). Sarcoid bone lesions are more often cystic than sclerotic or lytic.

Bone involvement is reported most frequently in the proximal and middle phalanges, but the skull, nasal bones, maxilla, sternum, ribs, vertebra, pelvis, tibia and femur may also be affected. In the existing literature peripheral bone involvement is more frequently described, however increasing use of advanced imaging modalities (PET-CT or MRI) is revealing a higher proportion of patients with axial involvement. Sparks et al identified incidental sarcoidosis affecting the spine or pelvis in 90% of their cohort, while only 10% had isolated appendicular skeleton

involvement. In this study all patients had involvement in more than one bone site (Sparks, McSparron et al. 2014).

Bone lesions are usually detected by plain film radiography but in some cases may only be seen on MRI imaging. MRI has proven valuable in detecting silent disease, however there are no morphologic criteria to reliably distinguished osseous sarcoidosis from metastatic lesions (Moore, Teirstein et al. 2005).

Serum calcium or alkaline phosphatase levels are typically normal despite multiple affected bones. This finding reflects a distinct pathophysiology compared to other diseases, such as Paget's, malignancy, osteoporosis, or osteomalacia (Sparks, McSparron et al. 2014).

The presence of bone involvement is often suggestive of chronic severe sarcoidosis with multi-organ involvement. Bone lesions in themselves are not an indication for specific treatment unless symptomatic. Corticosteroids can ameliorate soft tissue swelling but do not improve the abnormal bone architecture (Johns and Michele 1999). Methotrexate and hydroxychloroquine have been used as corticosteroid sparing agents in bone disease with documenting varying success (Kaye, Palazzo et al. 1995). Case reports describe varying success with anti-TNF inhibitors for resistant cases (Garg, Garg et al. 2008, Hasni, Kunz et al. 2010).

2.5.3.8 Vasculitis

Vasculitis is very rare in sarcoidosis, but it may be the presentation symptom and can be life threatening. It has been reported in the form of leukocytoclastic vasculitis and affecting small, medium or large arteries, and granulomatous vasculitis. (Fernandes, Singsen et al. 2000)

2.5.4 Dermatological manifestations

Involvement of the skin can occur in up to 30% of patients with sarcoidosis, and is often a presenting feature. Lesions may be asymptomatic and therefore careful dermatologic examination is an essential component of assessment in suspected sarcoidosis. When present, lesions are characterised by the presence of granulomas on histopathological examination (Elgart 1986, Roberts, Mirowski et al. 2004).

- *Papular sarcoidosis*: common finding of numerous, 1 to 10mm papules located on the face with a predilection for the eyelids and nasolabial folds. Coalescence may lead to the formation of plaques.
- *Maculopapular sarcoidosis*: slightly hyperpigmented patches around 1 mm in diameter.
- *Nodular sarcoidosis*: waxy pink nodular lesions on face, trunk and extensor surface of extremities. It can affect the subcutaneous tissue commonly located on the upper extremities.

- *Lupus pernio*: violaceous indurated plaques or nodules distributed on the central face, usually nasal tip, and cheeks, ears and lips. It is associated with chronic disease and pulmonary fibrosis (figure 5).
- *Erythema nodosum*: erythematous, tender, subcutaneous plaques and nodules predominantly located on the anterior tibial areas.(Neville, Walker et al. 1983) Histopathologic findings are consistent with a septal panniculitis.
- Other atypical findings include ulcerative, psoriasiform, hypopigmented, follicular, angioid, rosacea-like or morpheaform lesions

Figure 5. *Lupus pernio*. (Source: CRI <http://www.cri-net.com>)



2.5.5 Ophthalmologic manifestations

Eye involvement occurs in up to 25% of patient with sarcoidosis and is the presenting feature in 5%. Several ophthalmologic manifestation of sarcoidosis can occur:

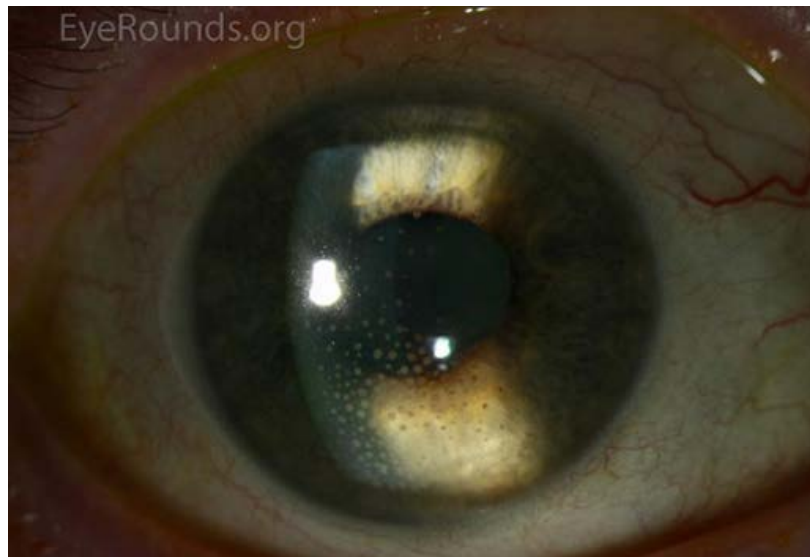
- Anterior uveitis
- Posterior uveitis
- Retinal vasculitis
- Keratoconjunctivitis
- Conjunctival follicles
- Scleritis (very rare)

The most common ocular manifestations are uveitis (30–70%) and conjunctival nodules (40%). Uveitis is subclinical in up to 80% of cases and as such patients with sarcoidosis should undergo ophthalmic evaluation(Abril and Cohen 2004). Anterior uveitis may either present as acute iridocyclitis, commonly seen in

Löfgren's syndrome, or as a chronic granulomatous uveitis with keratic precipitates, which may vary from cellular to large 'mutton fat' type (Umur, Tayfun et al. 2012, Liu and Birnbaum 2015) (Figure 6).

Anterior uveitis may resolve spontaneously or with the use of local corticosteroids, but posterior uveitis requires systemic treatment. Untreated this may progress to cause secondary glaucoma, cataract and blindness. Blindness can occur in 20% of patients with ophthalmic sarcoid.

Figure 6 'mutton fat' keratic precipitates (Source: <http://webeye.ophth.uiowa.edu/eyeforum/atlas>)



2.5.6 Reticuloendothelial manifestations

Reticuloendothelial manifestations are common in sarcoidosis. Up to 40% have peripheral lymphadenopathy and 25% have splenomegaly, of which 80% have splenic granulomata (figure 7). Massive splenomegaly is rare. Hypersplenism may cause anaemia, leukopenia and thrombocytopenia.

Hepatic involvement affects the majority of patients with sarcoid, although the clinical consequences of involvement are variable. Most patients are asymptomatic with only biochemical abnormalities. Hepatomegaly is present in up to 20%, with jaundice in less than 5%. The liver is homogeneous in appearance, but hypoattenuating nodules may rarely be seen which are reported as liver granuloma on biopsy. (Warshauer and Lee 2004). Rarely cirrhosis or cholestatic liver disease may occur. (Devaney, Goodman et al. 1993)

Figure 7 Splenic localisation of sarcoidosis. (Source: CRI <http://www.cri-net.com>)



2.5.7 Exocrine manifestations

Sarcoidosis may involve the exocrine glands in 3-9% of patients. (Abril and Cohen 2004). Painful or painless swelling of the salivary glands occurs in approximately 4%, and is self-limiting in 40%. Keratoconjunctivitis and salivary gland involvement in sarcoid may resemble Sjögren's syndrome or IgG4 disease. Heerfordt's syndrome is the combination of anterior uveitis, parotid gland involvement, facial palsy and fever. Sarcoid pancreatitis can also occur.

2.5.8 Endocrine manifestations

Endocrine involvement in sarcoidosis includes hypothalamic involvement from basilar granulomatous meningitis, and sometimes hormonal changes may be the first manifestation of a neural sarcoid. Hypothalamic infiltration is the predominant cause for endocrine abnormalities, which include more commonly, diabetes insipidus, adenopituitary failure or amenorrhea-galactorrhoea syndrome (Murialdo and Tamagno 2002).

Sarcoidosis can involve the testes and cause recurrent epididymitis although this is rare. Testosterone level may be reduced due to a dysfunctioning hypothalamus-pituitary-gonadotrophic axis, systemic inflammation or a side effect of corticosteroid therapy (Spruit, Thomeer et al. 2007). Sarcoid rarely involves the female genital tract and in the absence of severe disease, it does not affect fertility or the incidence of foetal or obstetrical complications (Selroos 1990). It will often improve during pregnancy possibly due to increases of maternal free cortisol.

Sarcoidosis can cause diffuse goitre or rarely a solitary thyroid nodule. Almost all patients are euthyroid (Porter, Beynon et al. 2003)

2.5.9 Gastrointestinal manifestations

Clinically recognisable gastrointestinal disease occurs in 0.1 to 0.9%, although the incidence of subclinical involvement may be greater. The stomach is the most commonly involved portion with peptic ulceration or narrowing of the gastric lumen due to granulomatous inflammation and associated fibrosis of the gastric wall. However, sarcoidosis of the oesophagus, appendix, colon, and rectum has also been described. Small bowel involvement is very rare. (Sprague, Harper et al. 1984, Dulai and Rothstein 2012).

2.5.10 Metabolic and renal manifestations

The most common electrolyte disturbance among patients with sarcoidosis is an abnormality of calcium metabolism, due to extra renal non-regulated hyperproduction of 1,25(OH) D₃ by activated macrophages in the granuloma. This primarily increases intestinal calcium absorption causing hypercalcemia (10-20% of cases), hypercalciuria (50% of cases), nephrocalcinosis and nephrolithiasis. (Inui, Murayama et al. 2001) If untreated, persistent renal calcium deposition may lead to renal failure. High 1,25(OH) D₃ also induces osteoclast activation and bone resorption increasing the risk of osteoporosis.

Primary renal manifestations are nephrolithiasis and nephrocalcinosis and acute interstitial nephritis with or without granuloma formation. The classic renal lesion of non-caseating granulomatous interstitial nephritis rarely causes clinically significant renal disease. It is commonly found on the initial presentation of sarcoidosis. The diagnosis is suggested by an elevated creatinine and bland urinary sediment. Renal biopsy reveals normal glomeruli, mononuclear cell infiltration, interstitial infiltration with non-caseating granulomas and tubular injury. These findings are suggestive, but not diagnostic of sarcoidosis. (Berliner, Haas et al. 2006) Other renal complications of sarcoidosis include membranous nephropathy, proliferative or crescentic glomerulonephritis, focal segmental glomerulosclerosis or polyuria due to diabetes insipidus.

2.5.11 Cardiovascular

Granulomas may involve all layers of the heart and both ventricles and atria. The most commonly affected area is the left ventricular free wall, particularly at the base, followed by the basal interventricular septum. Clinical manifestations relate primarily to the location and inflammatory effects of the granulomas. (Skali, Schulman et al. 2013)

Infiltration of the ventricular septum and conduction system may lead to ventricular tachyarrhythmias or conduction block and sudden death. Complete heart block is the most common finding in patients with clinically evident cardiac sarcoidosis. Ventricular arrhythmias are the second most common presentation arising when sarcoid granulomas within the myocardium become foci for abnormal automaticity, or may disrupt ventricular activation and recovery causing re-entrant arrhythmias. Electrocardiography reveals ventricular arrhythmias in 22% of patients. (Yoshida, Morimoto et al. 1997). It is important to perform Holter ECG and echocardiogram if

cardiac involvement is suspected (Chapelon-Abric, de Zuttere et al. 2004), although standard cardiac imaging may be normal despite disease.

Extensive granulomatous infiltration of the myocardium can cause both systolic and diastolic dysfunction. Patients may present with heart failure or dilated cardiomyopathy (Yazaki, Isobe et al. 1998). Unlike with other infiltrative cardiomyopathies, myocardial involvement in sarcoidosis is typically patchy. An endomyocardial biopsy can confirm the diagnosis, however, this carries risks and lacks sensitivity given the heterogeneous myocardial involvement. Cardiac MRI or FDG PET are non-invasive techniques to aid diagnosis and may help in assessing disease activity and response to treatment. (Skali, Schulman et al. 2013).

Sarcoidosis may cause cor pulmonale secondary to advanced fibrotic pulmonary disease.

2.5.12 Neurological

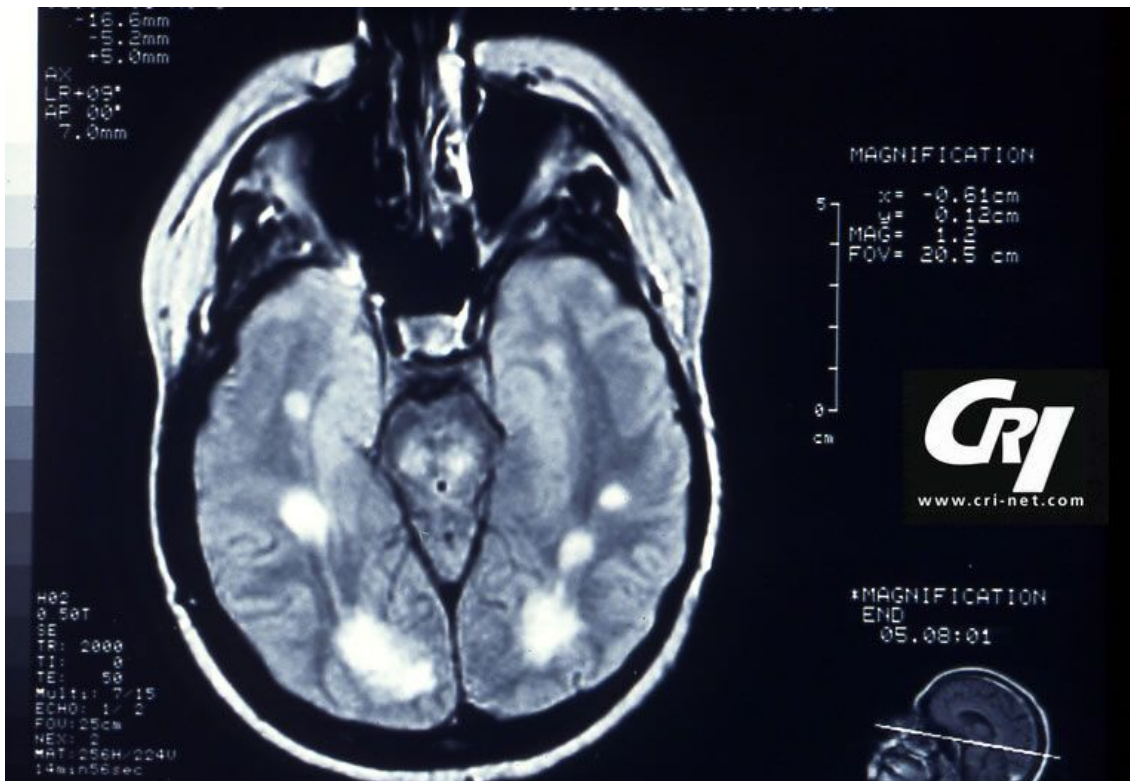
Neurologic complications occur in approximately 5-10% of patients with sarcoidosis (Baughman, Teirstein et al. 2001, Burns 2003, Terushkin, Stern et al. 2010). The central (figure 8) or peripheral nervous system can be affected. Manifestation may occur early in the disease and sometimes are severe and may be life threatening (Nozaki and Judson 2012).

Granulomatous inflammation in a perivascular distribution of the brain can produce focal or generalized seizures, or an encephalopathy or vasculopathy. Patients may present with cognitive or psychiatric problems and/or focal neurologic deficits. In rare cases, this manifests as a focal cerebral infarction (Navi and DeAngelis 2009). Meningeal involvement can present as an acute aseptic meningitis or a chronic meningitis, and meningeal mass lesions are reported. Communicating or non-communicating hydrocephalus may develop acutely or sub acutely. (Brouwer, de Gans et al. 2009) A myelopathy or radiculopathy can occur if granulomatous inflammation affects the spinal cord.

Neuroendocrine dysfunction may occur with hypothalamic infiltration. Cranial mononeuropathy may occur; a peripheral facial nerve palsy develops in 25-50% of patients with neurosarcoidosis (Stern, Krumholz et al. 1985).

Peripheral neuropathy is seen in later stages of disease and associated with poor response to treatment. These include mononeuropathy, mononeuritis multiplex, sensory, small fibre sensory, sensorimotor, autonomic and motor polyneuropathies. (Zuniga, Ropper et al. 1991). Electromyography reveals an axonal neuropathy.

Figure 8 Brain sarcoidosis localisation; MRI aspect. (Source: CRI <http://www.cri-net.com>)



2.6 Investigations

A comprehensive assessment should be performed in cases of suspected sarcoidosis to obtain additional evidence supporting the diagnosis, exclude alternative diagnoses and identify the degree of organ involvement.

2.6.1 Laboratory

A variety of laboratory abnormalities may be seen in patients with sarcoidosis:

- Anaemia occurs in 4-20% of patients. It usually results from the anaemia of chronic disease, although may also be due to hypersplenism, autoimmune haemolytic anaemia or bone marrow involvement. (Lower, Smith et al. 1988)
- Leukopenia, and more precisely lymphopenia occur in 40% of patients, eosinophilia may be seen (Renston, Goldman et al. 2000) while thrombocytopenia is rare.
- The erythrocyte sedimentation rate is frequently raised but is not useful in assessing disease activity.
- C-reactive protein (CRP) may be mildly elevated in one third of patients with sarcoidosis
- Hypercalciuria occurs in 50% of cases, hypercalcemia in 10-20%
- A moderate elevation in serum alkaline phosphatase concentration suggests diffuse granulomatous hepatic involvement
- Hypergammaglobulinaemia

2.6.1.1 Serological markers

Certain serologic markers have been identified which may play a role in diagnosis or monitoring disease activity:

Angiotensin converting enzyme (ACE) :

Serum ACE is produced by epithelioid cells and macrophages within the granulomata. It may participate in granuloma formation by producing angiotensin-II which is chemotactic for macrophages. The ACE level is elevated in 40-90% of untreated chronic sarcoidosis. (Abril and Cohen 2004). However, levels are frequently normal in acute disease. Some patient with active pulmonary sarcoidosis may have elevated levels which decrease with successful treatment. However serum ACE has limited utility as a diagnostic test, due to poor sensitivity and insufficient specificity (10% false positive results) (Ungprasert, Carmona et al. 2016). It may have a limited role in supporting the diagnosis of sarcoidosis in the situation where the pre-test probability is high.

Soluble interleukin-2 receptor (sIL2R) :

Cytokines IL1 and IL-6 stimulate macrophages to produce IL-2 which activate T-cells. Active T-cell surfaces possess IL-2 receptors and after activation, a soluble chain of the IL-2R is released. It has been reported that sIL2R increases in the active sarcoidosis and may be a useful marker for determination of extra pulmonary involvement in sarcoidosis patients (Grutters, Fellrath et al. 2003, Rothkrantz-Kos, van Dieijen-Visser et al. 2003, Gungor, Ozseker et al. 2015).

2.6.1.2 Lumbar puncture

Cerebrospinal fluid (CSF) fluid results characteristically demonstrate an elevated raised total protein in 2/3rd of patients, typically up to 250 mg/dL and a pleocytosis in approximately 50%. CSF ACE concentration is occasionally elevated, but reliable normal values are lacking. (Joseph and Scolding 2009)

2.6.2 Imaging

2.6.2.1 Chest radiograph (See above)

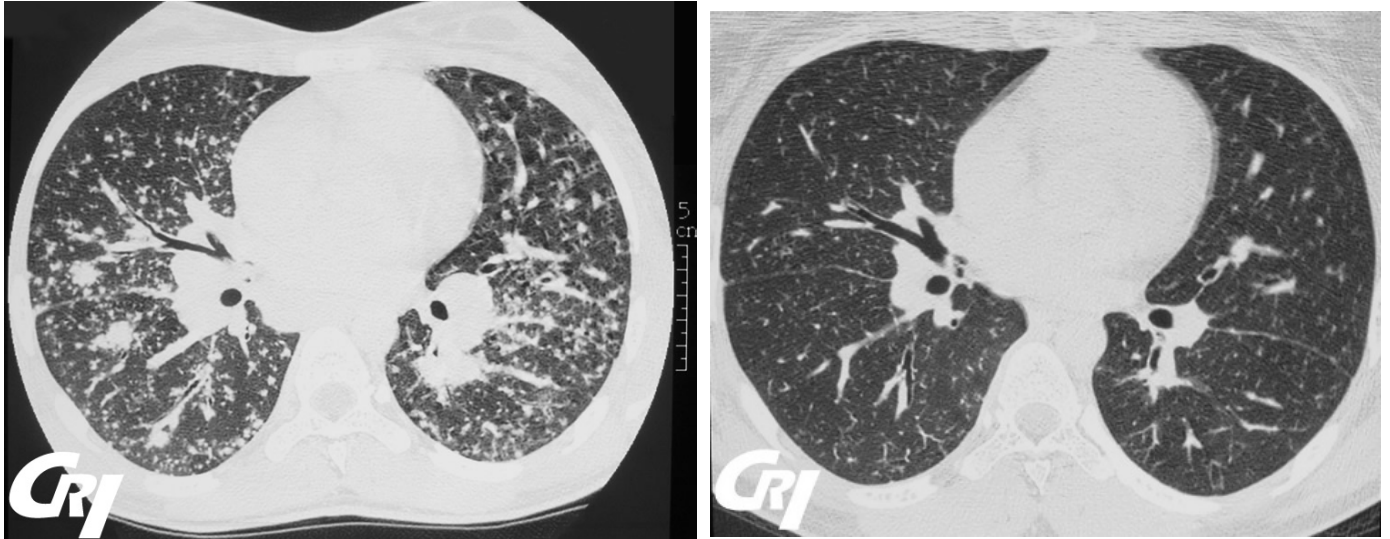
2.6.2.2 Chest computed tomography

High resolution computed tomography (HRCT) of the chest may typically reveals lung parenchymal changes in mid-to-upper zone predominance (figure 9). Findings may include:

- Hilar and mediastinal lymphadenopathy
- Beaded or irregular thickening of the Broncho vascular bundles
- Nodules along bronchi, vessels, and sub pleural regions
- Bronchial wall thickening
- Ground glass opacification

- Parenchymal masses or nodular consolidation, occasionally with cavitation
- Parenchymal bands / cysts
- Fibrosis with distortion of the lung architecture and traction bronchiectasis

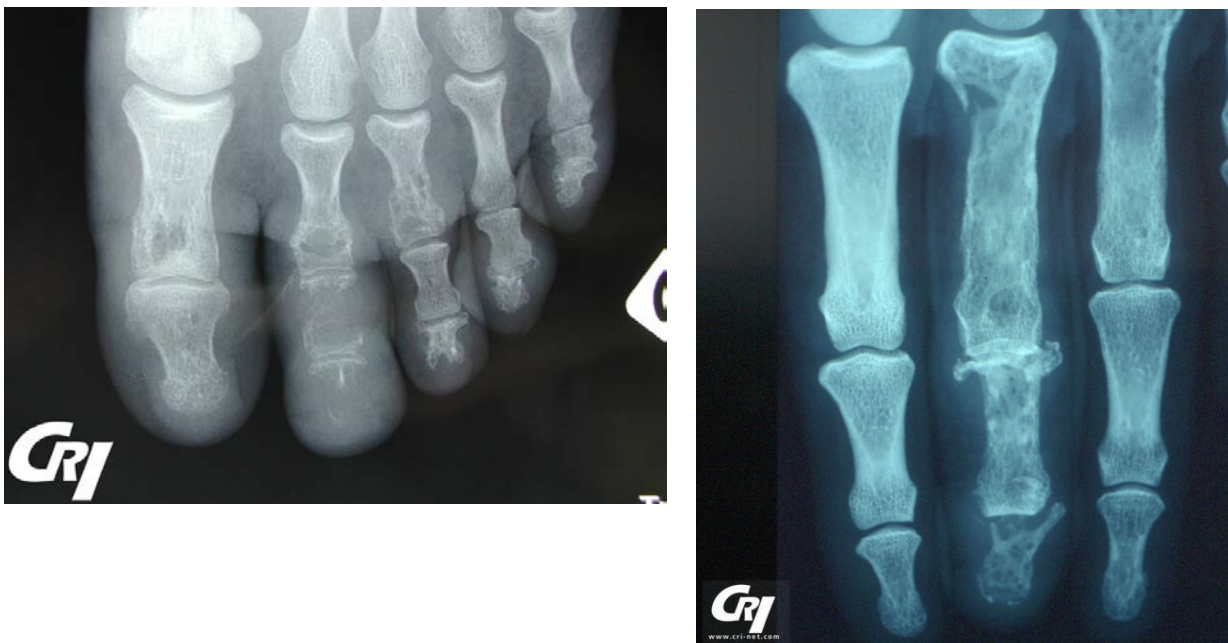
Figure 9 High-resolution CT scan. A) Diffuse micronodules with a lymphatic distribution. Macronodules are formed by the confluence of micronodules. B) Same patient, with complete resolution of the lesions with steroids. These lesions are all potentially reversible with treatment. (Source: CRI <http://www.cri-net.com>)



2.6.2.3 Joint and bone

Plain radiographs in sarcoid bone involvement may show cystic lytic or sclerotic bone lesions. Most frequently the proximal and middle phalanges are affected, but other bone may be involved (figure 10).

Figure 10 A. Bone sarcoidosis. Lytic lesions of different size in toe phalanges. B. Chronic arthritis in a young woman with sarcoidosis. (Source: CRI <http://www.cri-net.com>)



2.6.2.4 Isotope imaging

PET imaging has superseded other radiotracer scan techniques in the evaluation of sarcoidosis. ¹⁸F-FDG PET may be useful for evaluating the extent of sarcoidosis and recognising lesions at different sites which may be more accessible to biopsy (figure 11). However, it does not differentiate sarcoidosis from malignancy as ¹⁸F-FDG PET may be positive in both processes, with elevations of standardized uptake value (SUV) into the “malignant” range (Teirstein, Machac et al. 2007, Braun, Kessler et al. 2008). The use of other tracers that can differentiate sarcoidosis may improve the utility of this imaging modality in the future. FDG-PET can detect active cardiac sarcoidosis with high sensitivity but has lower specificity as uptake is seen in other inflammatory myocardial diseases. (Skali, Schulman et al. 2013).

Radiotracer-based scanning using gallium-67 citrate or technetium-99m bisphosphonate may be useful in localising inflammatory foci, detecting active alveolitis, and assessing the response to treatment. However increased uptake in the lungs is not specific for sarcoidosis and a negative scan does not exclude disease (Baughman, Shipley et al. 1987). Gallium scans may show the combination of the "panda" and "lambda" signs that are useful in the diagnosis of sarcoidosis if none of the sites of disease are amenable to biopsy (figure 12 and 13). The "panda" sign occurs with bilateral uptake in the lacrimal and parotid glands is superimposed on the normal uptake by the nasopharyngeal mucosa. The "lambda" sign refers to gallium uptake by the right Paratracheal and bilateral hilar lymph nodes results in a pattern similar to the Greek "lambda" symbol.

Figure 11: ¹⁸F-FDG-PET/CT imaging in a patient with sarcoidosis. Intense uptake in the hilar lymph nodes and muscle.

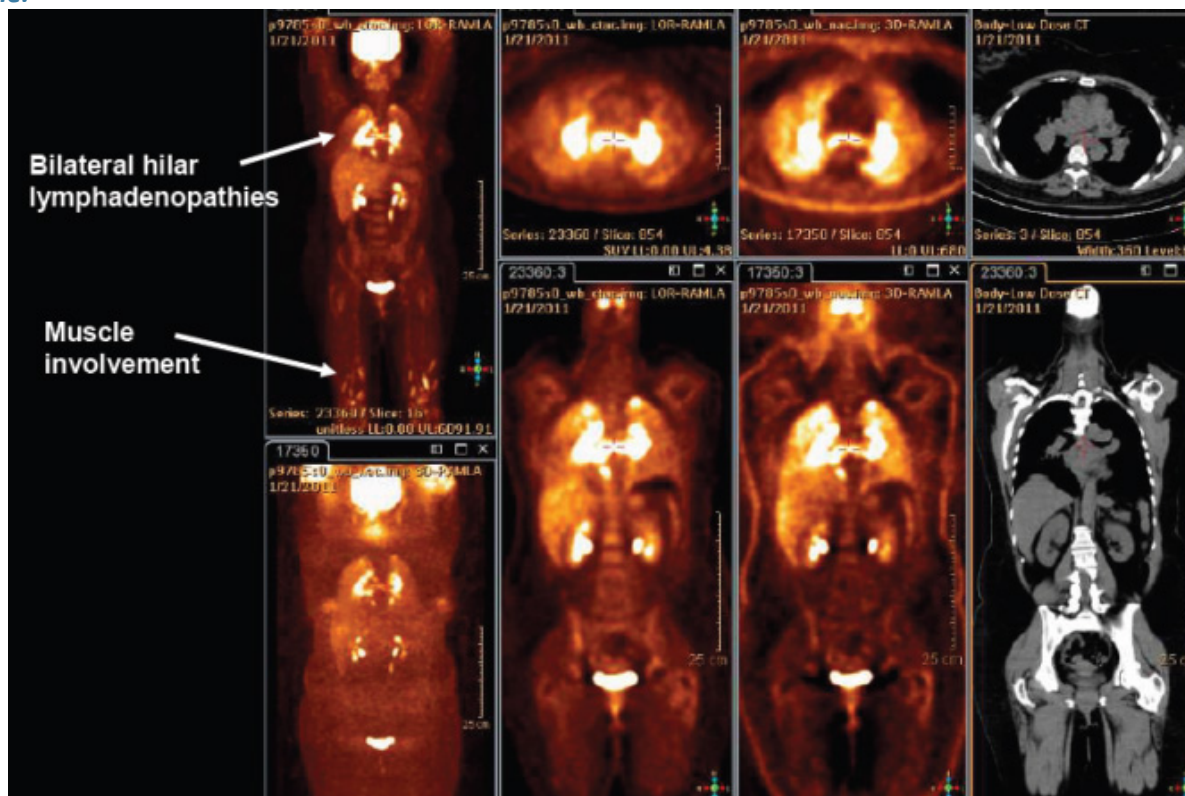


Figure 12 Bilateral hilar lymph nodes on gallium scintigraphy at 72 h. (Source: CRI <http://www.cri-net.com>)

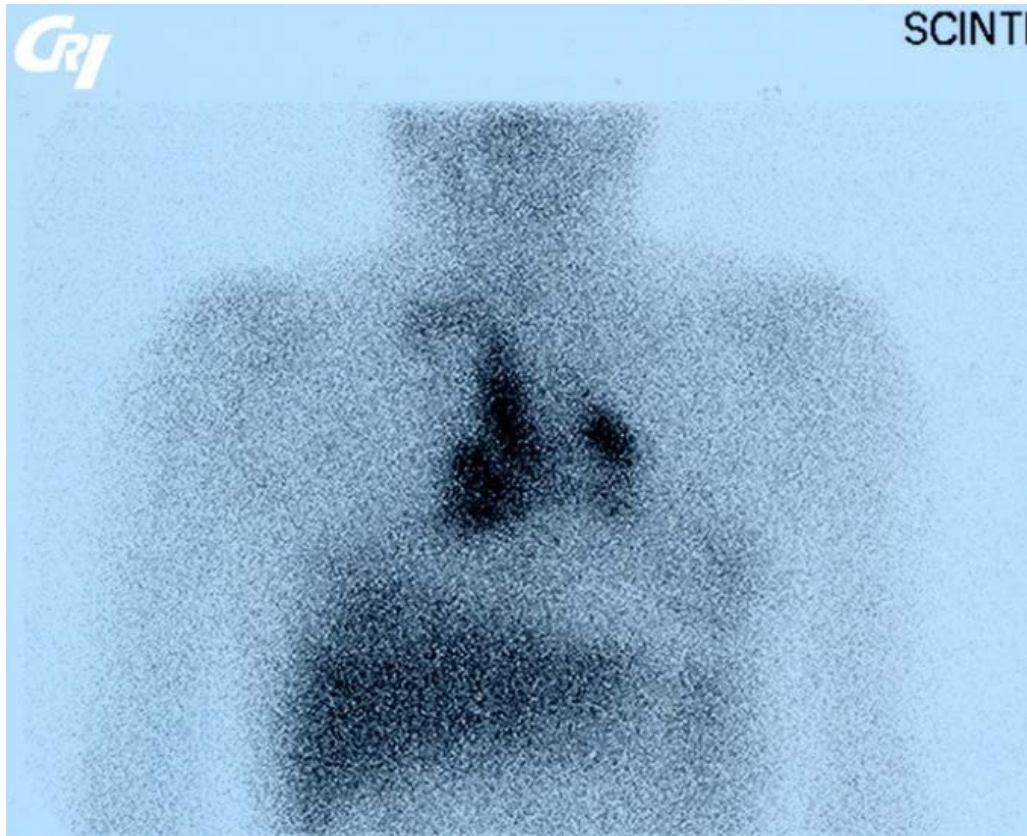
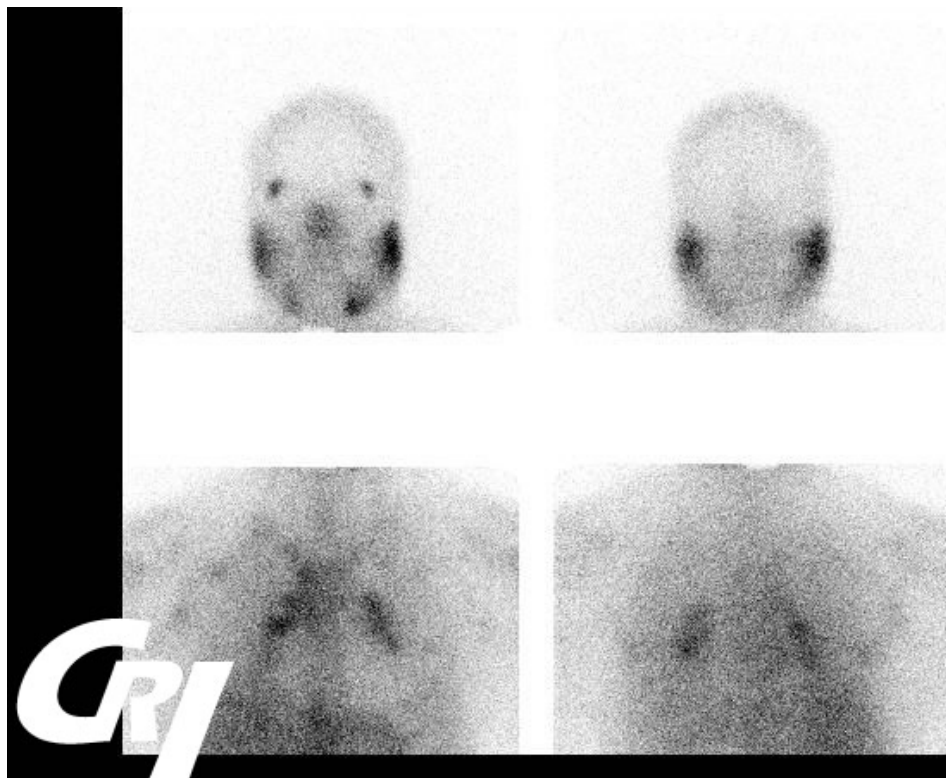


Figure 13 Gallium scintigraphy in a patient with sarcoidosis. Strong uptake in the lachrymal glands, the parotid and submaxillary glands and in the pituitary mucosa (panda sign). Intense uptake in the hilar lymph nodes and in right axillary lymph nodes. (Source: CRI <http://www.cri-net.com>)



2.6.3 Pulmonary function test

Pulmonary function tests assess severity of respiratory impairment and serial measurements monitor the course of disease. They characteristically reveal a restrictive pattern (reduced vital capacity and total lung capacity) associated with a reduction in the diffusing capacity for carbon monoxide (DLCO)(Dunn, Watters et al. 1988). Although endobronchial sarcoidosis may lead to an obstructive pattern.

2.6.4 Bronchoalveolar Lavage (BAL)

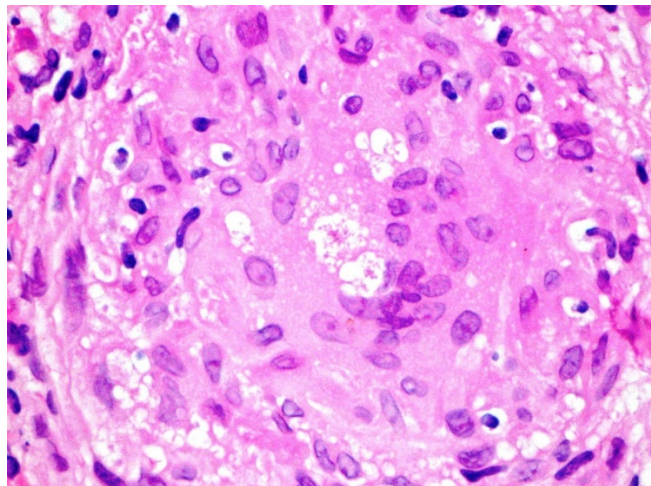
In sarcoidosis BAL is used to exclude infections and malignancy as alternative diagnoses, but can also be used as an adjunctive to support the diagnosis. A lymphocytosis is common (30-50% lymphocytes), with reduced number of CD8 cells, elevated CD4:CD8 ratio (>3.5) and an increased number of activated T cells, CD4 cells, immunoglobulins, and IgG-secreting cells.

2.6.5 Histology

Histological proof is not required in patients presenting with classical Lofgren syndrome, although diagnostic yield from lymph node or lung biopsy is $>90\%$. For all other patients with suspected sarcoidosis, tissue is usually required to confirm diagnosis. If no easily accessible lesion is available, bronchoscopy with ultrasound guided trans bronchial lung biopsy may be considered (von Bartheld, Dekkers et al. 2013). Synovial tissue biopsy may be warranted in the diagnosis of sarcoid arthropathy, the findings of sterile non-caseating granulomatous inflammation on biopsy is supportive but not diagnostic. Liver biopsy is not recommended as liver granulomata occur in a variety of other liver disorders (Awada, Abi-Karam et al.) nor is biopsy of erythema nodosum.

The characteristic morphologic feature of sarcoidosis is the non-caseating granuloma. The appearance of the granuloma in sarcoid is not distinguishable from those observed in other granulomatous disorders, although the presence of asteroid bodies is supportive (figure 14)(Iwai, Tachibana et al. 1993, Costabel, Hunninghake et al. 1999, Heinle and Chang 2014). Certain infections including tuberculosis mycobacterium, inflammatory bowel disease, systemic vasculitis and lymphoproliferative disorders are established causes of granulomatous inflammation, all of which have musculoskeletal manifestations. Granulomas occurring outside of the typical syndromes associated with sarcoid should arouse suspicion of alternative diagnoses.

Figure 14 Haematoxylin and eosin stained bone marrow specimen showing pink star shaped inclusion in clearing within granuloma. Figure courtesy of Dr. Jon Salisbury.



2.7 Diagnosis

There are no specific diagnostic tests for sarcoidosis. The diagnosis relies on a combination of clinical and radiological manifestations, histological proof of non-caseating granulomata and exclusion of other diseases with similar presentations

2.8 Course

There is no known cure for sarcoidosis however the spontaneous remission occurs in 60–70% of cases, most frequently in Löfgren's syndrome (Awada, Abi-Karam et al.), and if the disease persists it may not cause sufficient symptoms or injury to require therapy. However, a substantial minority do develop progressive disease with concomitant morbidity, and a small proportion might present with life threatening manifestations. Adverse prognostic factors are outlined in Box 2. Reported mortalities in sarcoidosis vary from 1% to 7 % depending on the setting and population studied. (Reich 2002, Gribbin, Hubbard et al. 2006, Nicholson, Plant et al. 2010, Tukey, Berman et al. 2013). Insight regarding the prognosis influences treatment decisions.

Box 2. Adverse Prognostic Factors (Awada et al., Wijsenbeek and Culver 2015)

- Black origin
- Age of onset after 40
- Pulmonary:
 - pulmonary hypertension,
 - significant lung function impairment,
 - moderate to severe dyspnoea,
 - BAL neutrophilia
- Extra pulmonary :
 - Cardiac involvement
 - Neurosarcoidosis (except isolated CN palsy)
 - Chronic hypercalcaemia / Nephrocalcinosis
 - Splenomegaly
 - Osseous disease
 - Lupus pernio
 - Chronic uveitis

2.9 Treatment

Treatment of sarcoidosis should be based on extent, severity and activity of disease and the impact on the patient's life. Indications for therapy are outlined in Box 3 (Wijsenbeek and Culver 2015)

Box 3. Indication for therapy (Wijsenbeek and Culver 2015)

- **Respiratory:**
 - Symptomatic pulmonary disease with infiltrates
 - Progressive deterioration of pulmonary function tests
 - Significant upper respiratory tract sarcoidosis
- **Musculoskeletal:**
 - inflammatory joint or tendon disease
 - active focal or acute myopathy
 - progressive symptomatic bone lesions
- **Ocular:**
 - Posterior or intermediate uveitis
 - Anterior uveitis refractory to topical therapy or with toxicities from topical therapy
- **Cutaneous :**
 - Disfiguring lesions (patient choice)
- **Hepatic :**
 - Impaired synthetic function
 - Hyperbilirubinemia
 - Progressive increase of transaminase levels
 - Portal hypertension
- **Splenic :**
 - Pain or early satiety caused by enlargement
 - Cytopenias caused by hypersplenism
- **Cardiac :**
 - Second-degree or third-degree conduction block
 - Ventricular dysrhythmias
 - Cardiomyopathy
 - *Treatment of diastolic heart failure and supraventricular dysrhythmias is unclear*
- **Neurologic :**
 - Any brain or spinal cord involvement
 - Granulomatous peripheral nerve disease
 - *Possible exceptions: isolated cranial nerve VII palsy, mild acute aseptic meningitis*
- **Bone marrow :**
 - Cytopenia
- **Endocrine :**
 - Significant hypercalcemia/hypercalciuria
 - Nephrolithiasis
 - Pituitary sarcoidosis

2.9.1 Corticosteroids

The first line systemic treatment is corticosteroids, which suppress the pro-inflammatory cytokines and chemokines involved in cell-mediated immune responses and granuloma formation. (16) Corticosteroid act by reducing gene transcription of inflammatory genes, *e.g.* IL-1 and TNF- α , adhesion molecules and receptors, by interaction with pro-inflammatory transcription factors nuclear factor- κ B (NF- κ B). 10–100 genes are thought to

be directly or indirectly regulated by corticosteroids. (Drent, van den Berg et al. 2001, Grutters and van den Bosch 2006).

2.9.1.1 Corticosteroids in pulmonary sarcoid

For pulmonary sarcoid, the balance of evidence suggests that oral glucocorticoids improve respiratory symptoms and radiographic abnormalities, although not necessarily pulmonary function tests (Paramothayan, Lasserson et al. 2005). End stage fibrosis is not responsive to immunosuppressive therapy. While the optimal dose is not known, the following treatment schedule has been recommended (Schutt, Bullington et al. 2010). Inhaled corticosteroids may be used for symptomatic cough.

Initial treatment:

- Daily dose: 0.3-0.6 mg/kg (20-40 mg/day) for 4-6 weeks.
- If disease parameters are stable or improved, the dose is tapered by 5-10 mg decrements every 4-8 weeks down to 0.2-0.4 mg/kg (10-20 mg/day)
- If the disease parameters are unimproved, the initial dose is continued for another 4-6 weeks.
- Higher doses (80-100 mg/day) may be warranted in acute respiratory failure or cardiac, neurologic, ocular or upper airway disease.

Maintenance therapy:

- There are no formal data to guide maintenance dosing. Based on clinical experience, a maintenance dose of 0.25-0.5 mg/kg (10-20 mg) will prevent worsening of disease.
- This is continued for six to eight months, providing a total treatment period of about 1 year, where the majority are able to discontinue systemic glucocorticoids.
- 1/3rd may relapse and require another course of therapy, whilst a minority may require long-term or indefinite maintenance therapy to control their symptoms

2.9.1.2 Corticosteroid in musculoskeletal sarcoid

Löfgren's syndrome is a self-limiting process and in many circumstances non-steroidal-anti-inflammatory drugs (NSAIDs) are sufficient (Baughman and Lower 2014). For systemic disease, corticosteroids are the mainstay of treatment. Where corticosteroids are used to treat articular manifestations, prednisolone 10-20mg is usually sufficient to control acute arthritis, and in patients with chronic disease lower doses are acceptable (Sweiss, Patterson et al. 2010).

There are no randomized controlled trials of treatments in sarcoid myopathy. Corticosteroids are widely used with the same regimes used for other inflammatory myopathies. They are generally efficacious in acute and

nodular muscular sarcoidosis, although less so in chronic sarcoid myopathy. The earlier the treatment, the more effective it is. However despite initial success a high rate of relapse is reported (Fayad, Liote et al. 2006). Intralesional injections of triamcinolone have been successfully administered for painful nodular lesions (Janssen, Dijkmans et al. 1991).

2.9.2 Methotrexate (MTX)

Immunosuppressive drugs are used in corticosteroids refractory disease or in those who require high doses of steroids for prolonged periods.

The World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) advocates methotrexate as first choice drug for progressive lung disease (Cremers, Drent et al. 2013). However, the evidence is limited and largely observational (Lower and Baughman 1990, Suda, Sato et al. 1994, Agbogu, Stern et al. 1995, Kaye, Palazzo et al. 1995, Baughman, Winget et al. 2000). One small randomised trial, several small series, and case reports suggest efficacy in lungs, skin, eyes, and neurological disease. Response rates are around 40-60% (Lower and Baughman 1995). Baughman et al demonstrated MTX effectiveness in a randomized control study as corticosteroid sparing in the first year of corticosteroid therapy in acute sarcoidosis (Baughman and Lower 1999). Vorselaars et al compared azathioprine versus MTX in a retrospective cohort study and suggested significant steroid-sparing potency and comparable side effects, except for a higher infection rate in the azathioprine group (Vorselaars, Wuyts et al. 2013).

MTX dose administration and monitoring is similar to those in rheumatoid arthritis. However MTX associated liver fibrosis may occur more frequently in sarcoidosis, seen in up to 10% receiving long term treatment (Baughman and Lower 1999). MTX-associated interstitial pneumonitis resulting in pulmonary fibrosis is rare but may be difficult to distinguish from progressive interstitial lung changes secondary to sarcoidosis (Baughman and Lower 1999).

There are, however, no trials of methotrexate use in sarcoidosis arthritis. The choice of steroid sparing agent is largely without an evidence base. Although positive case reports exist publication bias is likely. (Kaye, Palazzo et al. 1995, Baughman and Lower 1999, Braun and Rau 2009).

2.9.3 Azathioprine

Azathioprine is used as second line therapy for pulmonary sarcoidosis in patients who have failed MTX. It is used in combination with glucocorticoids rather than as monotherapy. There are no randomized trials although efficacy has been demonstrated in two open-label series (Pacheco, Marechal et al. 1985, Muller-Quernheim, Kienast et al. 1999).

2.9.4 Leflunomide

Leflunomide has been evaluated in 2 retrospective series involving a total of 108 patients (Baughman and Lower 2004, Sahoo, Bandyopadhyay et al. 2011). Baughman et al demonstrated leflunomide to be as effective as MTX in ocular and pulmonary disease when used alone or in combination with methotrexate (Baughman and Lower 2004). Leflunomide has also been successfully used as an alternative or addition to methotrexate in facilitating steroid dose reduction in both pulmonary and extra pulmonary disease (Sahoo, Bandyopadhyay et al. 2011). Leflunomide seems to be most effective when used in combination with MTX.

2.9.5 Mycophenolate

MMF does not appear to provide extra benefit in sarcoidosis patients that are unresponsive to previous corticosteroid-sparing agents. The largest series of mycophenolate therapy in pulmonary sarcoid included 37 patients (Hamzeh, Voelker et al. 2014). There was no statistically significant improvement in lung function although the mean daily prednisone dose was successfully tapered. Case reports and a small series have suggested a role for MMF in neurosarcoid especially with CNS involvement (Androdias, Maillet et al. 2011). Lastly, there is some reported efficacy in renal sarcoidosis, which is useful as mycophenolate is safer in those with poor renal function (Moudgil, Przygodzki et al. 2006).

2.9.6 Antimalarial agents

Hydroxychloroquine has been used successfully for patients with cutaneous sarcoidosis (Jones and Callen 1990, Doherty and Rosen 2008). A systematic review prior to 2004 found 82% treated with chloroquine or hydroxychloroquine had a favourable response to therapy (Zic, Horowitz et al. 1991). To date, no comparative studies are available.

2.9.7 Other therapies

Cyclophosphamide, chlorambucil, and thalidomide are medications that have been used historically, although are less commonly used in contemporary practice. Apremilast has some efficacy in cutaneous sarcoidosis. (Baughman, Judson et al. 2012)

2.9.8 Biologics

Tumour necrosis factor alpha (TNF- α) plays a pivotal role in maintenance of granulomas formation in sarcoidosis, and thus is a potential therapeutic target. Despite positive case reports and series, randomized control trials, especially in pulmonary disease have been disappointing.

2.9.8.1 Infliximab

Infliximab has been use in patients with pulmonary and extra pulmonary sarcoidosis refractory to corticosteroids in case reports and small case series with success. (Baughman and Lower 2001, Ulbricht, Stoll et al. 2003,

Pritchard and Nadarajah 2004) (Hostettler, Studler et al. 2012). Randomised controlled trial data has been disappointing. Baughman et al reported an improvement in predicted FVC% in 138 patients with chronic pulmonary sarcoidosis. However the effect size was small and clinically insignificant (Baughman, Drent et al. 2006). Rossman et al reviewed 19 patients with active pulmonary sarcoidosis resistant to corticosteroids and did not demonstrate any significant benefit in lung function. (Rossman, Newman et al. 2006). A RCT in extra pulmonary disease demonstrated a modest improvement in the infliximab group, although this was not maintained during the 24 month follow-up period. (Judson, Baughman et al. 2008). There are suggestions that a subset of patient with peripheral blood CD4 T cell lymphopenia may be more likely to respond to infliximab (Crouser, Lozanski et al. 2010).

2.9.8.2 Etanercept

Etanercept has failed to demonstrate efficacy in sarcoidosis. A study in pulmonary sarcoidosis was terminated after the enrolment of 17 patients as interval assessment noted treatment failure in 11 patients (Utz, Limper et al. 2003). In refractory ocular sarcoidosis, Baughman et al did not report any significant improvement with Etanercept therapy. (Baughman, Lower et al. 2005). Paradoxically, there are case reports on the development of sarcoidosis in RA during etanercept treatment. The pathogenesis for this is unclear. Mediastinal or pulmonary symptoms typically resolve after withdrawal of etanercept therapy. (Thongpooswan and Abrudescu 2014)

2.9.8.3 Adalimumab

There have been reports of improvement with adalimumab therapy in extra pulmonary sarcoidosis in case reports and small case series (Patel 2009, Field, Regan et al. 2010, Milman, Graudal et al. 2012). Pariser et al demonstrated effective and relatively safe treatment of adalimumab in a randomized controlled trial in cutaneous sarcoidosis (Pariser, Paul et al. 2013).

2.9.8.4 Other

Judson et al evaluated ustekinumab (anti-IL-12/23) or golimumab (anti-TNF α) treatment in a randomized placebo-controlled trial in chronic pulmonary and/or skin sarcoidosis. There was no significant difference in primary or secondary end points compared to placebo. (Judson, Baughman et al. 2014). Rituximab has been used in refractory pulmonary disease with inconsistent response (Sweiss, Lower et al. 2014). Of a series of four patients with refractory sarcoid granulomatous eye disease, three had clinical improvement with rituximab (Lower, Baughman et al. 2012). Positive individual case reports exist of rituximab use in cardiac and neurological sarcoid. (Bomprezzi, Pati et al. 2010, Krause, Cooper et al. 2016)



SUMMARY POINTS

- Sarcoidosis is a multisystemic inflammatory disorder characterised by the presence of epithelioid non-caseating granulomata in affected organs.
- It has a worldwide distribution and is slightly more common in women than in men. Prevalence peaks between 20 and 40 years of age and in women over 50. Studies on sarcoidosis show significant heterogeneity in incidence, prevalence, disease presentation and severity among different ethnic racial groups.
- The aetiology of sarcoidosis remains unknown, but several infectious agents and genetic factors have been implicated.
- Pulmonary involvement is present in 90% of cases with sarcoidosis, and up to 30% of patients present with extra pulmonary disease, including musculoskeletal, dermatological, ocular, cardiovascular, neurological and renal manifestations.
- Pulmonary involvement in sarcoidosis may range from radiographic stage I disease with bilateral hilar adenopathy without parenchymal involvement, to stage III or IV disease with pulmonary fibrosis, lung insufficiency and/or cor pulmonale.
- Musculoskeletal manifestations in sarcoidosis include acute arthritis, Lofgren's syndrome, chronic arthritis, tenosynovitis, myopathy and bone involvement.
- Lofgren's syndrome is characterised by hilar adenopathy, acute arthritis/arthralgias (ankle involvement is typical), and erythema nodosum. Lofgren's syndrome is usually self-limiting and has a good prognosis, usually requiring treatment with non-steroidal anti-inflammatory drugs only.
- A variety of non-specific laboratory abnormalities may be seen in patients with sarcoidosis. Sarcoidosis has been associated with hypercalciuria, hypercalcaemia and elevations in serum angiotensin-converting enzyme levels.
- Pulmonary imaging may reveal different stages of pulmonary sarcoidosis. Joint and bone radiographs may show non-specific radiographic changes.
- There are no specific diagnostic tests for sarcoidosis. The diagnosis rests on a combination of compatible clinical and radiographic manifestations, histological proof of non-caseating granulomata and exclusion of other diseases with similar presentation.
- Histological proof is not required in patients presenting with classic Lofgren's syndrome, but for all other patients with suspected sarcoidosis, biopsy is usually needed to confirm the diagnosis.
- Sarcoidosis is often a benign disease with good prognosis, unless there is cardiac and neurological involvement. Spontaneous remission occurs in 60–70% of cases, even more frequently in Lofgren's syndrome, and relapses are uncommon. Mortality is <5% and mainly results from respiratory failure related to pulmonary fibrosis, and refractory neurological or cardiac involvement.
- Glucocorticoids have been the most commonly used agents for the treatment of pulmonary and extra pulmonary sarcoidosis. Experience with other drugs is limited.

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3. Palindromic rheumatism

LEARNING OUTCOMES

- Describe the clinical manifestations of palindromic rheumatism in terms of its episodic character, type, severity, duration of symptoms and distribution of joints involved
- Describe and evaluate laboratory and radiographic findings in palindromic rheumatism
- Describe the differential diagnosis of palindromic rheumatism
- Describe the clinical course of palindromic rheumatism by its disease patterns
- Describe and evaluate prognostic factors for the development of rheumatoid arthritis or other rheumatic diseases in patients with palindromic rheumatism
- Describe treatment options in palindromic rheumatism, and evaluate their level of evidence, efficacy and side effects
- Discuss the argument as to whether palindromic rheumatism should be viewed as a distinct clinical entity, or as a variant mode of onset of rheumatoid arthritis

3.1 Introduction

Palindromic rheumatism is a clinical entity originally described by Philip Showalter Hench and Edward Frank Rosenberg in 1944 (Hench and Rosenberg 1944). They described in great clinical detail and with many years of follow-up, 34 patients with a new distinct clinical entity, which they named 'palindromic rheumatism'. The condition is termed 'palindromic' because the rise in severity of symptoms and signs before reaching their maximum is mirrored by the subsequent decline in symptoms and signs back to normality. (A palindrome is a word, phrase or number that reads the same forwards as backwards, such as 'Amor Roma')

Palindromic rheumatism is characterized by multiple, recurrent, transient, episodes of acute arthritis and periarticular inflammation (associated tissue swelling around affected joints). Episodes last for a few hours to several days and then spontaneously resolve. Between acute inflammatory episodes there are no residual joint manifestations.

Although first described more than 60 years ago not much is known about palindromic rheumatism. Fifteen years after its initial description, the condition was revisited by Barbara Ansell and Eric Bywaters (Ansell 1959). They concluded that palindromic rheumatism is a variant or a mode of presentation of rheumatoid arthritis (RA). The majority of cases from their series of 28 patients with palindromic rheumatism eventually developed RA. The literature so far identifies a third to a half of all cases of palindromic rheumatism evolving into RA. However no clinical, immunologic, or genetic factor to predict who would develop RA has been identified. The question still remains whether palindromic rheumatism is a separate clinical entity or whether it should be considered a variant mode of onset of RA (Guerne and Weisman 1992).

3.2 Epidemiology

The prevalence of palindromic rheumatism in the general population is difficult to establish. It appears to be an extremely rare disease, although significant misclassification (as RA) cannot be ruled out. The prevalence is estimated to be one twentieth to one eighth that of RA (Pasero and Barbieri 1986, Guerne and Weisman 1992). The original description of palindromic arthritis did not find a clear female predominance. However, a recent cohort has identified 65% of cases were female, which is more in keeping with the sex distribution of RA (Gonzalez-Lopez, Gamez-Nava et al. 1999). The mean age of onset of palindromic rheumatism is about 45 years, but may vary from 20 to 80 years (Guerne and Weisman 1992). There is no known ethnic predisposition.

3.3 Pathogenesis

Pathogenesis of this disease is unknown.

3.3.1 Histopathological findings

Few histopathological studies have been performed in palindromic rheumatism, and histological findings are non-specific (Hench and Rosenberg 1944, Schumacher 1982, Guerne and Weisman 1992). Tissues obtained during an arthritic episode demonstrate periarticular oedema with gross thickening of the joint capsule and infiltration of large numbers of polymorphonuclear leucocytes. Similar changes were also noted in tendon sheaths. In between episodes, histological examination of joint and tendon tissues showed no significant inflammation. No pannus formation or cartilage destruction was found (Hench and Rosenberg 1944, Schumacher 1982, Guerne and Weisman 1992).

3.3.2 Genetics

Several studies have examined possible associations between HLA gene susceptibility and palindromic rheumatism to establish whether patients with palindromic rheumatism and patients with RA share the same immunogenetic characteristics.

The association of RA with MHC class II antigens is clearly established. Several studies have examined the role of HLA genes in predisposition to palindromic rheumatism and progression to RA. Some, but not all have reported associations with HLA-DR4. One study found similar HLA-DR4 frequencies in patients with RA and palindromic rheumatism; HLA-DR4 prevalence was 36.6% in controls, as compared with 60% in patients with palindromic rheumatism ($p < 0.05$) and 70% in patients with RA ($p < 0.005$) (Fisher, Kirk et al. 1986). However, other studies have found no clear associations (Gran, Husby et al. 1984). There is a report of two brothers with palindromic rheumatism sharing the HLA-DR4 and followed for 12 years, with arthritis remaining palindromic in the first brother, whilst the second developed chronic deformities and classical RA early in the course of the disease (Hannonen, Hakola et al. 1985). Bregeon et al demonstrated HLA-DR4 prevalence of 30.3% in controls, 31.2% in patients with palindromic rheumatism and 36% in patients with palindromic rheumatism who would later evolve to RA (Bregeon, Dajon et al. 1986).

In another series of 147 patients with palindromic rheumatism, the frequencies of HLA-DRB1 alleles were compared with those in 149 patients with RA and 149 controls (Maksymowych, Suarez-Almazor et al. 2002). The prevalence of the shared epitope was 39% in controls versus 65% in palindromic rheumatism (odds ratio 2.9, $p < 0.001$) and 77% in RA (odds ratio 5.1, $p < 0.001$). This was due to an increased prevalence of the DR1-0401 and 0404 alleles, but not DRB1-01.

Based on these similar immunogenetic risk profile, palindromic rheumatism may be considered as a continuous entity in which genetic factors influence the risk of progression from palindromic rheumatism to RA.

3.4 Clinical manifestations

3.4.1 Short-lived attacks of arthritis

The main distinctive feature of palindromic rheumatism is multiple, recurrent, transient, afebrile episodes of acute arthritis and periarticular disease. The episodes have a very sudden onset without any obvious inciting event. Symptoms progressively intensify with a peak within several hours. In most cases the episodes last for ≤ 48 h, sometimes for as little as 2h, and then spontaneously resolve (Guerne and Weisman 1992). Between arthritic episodes there are no residual articular effects, and patients are free of symptoms. The frequency of episodes is highly variable, ranging from one attack every other month to almost daily attacks (Hannonen, Mottonen et al. 1987). Patients with a high frequency of episodes may be more likely to develop RA (Bregeon, Dajon et al. 1986)

3.4.2 Joint distribution

Palindromic rheumatism attacks are typically monoarticular, although in rare cases several joints may be affected simultaneously. Different joints can be affected with each ensuing episode. Attacks are often excruciatingly painful and temporarily debilitating. Any may be affected, although palindromic rheumatism predominantly involves the wrists and the metacarpophalangeal and the proximal interphalangeal joints of the hands, followed by the knees, shoulders and ankles (table 1) (Mattingly 1966, Hannonen, Mottonen et al. 1987, Guerne and Weisman 1992, Emad, Anbar et al. 2014). One series suggests the involvement of hand joints is a clinical predictor of progression into RA within a year (Emad, Anbar et al. 2014). The spine and the jaw are rarely affected. When the spine is involved, it is usually at the cervical level (Guerne and Weisman 1992).

Table 1 Distribution of joints involved in episodes of palindromic rheumatism. (Adapted from Guerne and Weisman, *Am J Med* 1992;93:451–60)

Joint	% Of patients (mean)	% Of patients (range)
MCP/PIP	91	34.4–100
Wrists	78	5–82
Knees	64	10–94
Shoulders	65	5.5–75
Ankles	50	10–67
Feet	43	15–73
Elbows	38	13–60
Hips	17	0–40
Jaw	8	0–28
Spine	4	0–11
Sternoclavicular	2	0–6

MCP, metacarpophalangeal; PIP, proximal interphalangeal.

3.4.3 Periarticular inflammation

In one-third of patients, a characteristic periarticular or para-articular inflammation with marked redness is seen, especially when attacks involve the hands or the wrists. It resolves in a few hours or days (Guerne and Weisman 1992).

3.4.4 Transient nodules

A concomitant appearance of transient nodules during episodes of arthritis has been described. They are usually symmetrical and occur on the extensor surfaces of the hands. The nodules are smaller than those commonly seen in RA, and lack the typical histological features seen in rheumatoid nodules (Hench and Rosenberg 1944, Mattingly 1966, Guerne and Weisman 1992)

3.4.5 Other rare symptoms

Patients with palindromic rheumatism rarely present with constitutional symptoms, such as fever or weight loss, or with morning stiffness. Patients with these constitutional symptoms may be more likely to develop RA (Hannonen, Mottonen et al. 1987).

3.5 Laboratory findings

3.5.1 General

The erythrocyte sedimentation rate and the C-reactive protein are often mildly to moderately elevated during episodes of acute arthritis. In between episodes the acute phase reactants are usually not raised (Hench and Rosenberg 1944, Guerne and Weisman 1992). White blood counts and biochemistry studies are usually normal throughout the course of the disease. Transient anaemia was reported in a few patients (Mattingly 1966). Other investigations should be performed to exclude important differential diagnoses including uric acid, viral screen and Lyme serology.

3.5.2 Rheumatoid factor

Rheumatoid factor (RF) is found in serum samples of 30–60% of patients with palindromic rheumatism, according to different series (Wajed, Brown et al. 1977, Hannonen, Mottonen et al. 1987, Guerne and Weisman 1992, Russell, Devani et al. 2006, Emad, Anbar et al. 2014). Its presence has been associated both with greater severity of palindromic rheumatism and with a higher probability of developing RA during follow-up (Wajed, Brown et al. 1977, Bregeon, Dajon et al. 1986, Hannonen, Mottonen et al. 1987)(table 2).

Table 2 Percentages of RF-positive patients; among those who remained palindromic (PR–PR) during follow-up, and those who developed rheumatoid arthritis (PR–RA). (Adapted from Guerne and Weisman)

Reference	PR–PR (%)	PR–RA (%)	Follow-up (years)
Hannonen <i>et al</i> , 1987	11/25 (44%)	29/35 (83%)	5
Bregeon <i>et al</i> , 1986	3/16 (19%)	16/25 (64%)	10
Wajed <i>et al</i> , 1977	2/22 (9%)	16/17 (94%)	10

PR, palindromic rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor.

In one study, 29/35 (83%) patients with palindromic rheumatism who eventually developed RA were RF positive, compared with 11/25 (44%) patients who remained palindromic during follow-up. (Hannonen, Mottonen et al. 1987)

Seroconversion from RF negative to positive occurs in about 33% of seronegative patients with palindromic rheumatism, almost always shortly before they develop chronic arthritis. The percentage of RF-positive patients among those who remain palindromic is still higher than in the general population (Guerne and Weisman 1992).

3.5.3 Anti-cyclic citrullinated peptide

High frequencies of anti-cyclic citrullinated peptide (anti-CCP) antibodies have been found in serum samples of about half of patients with palindromic rheumatism (Salvador, Gomez et al. 2003, Russell, Devani et al. 2006, Emad, Anbar et al. 2014).

In one study the prevalence of anti-CCP antibodies was found in 56.3% of patients with palindromic rheumatism, 55% in the RA group and 2.5% in the spondyloarthropathy group (Salvador, Gomez et al. 2003). The presence of RF with anti-CCP antibodies was highly correlated in patients with palindromic rheumatism; a positive RF was found in 55.6% patients with anti-CCP antibodies and in only 21.4% patients without anti-CCP antibodies (Salvador, Gomez et al. 2003).

In another study of 61 patients with palindromic rheumatism 51% were RF positive and 56% were anti-CCP positive. Of these patients, 48% developed RA after a mean follow-up of 5.4 years (range 1–14 years) (Russell, Devani et al. 2006). Among those that developed RA, 83% were anti-CCP positive at presentation and 66% were RF positive. Three patients developed other rheumatic diseases (SLE, Behçet's disease, psoriatic arthritis). All three did not have anti-CCP (Russell, Devani et al. 2006). In another study of 90 patients with palindromic rheumatism the involvement of hand joints and positive anti-CCP were the only predictors that determined progression into RA within a year ($p < 0.001$ and $p = 0.02$, respectively) (Emad, Anbar et al. 2014).

However, a significant proportion of patients with palindromic rheumatism do not evolve to RA, even those with high titers of ACPA and a long follow up period. A recent study of 71 patients with palindromic rheumatism followed up for 7.6 ± 4.7 years found RA was more frequently seen in ACPA-positive than in ACPA-negative patients but the difference was not significant (Sanmarti, Cabrera-Villalba et al. 2012).

The results of these studies support the suggestion that palindromic rheumatism is a variant mode of onset of RA, and that anti-CCP antibodies, and RF, may be useful for predicting outcome.

3.5.4 Antinuclear antibodies

Antinuclear antibody studies are usually negative in palindromic rheumatism (Guerne and Weisman 1992). Complement levels are normal.

3.5.5 Synovial fluid analysis

Studies which carry out synovial fluid analyses are rare in palindromic rheumatism. Synovial fluid analysis may show variable cell counts (with up to 12 700 leucocytes/mm³), with variable differentials (2–66% polymorphonuclear cells)(Schumacher 1982). These findings do not correlate with the severity of the episodes (Guerne and Weisman 1992).

3.6 Radiographic findings

Radiographs are always normal in palindromic rheumatism. Erosions, joint space narrowing and periarticular osteopenia are absent(Hench and Rosenberg 1944, Guerne and Weisman 1992). Patients with palindromic rheumatism who progress to RA may develop erosions, with radiographic findings that are the same as those seen in classic RA) (Guerne and Weisman 1992).

Synovitis of wrists and small joints of the hands is detectable by ultrasound during the attacks in 36% of patients and more commonly in the presence of RF or anti-CCP antibodies (30% vs 5.6% and 26.7% vs 5.6%) (Chen, Lan et al. 2009) In the intercritical period most patients with palindromic rheumatism do not have US evidence subclinical synovitis, even those who are ACPA-positive.(Sanmarti, Cabrera-Villalba et al. 2012)

3.7 Diagnostic criteria

Several diagnostic criteria have been proposed for palindromic rheumatism, but none have been adopted by the American College of Rheumatology (Pasero and Barbieri 1986, Hannonen, Mottonen et al. 1987). One proposed set requires five criteria for the diagnosis of palindromic rheumatism (Pasero and Barbieri 1986)

1. 6-month history of brief, sudden-onset and recurrent episodes of monoarthritis or polyarthritis;
2. Direct observation of at least one attack by a physician;
3. Involvement of three or more joints, although they may be affected at different times;
4. Absence of erosions on radiographs;
5. Exclusion of all other arthritides.

Negative RF or anti-CCP antibodies do not seem to be an adequate diagnostic criterion, since a high prevalence of these antibodies is found in all palindromic rheumatism series, even in those patients who do not develop RA (Pasero and Barbieri 1986, Sanmarti, Cabrera-Villalba et al. 2012)

3.8 Differential diagnosis

In establishing the diagnosis of palindromic rheumatism, other forms of recurrent arthritis must be excluded. These include; crystal arthropathy, the most common cause of recurrent arthritis and several systemic diseases that may present clinically as intermittent monoarthritis or polyarthritis, such as reactive arthritis, systemic auto-inflammatory disorders (periodic fever syndromes) or Whipple's disease (Box 1) (Emad, Anbar et al. 2014).

Box 1 Diseases associated with recurrent attacks of arthritis (differential diagnosis of palindromic rheumatism)

- Crystal arthritis (gout, chondrocalcinosis, hydroxyapatite arthritis)
- Reactive arthritis
- Arthritis associated with inflammatory bowel disease (Crohn's disease, ulcerative colitis)
- Infectious arthritis (Whipple's disease, Lyme's disease, B and C hepatitis)
- Systemic autoinflammatory disorders (familial Mediterranean fever, TRAPS syndrome, hyper-IgD syndrome)
- Familial hyperlipidaemia
- Intermittent hydrarthrosis
- Sarcoidosis
- Vasculitis (ANCA vasculitis, cryoglobulinaemia, Behçet's disease, relapsing polychondritis)

TRAPS, tumour necrosis factor receptor associated periodic syndrome.

3.9 Course

In the natural history of palindromic rheumatism, three patterns of disease evolution have emerged (Guerne and Weisman 1992)

- Clinical remission of the attacks;
- Recurrent attacks, without persistent joint involvement;
- Progression to a chronic disease, which in most cases (93%) is RA

The RA which develops follows a similar course and has a similar severity to that of typical RA (Mattingly 1966, Williams, Sheldon et al. 1971, Wajed, Brown et al. 1977, Bregeon, Dajon et al. 1986, Hannonen, Mottonen et al. 1987, Guerne and Weisman 1992, Gonzalez-Lopez, Gamez-Nava et al. 1999, Koskinen, Hannonen et al. 2009, Emad, Anbar et al. 2014). The interval between the onset of palindromic rheumatism and the development of RA may vary from a few weeks to >20 years (Hannonen, Mottonen et al. 1987, Guerne and Weisman 1992). Emad et al study of 90 patients with palindromic rheumatism identified 27.5% progressed to RA at 1 year of follow-up (Emad, Anbar et al. 2014).

Other disorders that may rarely develop in patients with palindromic rheumatism include SLE (Russell, Devani et al. 2006, Koskinen, Hannonen et al. 2009, Emad, Anbar et al. 2014) and, anecdotally, spondyloarthropathies, psoriatic arthritis, Behçet's disease (Koskinen, Hannonen et al. 2009) or granulomatosis with polyangiitis (formerly Wegener's granulomatosis) (Gonzalez-Lopez, Gamez-Nava et al. 1999).

Nevertheless, significant numbers of patients with palindromic rheumatism do not change at all (about 50%), or enter into prolonged remission or are cured (about 15%). However, rates of remission and cure vary between studies, and may reflect heterogeneities between study populations and differences in criteria for remission and cure (Guerne and Weisman 1992)

3.10 Prognosis

Prognosis is generally good except in patients who progress to a chronic disease; the prognosis is then, that of the chronic disease (more often RA).

3.11 Treatment

No randomised, controlled trials have investigated drug treatment in palindromic rheumatism. Owing to of the relationship between palindromic rheumatism and RA, several drugs commonly used in RA have also been tried in palindromic rheumatism, including NSAIDs, antimalarial agents, gold salts, penicillamine and sulfasalazine. However, all subsequent reports on drug efficacy were from open, non-controlled clinical trials with a relatively small sample size. Therefore, conclusions on the true efficacy of these drugs in palindromic rheumatism should be considered with caution (Sanmarti, Canete et al. 2004).

3.11.1 Non-steroidal anti-inflammatory drugs

Treatment with NSAIDs may be effective in acute attacks, providing partial relief of joint pain in some patients. However they do not shorten the duration of attacks and rarely induce long-term remission. In two series of patients with palindromic rheumatism, treatment with NSAIDs appeared effective in about 68% of patients (Grattan, Kennedy et al. 1984, Eliakim, Neumann et al. 1989). However, in another clinical survey, only two out of 60 patients with palindromic rheumatism responded to NSAID treatment (Hannonen, Mottonen et al. 1987). Oral glucocorticoids are often used, but their effectiveness has not been demonstrated.

3.11.2 Antimalarial agents

Response rates with antimalarial agents vary between 15% and 80% in different studies. High response rates were found in a series of 51 patients with palindromic rheumatism; 80% patients experienced marked

improvement, with a reduction of the intensity or frequency of attacks. Nevertheless, 23% of the patients eventually developed RA, despite use of chloroquine (Youssef, Yan et al. 1991). In another series of 90 patients, 43 responded to hydroxychloroquine with complete remission (Emad, Anbar et al. 2014)

In a retrospective study of 113 patients with palindromic rheumatism from the same institution, the use of antimalarial drugs was associated with a reduced risk for the development of RA (Huskisson 1976). Although the proportions of treated (24%) and untreated (35%) patients who finally developed RA were not significantly different, the estimated time to development of chronic arthritis was a median of 162 months in those treated with antimalarials and a median of 56 months in untreated patients. This study thus suggests a possible role for antimalarial agents in preventing or delaying the development of RA in patients with palindromic rheumatism (Huskisson, 1976).

3.11.3 Other disease-modifying antirheumatic drugs

Surprisingly, there is little or nothing in the literature about the use of methotrexate, leflunomide or anti-TNF- α , or glucocorticoids in palindromic rheumatism.

Sulfasalazine has also been found to be effective, with a favourable response in about 50% of patients (Hannonen, Mottonen et al. 1987, Golding 1988).

Gold salts were widely used in the treatment of palindromic rheumatism, although their use has gone out of fashion. Response was noted in up to 66% of patients treated with injectable gold, often after only a few weeks of treatment (Mattingly 1966, Hannonen, Mottonen et al. 1987, Eliakim, Neumann et al. 1989) However, one of these series reported high numbers of cutaneous side effects (Mattingly 1966). In another series of patients with palindromic rheumatism, gold treatment was associated with disease remission in only 20% of the patients, while spontaneous remission occurred in 42% of untreated patients (Bregeon, Dajon et al. 1986).

Penicillamine seemed to be very effective in one case series, inducing complete remission in four out of five patients with palindromic rheumatism (Huskisson 1976). Other case series did not show such good responses (Bregeon, Dajon et al. 1986, Hannonen, Mottonen et al. 1987)

Colchicine has been used for the treatment palindromic rheumatism due to the similarity with familial Mediterranean fever. In a small series of five patients, a dose of 0.6 mg twice daily achieved good results in all five patients (Schwartzberg 1982).

3.12 RA or not RA

Arguments for considering palindromic rheumatism a variant mode of onset of RA include:

- Up to 50% of patients with palindromic rheumatism develop RA.
- High prevalence of the shared epitope in palindromic rheumatism.
- High prevalence (about 50%) of patients with RF and anti-CCP in palindromic rheumatism.
- Presence of subcutaneous nodules, albeit usually with dissimilar histopathology.
- There is some response to common treatments of RA, however, the responses are variable and not as effective as in RA.

Arguments for considering palindromic rheumatism as a distinct clinical entity:

- Different epidemiology and demographics
- No strong HLA-DR4 association.
- Different disease pattern, with recurrent episodes of acute arthritis separated by asymptomatic intervals.
- No constitutional symptoms, no morning stiffness.
- Different histopathology, no pannus formation, no erosions, no bone or joint destruction.

SUMMARY POINTS

- **Palindromic rheumatism is characterised by recurrent transient episodes of acute arthritis and periartthritis. Episodes last for a few hours to several days and then spontaneously resolve, with symptom-free periods that may last from days to months.**
- **Attacks are typically monoarticular, affecting the hands, wrists, knees, shoulders and ankles. Transient subcutaneous nodules may be seen.**
- **Palindromic rheumatism affects men and women equally.**
- **Several diseases should be ruled out in the differential diagnosis, especially crystal arthritis.**
- **Imaging studies in palindromic rheumatism show no pannus formation, no erosions and no bone or joint destruction.**
- **There is a high prevalence of rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti-CCP) in palindromic rheumatism.**
- **Three patterns of disease evolution may be seen in palindromic rheumatism: clinical remission of the attacks in 15%, clinical course of recurrent attacks without persistent joint involvement in 35%, evolution, predominantly to rheumatoid arthritis, in 50%.**
- **Risk factors for the evolution of palindromic rheumatism to rheumatoid arthritis appear to be RF and/or anti-CCP antibodies positivity, female sex and involvement of the hands.**

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Miscellaneous inflammatory arthritides:

Adult Still's disease

Sarcoidosis

Palindromic rheumatism

Paraneoplastic arthritis

Hypertrophic
osteoarthropathy

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IN-DEPTH DISCUSSION I

Paraneoplastic rheumatic conditions

Introduction

Paraneoplastic syndromes are collections of disorders that are the indirect result of a tumour or its metastases. They are mediated by hormones and cytokines from a tumour, or a consequence of humoral or cellular immune defence mechanism against tumour cells cross-reacting with normal tissues at regions distant from the underlying malignancy. Paraneoplastic syndromes in rheumatology are rare. However, causative malignancies are often non-metastatic and thus potentially curable.

Musculoskeletal symptoms arise in joints, fasciae, muscles, vessels or bones, and generally present generally no longer than 2 years before the diagnosis of an associated neoplasm. Rheumatologists should be aware that signs and symptoms compatible with a benign rheumatic condition might be caused by malignancies. Signs and symptoms not fitting the clinical pattern of the simulated rheumatic condition often provides diagnostic clues.

Rheumatological manifestations of paraneoplastic conditions

Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy (HOA) may be seen in lung cancers and pleural mesothelioma. Tibial and femoral bone pain is the typical musculoskeletal symptom, and arthralgia or synovitis of adjacent joints is common. On X-ray, typical elevation (thickening and detachment) of the periosteum may be present and the formation of new osseous tissue leads to increased tracer uptake on bone scans or PET (figure 1).

Digital clubbing is another characteristic finding of HOA (figure 1). It presents with periungual erythema and hyperextensibility of the distal interphalangeal joints. A lesser-known clinical sign found in association with HOA in cancer is acanthosis palmaris (also known as tripe palms), a hyperkeratotic accentuation of dermatoglyphic lines, which gives the palmar skin a gyrated, velvety appearance. (Manger and Schett 2014)

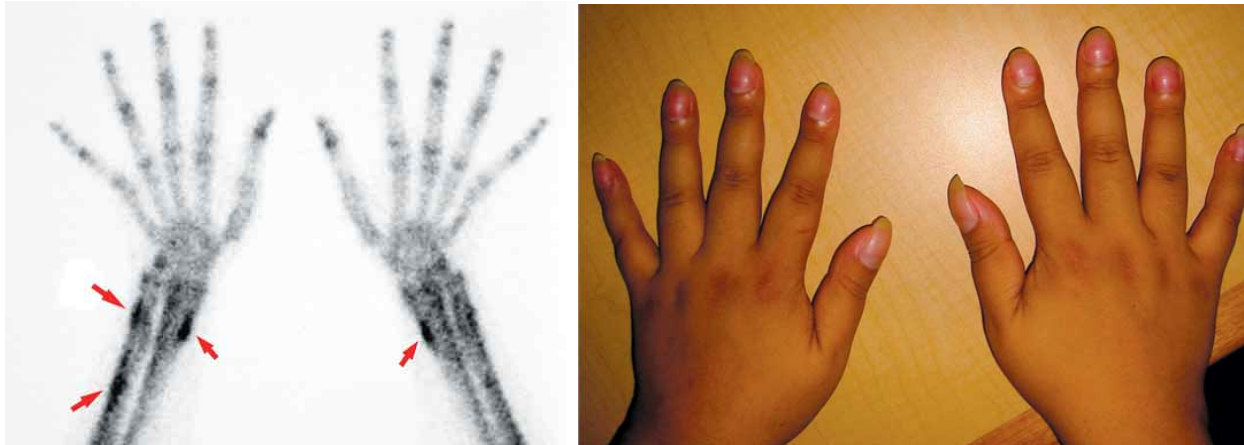
With treatment of lung cancer, around 50% have improvements in symptom and bone scintigraphy. Periostitis and bone pain respond well to NSAIDs, and zoledronic acid have also been used successfully. (Jayakar, Abelson et al. 2011)

HOA may develop in the absence of malignancy. Indeed, the original description of clubbing has been attributed to Hippocrates in the setting of chronic empyema. Any chronic suppurative lung or gastrointestinal disease (e.g. cystic fibrosis or Crohn's disease) can cause digital clubbing. The postulated mechanism of the disease relates to excess prostaglandin E₂ production. An inherited pattern HOA is also described, with a

typical onset during teenage years – and inherited in an autosomal dominant manner. Mutations in genes encoding prostaglandins (e.g. *SLCO2A1*) have been identified (Zhang, Xia et al. 2012).

Other paraneoplastic bone disease includes tumour-induced osteomalacia and hypercalcemia of malignancy.

Figure 1 A patient with clubbing of the fingers and toes. A bone scan disclosed periostosis in the wrists as a paraneoplastic syndrome (hypertrophic osteoarthropathy).



Paraneoplastic polyarthritis

The coexistence of polyarthritis and cancers does not indicate a causal relationship, unless there is a close temporal association or treatment of the tumour leads to remission of joint symptoms (Naschitz and Rosner 2008). The history is typically of an explosive onset, migratory or additive non erosive asymmetric polyarthritis. It can be accompanied by constitutional symptoms and elevated markers of inflammation (Racanelli, Prete et al. 2008). Response to corticosteroids and disease-modifying antirheumatic drugs is typically poor.

Paraneoplastic polyarthritis arise from haematologic malignancy in one third of cases. The most common haematological diagnosis is myelodysplastic syndrome, and the pattern of polyarthritis is typically that of a seronegative rheumatoid. Polyarthritis is also occasionally observed in the setting of solid tumours such as adenocarcinomas of the lung and breast. Carcinoma of the pancreas may present as arthritis of the large lower limb joints, accompanied by erythema nodosum-like lesions. (Manger and Schett 2014).

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE)

RS3PE is a symmetrical polyarthritis involving the small joints with marked pitting oedema on the dorsum of the hands and feet. It characteristically seen in elderly people, and has a sudden inflammatory onset. In 5 small case series, with a total of 89 patients with RS3PE, malignancy was reported in 22 patients (24.7%). (Sibilia, Friess et al. 1999, Paira, Graf et al. 2002, Russell 2005, Manger and Schett 2014).

Whilst idiopathic and paraneoplastic RS3PE are similar demographically and clinically, idiopathic disease demonstrates a rapid response to corticosteroid therapy, whilst response may be diminished or delayed in paraneoplastic disease.

Polymyalgia Rheumatica (PMR)

Polymyalgia rheumatica is a relatively common disease in the elderly. Its association with cancer is controversial but an atypical picture; age <50 year, limited or asymmetrical involvement of typical sites, poor or incomplete response to low doses of glucocorticoids should suggest this possibility. Myelodysplastic syndromes and myeloproliferative syndromes are malignancies associated with PMR.

Palmar fasciitis and polyarthritis syndrome (PFPAS)

Palmar fasciitis and polyarthritis also known as palmar fibromatosis is a rare disorder described in association variety of malignant neoplasms, most commonly ovarian cancer.

It presents with erythema and thickening of the palmar fascia with the development of firm, painful nodules. This is associated with digital swelling and flexion contractures, reminiscent of Dupuytren's contracture but more widespread. Polyarthritis may sometimes accompany the fibrosis. (Azar and Khasnis 2013)

Amyloid arthropathy

Amyloid arthropathy is very rarely seen in myeloma, renal carcinoma and lymphoma. Amyloid can deposit in the synovium leading to rheumatic symptoms, most commonly at the shoulders, knees, wrists, and metacarpophalangeal and proximal interphalangeal joints. Other findings include subcutaneous nodules, similar to rheumatoid nodules, carpal tunnel syndrome and macroglossia. Congo red staining of synovial sediment demonstrates amyloid deposits.

Cancer-associated myositis

About 13–42% of patients with dermatomyositis (DM) (figure 2) and 3–18% of patients with polymyositis have associated malignancy. The leading malignancies in DM are ovarian and breast cancer in women, and lung cancer in men. These may be present in patients either before, after or during diagnosis of myositis.

The clinical picture in patients with cancer associated myositis is often severe muscle and cutaneous involvement. Skin ulceration may occur. Interstitial lung disease is less common.

Anti-NXP-2 and anti-155/140 antibodies targeting transcription intermediary factor 1 (TIF-1) family proteins (particularly, TIF-1γ) are often found in DM (55% of patients) and are present in most patients with cancer-associated DM (Chinoy, Fertig et al. 2007, Fiorentino, Chung et al. 2013). The presence of myositis-specific

(anti-synthetase antibodies, anti-Mi-2, anti-SRP) and myositis-associated antibodies (anti-RNP, anti-PM-Scl, anti-Ku) make an underlying malignancy less likely.

Figure 2 Scaly, erythematous plaques located over the knuckles (Gottron's papule as a pathognomonic signs of dermatomyositis).



Connective tissue disorder symptoms

Raynaud's phenomenon and scleroderma-like syndrome may occasionally be a paraneoplastic. Asymmetric involvement of the fingers, rapidly evolving to necrosis with a poor response to vasodilator therapy and sympathectomy should arouse suspicion of paraneoplastic Raynaud's phenomenon. The absence of Raynaud's with a normal capillaroscopy pattern can be a distinguishing feature of cancer-induced systemic sclerosis. (Racanelli, Prete et al. 2008) Skin changes resembling scleroderma may also occur in patients with osteosclerotic myeloma (POEMS syndrome). The widespread form of scleroderma is found in malignancies of the breast, uterus and lung, whilst the localised form is seen in carcinoids and bronchoalveolar lung tumours. The association between lupus and malignancy is rare.

Vasculitis

The incidence of malignancies in patients with vasculitides has been estimated to be 8%. Cutaneous leucocytoclastic vasculitides is the most common paraneoplastic type, which has a high association with lymphoproliferative disorders and myelodysplastic syndromes; solid neoplasms are less common. Henoch Schönlein purpura (HSP) in adults has been described in association with solid tumours (Podjasek, Wetter et al. 2012). Relapsing polychondritis (RP) has been reported in association with myelodysplastic syndromes and haematological manifestations can precede, occur simultaneously or develop subsequently to RP (Van Besien, Tricot et al. 1992, Myers, Gould et al. 2000).

Chemotherapy-related musculoskeletal conditions

Aromatase inhibitors: Aromatase inhibitors used in the treatment of breast cancer are associated with arthralgia and subjective joint stiffness, occurring in 40-50%, which can result in discontinuation in 10% of patients (Henry, Giles et al. 2008). The musculoskeletal symptoms can persist for many months after withdrawal of therapy.

Bleomycin: Cases of scleroderma and Raynaud phenomenon have been noted in association with the use of bleomycin.

Taxanes: Taxanes, such as paclitaxel and docetaxel can cause myalgia and arthralgia that is sometimes severe. Taxanes can also photosensitive-distribution skin rashes which is similar clinically and histologically to subacute cutaneous lupus.

Other organ manifestations of paraneoplastic conditions

Gastrointestinal

Diarrhoea accompanied by an electrolyte imbalance may lead to weight loss, confusion and exhaustion. These problems are typical of patients with proctosigmoid tumours and of prostaglandins producing tumours like the medullary thyroid carcinomas.

Renal

Patients with tumours that secrete adrenocorticotrophic hormone (ACTH) or ACTH-like substances (Cushing's syndrome) may have hypokalaemic nephropathy, which is characterised by urinary potassium leakage of >20 mEq/24 h. This occurs in 50% of people with ACTH-secreting tumours of the lung (ie, small-cell lung cancer). Other hormones like antidiuretic hormone may cause hyponatraemia (frequent in small-cell cancer).

A nephrotic syndrome is seen, although seldom, in patients who have Hodgkin's lymphoma; non-Hodgkin's lymphoma; leukaemia; melanoma; or malignancies of lung, thyroid, colon, breast, ovary or pancreatic head. Patients with myeloma, renal carcinoma or lymphomas present rarely with secondary amyloidosis of the kidneys, heart or central nervous system.

Haematological

Erythrocytosis or anaemia, thrombocytosis, disseminated intravascular coagulation and leukaemoid reactions may result from many types of cancers. Thrombocytosis ($>500 \times 10^9/L$) leads to migrating thrombophlebitis that is resistant to standard anticoagulant therapy and affects the arm veins, the inferior vena cava and the

jugular veins. It usually appears as oval formations along the little and middle veins, accompanied by cutaneous necrosis and marantic (non-bacterial) endocarditis characterised by thrombotic growths developing on the heart valves that may break and form clots and emboli.

Leukaemoid reactions, characterised by the presence of immature white blood cells in the bloodstream, are usually accompanied by hypereosinophilia and itching. These reactions typically are seen in patients with lymphomas or cancers of the lung, breast or stomach.

Cutaneous signs and symptoms

It is well known that itching (pruritus) is the most common cutaneous manifestation in patients with cancer. Herpes zoster, ichthyosis (figure 3), flushes, alopecia (figure 4) or hypertrichosis may also be presenting symptoms of cancer. Acanthosis nigricans (figure 5) and dermic melanosis are characterised by a blackish pigmentation of the skin and usually occur in patients with metastatic melanoma, gastric tumour or pancreatic tumours.

Figure 3 Ichthyosis, which in the early stages could mimic a benign dermatosis, is characterised by desquamation of the extensory surface of the limbs (resembles the scales of a fish, in ancient Greek ichthys means fish). (Source: SKINmed. Copyright 2004, Le Jacq Communications Inc. <http://www.medscape.com>)



Figure 4 Localised alopecia due to metastatic renal cell cancer.



Figure 5 Acanthosis nigricans and dermic melanosis are often diagnostic clues for the presence of a malignancy. They are similar but differ in location. Dermic melanosis is diffuse; acanthosis nigricans usually is accompanied by confluent papillomas and affects the oral, umbilical, axillary and inguinal areas.



Endocrine signs and symptoms

Cushing's syndrome, accompanied by hypokalaemia, very high plasma ACTH levels and increased serum and urine cortisol concentrations, is the most common example of an endocrine disorder linked to a malignancy. This is related to the ectopic production of ACTH or ACTH-like molecules from many tumours (eg, small-cell cancer of the lung). The syndrome of inappropriate antidiuretic hormone hypersecretion is found in up to 15% of patients with small-cell lung cancer but may be related to other malignancy.

Neuromuscular signs and symptoms

Each part of the nervous system can be affected by a neoplastic condition.

- Sensory neuropathy, originates from ganglionic degeneration.
- Mixed neuropathy appears with several malignancies and has an extremely variable presentation.

- The spinal cord can be affected by either subacute necrotic myelitis or subacute myelitis. A lateral amyotrophic syndrome (LAS) may occur, presenting with typical muscular asthenia and atrophy, hyper-reflexia with pyramidal fasciculations and degeneration of the second motor neuron. This form of LAS differs from the non-paraneoplastic form because it includes sensory involvement (ie, proprioception and pallesthesia).
- The cerebellum may be the site of subacute neuronal degeneration in patients with small-cell carcinoma or breast or gynaecological tumours.
- An example of paraneoplastic neuromuscular disorder is the Eaton–Lambert myasthenic syndrome, which manifests as asthenia of the scapular and pelvic girdles and a reduction of tendon reflexes. It may occur in patients with lymphomas; thymomas; or cancers of the pancreas, rectum, kidney, breast, prostate or uterus.

Management

Patients suspected of having a paraneoplastic condition need a complete diagnostic work-up. This ought to be individualised and based upon the presenting features, the physical examination, the differential diagnosis and the most likely underlying cause. Also, one should take into account the curability of possible underlying conditions. Tailored laboratory investigations, sometimes including tumour markers, autoantibodies and imaging studies, should lead to histological evidence for the underlying neoplasm.

In many cases successful treatment of the malignancy will lead to reduction and disappearance of the paraneoplastic symptoms. When indicated symptomatic treatment of the rheumatic symptoms includes the prescription of non-steroidal anti-inflammatory drugs, glucocorticoids or immunosuppressive drugs. However, the curative treatment of the underlying neoplasm always has priority. The role of the rheumatologist as part of the team of physicians treating a patient with a paraneoplastic condition is most important in the diagnostic phase.

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EULAR on-line course on Rheumatic Diseases

Miscellaneous inflammatory arthritides:

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IN-DEPTH DISCUSSION II

Hypertrophic osteoarthropathy

Introduction:

Hypertrophic osteoarthropathy (HOA) is a clinical syndrome characterized by excessive proliferation of skin and bone tissue at the distal parts of the extremities (Martinez-Lavin et al. 1993). The triad of HOA includes new periosteal bone formation (periostosis) in the tibia, fibula, radius or phalanges, thickening of the skin, most notable on the scalp and forehead, and clubbing of the fingers (first described by Hippocrates 2500 years ago) (Figure 1 & 2).

There is a rare familial primary form, also known as pachydermoperiostosis. This is not associated with any other medical disorders. A secondary form of HOA is associated with primarily non-small cell lung cancer (Pierre Marie-Bamberger syndrome), chronic pulmonary conditions (hypertrophic pulmonary osteoarthropathy, HPOA), chronic cardiac conditions, such as right-to-left cardiac shunts, and less often with hepatic (liver cirrhosis) or intestinal disease (Box 1). Patients with HOA may have joint symptoms, ranging from mild to severe arthralgias that involve the metacarpal joints, wrists, elbows, knees and ankles, to arthritis of the larger joints.

Figure 1: Frontal and lateral radiographs of the distal femur showing a thick, wavy periosteal reaction that involves the diaphysis but spares the epiphysis



Figure 2: Clubbing of the finger, also known as 'drumstick fingers', 'Hippocratic fingers' and 'watch-glass nails'.



Box 1. Secondary causes of HOA

Childhood Secondary HOA	Adulthood Secondary HOA
Pulmonary infections, Cystic fibrosis, Congenital cyanotic heart disease, Osteosarcoma and lung metastasis	Intrathoracic infections or cancer (90%) <ul style="list-style-type: none"> - Non-small cell (squamous cell/ adenocarcinoma) - Metastatic lung disease, - Pleural mesothelioma, - Oesophageal carcinoma, - Hepatocellular carcinoma, - Rhabdomyosarcoma - Renal cell carcinoma Other <ul style="list-style-type: none"> - Pulmonary fibrosis - Infective endocarditis - Arteriovenous fistula - Liver (cirrhosis, primary sclerosing cholangitis) - GI (chronic infections, laxative abuse, polyposis, IBD) - Miscellaneous (thymoma, POEMS syndrome, thalassemia, myelofibrosis)

Epidemiology:

There have been no systematic studies into the incidence and prevalence of HOA. Primary or idiopathic HOA appears to be a very rare condition. Only 3-5% of patients with HOA have primary HOA. The remaining 95-97% have secondary HOA.

Primary HOA has a male-to-female ratio of 9:1 and shows a predilection for blacks. There is a bimodal peak of onset in the 1st year of life and around the 15th year. Primary HOA usually has a chronic course. The activity of the illness is limited to the growth period, with adults becoming asymptomatic and demonstrating a normal life expectancy (Box 2). Long-standing finger clubbing and a positive family history suggest primary HOA (Martinez-Lavin et al. 1988).

In secondary HOA, the incidence and prevalence, sex ratio and mortality and morbidity depend upon, and vary with the associated illnesses (Yao et al. 2009).

Box 2. Epidemiologic Features of HOA

Primary HOA	Secondary HOA
Male/female: 9/1	Epidemiology that of underlying condition
Clustering in families	Morbidity/ mortality in accordance with underlying condition
Predilection for blacks	
Peak incidence in 1 st and 15 th year of life	
Chronic course	
Active disease during childhood	
Asymptomatic in adulthood, normal life expectancy	

Aetiology:**Primary HOA:**

Primary HOA (pachydermoperiostosis or Touraine-Solente-Gole syndrome) is an autosomal dominant condition that presents in childhood and clinically resembles secondary HOA. The genetic abnormality is a mutation in the HPGD gene that encodes 15-hydroxyprostaglandin dehydrogenase, the primary enzyme responsible for prostaglandin degradation (Uppal et al. 2008). However this is not identified in all case and more recently other mutations in genes encoding a prostaglandin transporter protein (e.g. SLCO2A1) have been identified (Zhang et al. 2012). Homozygous individuals have persistently elevated prostaglandin E2 (PGE2) concentrations and clinical symptoms of HOA, while heterozygous individuals have less pronounced biochemical and clinical manifestations. Interestingly due to persistent high levels of PGE2, in the postnatal period, affected individuals are prone to persistent patent ductus arteriosus. Circulating PGE2 might also be pathophysiologically important in secondary HOA as increased serum prostaglandin concentrations have been demonstrated in some of the underlying conditions.

Secondary HOA:

The exact aetiology of secondary HOA is unknown. Paraneoplastic, neurologic, hormonal and immune mechanisms, as well as vascular thrombi caused by platelets and antiphospholipid antibodies have all been proposed as possible causes.

Paraneoplastic growth factor: vascular endothelial growth factor (VEGF)

This hypothesis involves a paraneoplastic growth factor produced by the tumour and released into the circulation. This growth factors promotes the pathological hallmark features of HOA; vascular proliferation, oedema and subperiosteal new bone formation (Martinez-Lavin et al. 2008). One candidate for such a factor is vascular endothelial growth factor (VEGF). VEGF is a platelet-derived factor induced by hypoxic environments. It is angiogenic, permeability-enhancing and a bone-forming agent. Diverse types of cancer produce VEGF as a

mechanism of tumour dissemination. Two case reports have independently noted an association between lung tumour production of VEGF and clinical signs of HOA (Abe et al. 2002, Olan et al. 2004).

Circulatory bypass of the lungs

This hypothesis involves the possible circulatory bypass of the lungs. Many illnesses associated with HOA involve alterations of lung function with significant intrapulmonary shunting of blood. In patients with patent ductus arteriosus complicated by pulmonary hypertension and a right-to-left shunt, HOA is evident only in the limbs that receive unsaturated blood. Furthermore, HOA can be induced in dogs by surgically producing right-to-left shunts.

Normally, megakaryocytes are fragmented in the pulmonary microvasculature before they reach the general circulation. Having escaped fragmentation through shunting, megakaryocytes reach the distal extremities where they may cause local endothelial cell activation through the release of growth factors, such as platelet-derived growth factor, transforming growth factor and VEGF. This may initiate finger clubbing by inducing connective-tissue matrix synthesis and new bone formation through VEGF receptors expressed in subperiosteal bone-forming cells (Dickinson 1993).

Clinical manifestations

Primary HOA

The clinical manifestations may vary. Onset is usually insidious, slowly progressing and essentially asymptomatic. Patients rarely voluntarily report symptoms of clubbing and skin manifestations. These manifestations progressively become part of the patient's body image and the patient usually considers them more or less normal. Homozygous individuals may have more pronounced symptoms than heterozygotes.

In its complete form primary HOA manifestations include pachydermia (abnormal thickening of the skin), periostitis and cutis verticis gyrata (convoluted folds and furrows from a thickened skin of the scalp resembling a cerebriform pattern) (Figure 3). In the incomplete form there may be sparing of the scalp or pachydermia with only minimal or absent periostitis. Further symptoms may include enlargement of the hands and feet, clubbing of the distal fingers and toes, ptosis, excessive sweating, fatigability, bone and joint pain, hepatosplenomegaly, anaemia, and endocrine abnormalities (Castori et al. 2005).

Secondary HOA

The history, course and development of clinical manifestations of secondary HOA depend on the underlying illness. Secondary HOA usually progresses faster than primary HOA. Patients with HOA secondary to lung

cancer may have acute onset of digital clubbing, with a red colour, heat and burning sensation of the fingertips, with sweating, clumsiness, and stiffness of the hands. In addition, pain and swelling in joints and long bones and occasionally thickening of the skin is described. In one series of 111 consecutive patients with pathologically proven lung cancer, clubbing was present in 29%. Clubbing was more common among women than men (40% versus 19%) and in non-small cell cancer compared to small cell lung cancer (35% versus 4%) (Sridhar et al. 1998). Other types of secondary HOA may have a more insidious onset of digital clubbing, skin thickening and arthritis.

Clubbing

Digital clubbing is common but not universal in HOA. It usually progresses through several phases.

1. fluctuating softening (sponginess) of the nail bed. Palpation of the nail produces a rocking sensation of the nail due to oedema and increased soft tissue underneath.
2. loss of the normal 15° angle between the nail bed and cuticle (Lovibond angle) on lateral view
3. accentuation of the convexity of the nails
4. progressively clubbed appearance of the fingertips, accompanied by warmth and sweating
5. there is a shiny or glossy change in the nail and adjacent skin, with disappearance of the normal creases and the appearance of longitudinal striation of the nail

Normally, when the distal interphalangeal (DIP) joints and the nail bed of the right and left index finger are placed in apposition, an oblong diamond-shaped aperture is visible between the 2 juxtaposed nail beds. With clubbing, this diamond-shaped space disappears. The mean ratio of the nail bed circumference to the DIP joint circumference should normally be less than 1. If the ratio is greater, clubbing is present. Clubbing may be symmetrical (all the fingers and/or toes), unilateral (one hand or foot) or unidigital (one finger or toe) (Hansen-Flaschen and Nordberg 1987). Localized clubbing has been associated with local neurological or vascular lesions such as aneurysms, arteriovenous fistulas, venous abnormalities and infected arterial grafts.

Periostosis

Periostosis is especially associated with malignancies. It occurs more often in the tubular bones of the lower extremities than in the upper limbs. Periostosis may be asymptomatic or may cause a severe burning and deep-seated pain in the distal extremities. The pain is aggravated with hanging of the limb and relieved with elevation. It is usually painful on palpation of the involved area. Most often involved are the tibia, fibula, radius, ulna, femur, humerus, clavicle, metacarpal, and metatarsal bones (Martinez-Lavin et al. 1988).

Joint symptoms

Joint symptoms are present in 30-40% of patients with HOA at some time during the course of the disease. Often these articular symptoms are the presenting manifestations. Pain and tenderness occur most often in the knees, ankles, wrists, elbows and metacarpophalangeal joints. These symptoms are usually more severe during the night and exacerbate with movement. The range of motion of affected joints may be decreased. Involvement of the joints is usually symmetric, with synovial effusions of especially the larger joints. Arthrocentesis reveals a viscous non-inflammatory synovial fluid, with a cell count of less than 500 cells/ μ L and few leukocytes and neutrophils. The effusions are more likely to be a sympathetic reaction to nearby periostosis than an inflammatory synovitis. Some patients present with a painful arthropathy months in advance of clubbing, constitutional- or respiratory symptoms, and the presentation may thus initially resemble other polyarticular conditions, like rheumatoid arthritis.

Cutaneous symptoms

Cutaneous symptoms are more prominent in primary than in secondary HOA. Hypertrophy of soft tissues may occur, resulting in coarse facial features, cylindrical calves (elephant feet), ptosis of the eyelids, and cutis verticis gyrata or prominent frontal or scalp cerebriform wrinkles. Additionally dysfunction of exocrine glands within the skin results in acne, hyperhidrosis or seborrhoea. (Martinez-Lavin et al. 1988, Gomez Rodriguez et al. 2009)

Figure 3: cutis verticis gyrata: thickened skin of the scalp resembling a cerebriform pattern.



Workup:

A bone scan is a sensitive way to detect which bones are involved. However, neither radiographic nor radionuclide findings are specific for HOA.

Plain radiographs

Plain radiographs may show 2 types of changes

- bone formation with hypertrophy
- bone dissolution with acro-osteolysis (figure 4).

Hypertrophy predominates in patients with HPOA secondary to lung cancer, whereas acro-osteolysis predominates in patients with HOA secondary to cyanotic congenital heart disease. The type of bone remodelling process depends on the age when clubbing develops. If clubbing appears in childhood, osteolysis is more prominent and if it develops after puberty, hypertrophic changes take place.

Periosteal bone deposition occurs along the shafts of long bones, initially appearing in the proximal and distal diaphyses of the tibiae, fibulae, radii, ulnae, and less frequently the femora, humeri, metacarpals, metatarsals, and phalanges (with exception of the terminal phalanges). Various types of periosteal changes are seen: simple elevation of the periosteum, seen as a continuous thin line of sclerotic new bone separated from the subjacent cortex by a radiolucent area; laminated or 'onion-skin' appearance, with smooth layers of new bone formation; irregular areas of periosteal elevation; cortical thickening (Pineda et al. 1990).

Over time, the appearance of the periostosis may change; the periosteal new bone thickens and fuses with the cortex, and the process extends proximally to the diaphysis and metaphysis. In primary HOA periosteal new bone formation may extend into the epiphyseal regions. Acro-osteolysis may be seen in the distal tufts in patients with long-standing HOA with clubbing.

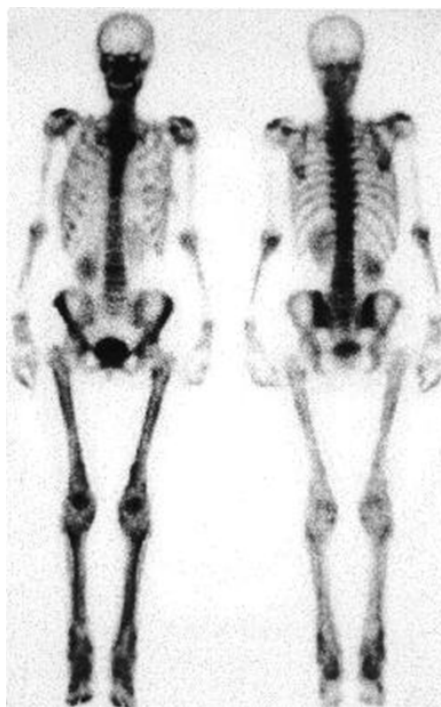
Figure 4: radiograph of both hands in a 42 year old man with primary HOA with finger clubbing and acro-osteolysis of the terminal phalanges.



Radionuclide bone imaging

Radionuclide bone imaging is a highly sensitive method for detecting bone abnormalities in primary or secondary HOA. Radionuclide bone scanning using technetium Tc 99m polyphosphate shows increased uptake of the tracer in the periosteum, often appearing pericortical and linear as a 'double stripe' or parallel track' (figure 5). Scintigraphic abnormalities frequently appear well before the radiographic findings and correspond well with clinical findings. Associated synovitis and clubbed digits may also show increased uptake in early passage flow studies. Angiography findings may demonstrate hypervascularisation of the finger pads (Hansen-Flaschen and Nordberg 1987).

Figure 5: 99m Tc-MDP bone scintigraphy in HOA secondary to bronchial carcinoma, showing linear, subperiosteal increased uptake along shafts of long bones.

Chest X-ray

When HOA is suspected, a chest X-ray should be performed because the most frequent cause of acute onset of HOA is lung cancer.

Treatment:

The most effective treatment for secondary HOA is treatment of the underlying condition. Removal of the primary tumour or treatment of the other causes of HOA usually results in regression of the clinical manifestations. As early as 1976, Atkinson et al reported that chemotherapy treatment of Hodgkin Lymphoma,

also led to complete resolution of HOA symptoms (Atkinson et al. 1976). With treatment of lung cancer, around 50% have improvements in symptom and bone scintigraphy (Ito et al. 2010). Correction of cyanotic heart malformation is also effective in relieving HOA symptoms. Frand et al reported two cases of HOA-associated cyanotic heart disease corrected by surgery led to complete resolution of clinical and radiological signs of HOA (Frand et al. 1982).

Periostitis and bone pain respond to steroidal anti-inflammatory drugs (NSAIDs). This may be related to blocking of cyclo-oxygenase-2 (COX-2), an enzyme that is involved in the formation of prostaglandins (PGE). Kozak et al reported the use of rofecoxib in a 65-year-old woman with HOA secondary to metastatic non-small cell lung cancer. Her pain was refractory to high-dose narcotics, but completely resolved with rofecoxib, although clubbing did persist (Kozak et al. 2006).

Another promising treatment is reported with octreotide, a somatostatin analogue. Its role is well-established in controlling growth and secretions in acromegaly and neuroendocrine tumours. It is suggested that the analgesia effect in HOA may due to its inhibitory effect on the production of VEGF and endothelial proliferation. (Nguyen and Hojjati 2011)

Lastly, in patients with refractory disease, bisphosphonates including pamidronate and zoledronic acid which are potent inhibitor of osteoclastic bone resorption have been used successfully (Jayakar et al. 2011) (Amital et al. 2004) (King and Nelson 2008). It is unclear how bisphosphonates fit in the scheme of suggested HOA pathogenesis mechanism, however while the inhibitory effects of bisphosphonates on bone metabolism may be responsible for its benefits, both pamidronate and zoledronic acids have been shown to decrease levels of plasma VEGF in patients with cancer. (Nguyen and Hojjati 2011).

It therefore plausible that other agents that inhibit VEGF may be successful in the treatment of HOA. This is especially interesting with the more recent use of anti-VEGF antibodies in the treatment of certain cancers. (Nguyen and Hojjati 2011).

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Infection and arthritis.

Reactive arthritis - Lyme - Whipple - HIV - Viral arthritis - Septic arthritis

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LEARNING OUTCOMES

- Distinguish between infectious arthritis and inflammatory arthritis
- Diagnose and treat reactive arthritis
- Treat infectious (septic) arthritis
- Diagnose and treat viral arthritides
- Diagnose and treat tuberculosis and leprosy related rheumatic diseases
- Diagnose and treat musculoskeletal symptoms during HIV infection
- Consider the role of infections in the propagation of chronic rheumatic diseases

1 Introduction

The complex association between microbes and autoimmunity has intrigued researchers for centuries. Pyogenic bacteria and viruses can be either causative or precipitating agents for acute infective arthritis, while chronic arthritis is generally caused by mycobacteria, fungi and parasites. Translational research over the past few years has bridged gaps in understanding the immuno-pathogenesis of infective arthritis to a large extent. This chapter gives a comprehensive view of various infection related arthritis.

The relationship between joints and infection can be categorised into two groups:

Group 1 : Septic or infectious arthritis – the causative agent is present within the affected joint and can usually be identified by culture or molecular techniques. It has usually reached the joint from a focus of infection elsewhere in the body;

Group 2 : Post-infectious arthritis – bacterial antigens can be detected in the joint. This includes: Reactive arthritis – infection usually originates in the urogenital or gastrointestinal system and can cause an inflammatory joint disease with features of spondyloarthritis.

2 Bacterial infections and acute arthritis

2.1 Septic arthritis

Septic arthritis refers to the articular manifestations due to the presence of bacteria or fungi within a joint. This is a medical emergency, causing rapid joint destruction if not recognised and treated early. In the majority of cases, the causative organism is a bacterium—the most common aetiological agent being *Staphylococcus aureus*. Infections due to fungi are much rarer. Most articular infections develop as a result of haematogenous seeding of the vascular synovial membrane after a bacteraemic episode. In children, usually there is a breach in the outer cortex of the bone, leading to seeding of bacteria into the intracapsular region. Bacterial arthritis may also arise secondary to penetrating cutaneous trauma, following, for instance, a plant-thorn wound or an animal bite. Bacteremia from gastrointestinal and genito-urinary tracts result in Gram negative septic arthritis. Very rarely, septic arthritis occurs as a result of local glucocorticoid joint injection, other intra-articular procedures or joint replacement surgeries.

Pyogenic bacterial arthritis typically presents as an acute, very painful monoarthritis with fever. Irreversible loss of joint function develops in 25–50% of patients, mainly related to delayed diagnosis and treatment. It can be a life-threatening condition and mortality has been reported to be as high as 10%. This mortality rate increases, with estimates as high as 50%, when sepsis involves several joints.

Septic (purulent) arthritis is usually divided into two entities: (a) non-gonococcal arthritis and (b) gonococcal arthritis. The division is useful in clinical practice because the risk factors, clinical features and treatment differ greatly between the groups (table 1).

Table 1 Non-gonococcal and gonococcal arthritis—predisposing factors, clinical and laboratory features

Clinical feature	Non-gonococcal	Gonococcal
Age	Risk increases with age	Sexually active young adults
Gender	No difference	4 times more common in females
Menstruation	No increased risk	Increases risk
Complement deficiency, systemic lupus erythematosus	Risk for <i>Neisseria meningitidis</i> infection	Risk for <i>Neisseria gonorrhoeae</i> infection
Presentation	Single joint involvement	Migratory polyarthritis
Tenosynovitis	Uncommon	Common
Polyarthralgia	Uncommon	Common
Pustular dermatitis	Absent	Does occur
Culture positivity	Nearly 90%	Less than 50%
Prognosis	Bad	Good

2.1.1 Non-gonococcal arthritis

2.1.1.1 Incidence

The incidence of acute joint infection (septic arthritis) is 5–9 per 100 000 person-years (Margaretten et al, 2007). A high suspicion of septic arthritis is pivotal, considering the swift damage it causes if not detected early and treated aggressively. Patients with advanced age, rheumatoid arthritis (RA) and those who are immunocompromised or have abnormal joint structure or a joint prosthesis are at increased risk for joint infection (box 1).

2.1.1.2 Clinical symptoms and diagnosis

In about half of the adult patients with septic arthritis, the infection occurs in abnormal joints. Usually the patient presents with an acutely swollen joint, often a large joint such as the knee or ankle. The joint is usually swollen, warm, can be even erythematous, tender on palpation and often very painful on movement (figure 1). The clinical presentation may vary according to the virulence of the causative organisms, which is low for mycobacterial and fungal infections. –In the case of pre-existing arthritis, the affected joint often shows signs that are out of proportion to disease activity detected in other joints.

Box 1 Risk factors for the development of septic arthritis

Systemic features

- Degenerative joint disease
- Immunosuppressive condition
 - o AIDS
 - o Chronic renal failure
 - o Organ transplantation
 - o Hypogammaglobulinaemia
- Diabetes mellitus
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Immunosuppressive therapy including some biologics

Local factors

- Trauma penetrating into the joint
- Prosthetic joints
- Open reduction of fractures
- Intra-articular procedures

Social factors

- Low socioeconomic status
- Occupational exposure to animals
- Alcoholism and chronic liver disease
- Intravenous drug abuse

Others

- Extremes of age

Figure 1 A 70-year-old man with fever and swollen right ankle for 1 week. Note septic skin lesions on the leg. Synovial fluid and blood cultures positive for *Staphylococcus aureus*.



Infection in more than one joint occurs in about 20% of patients, mostly with underlying chronic diseases, an immunosuppressive state or drug abuse. About 50% of patients have high fever, while sweats and rigors occur only in about a quarter. In patients with RA using glucocorticoid, immunosuppressive or biological treatments, the joint pain and symptoms of acute infection may be masked, which can lead to a delay in diagnosis.

The differential diagnosis of acute monoarthritis is presented in box 2.

Box 2 Differential diagnoses for acute monoarthritis

- Septic arthritis
- Crystal arthritides
 - o Gout
 - o Pseudogout
 - o Apatite-related arthropathy
- First symptom/presentation of inflammatory diseases such as rheumatoid arthritis
- Reactive arthritis
- Lyme arthritis
- Transient synovitis of the hip
- Pigmented villonodular synovitis
- Haemarthrosis
- Neuropathic arthropathy
- Osteoarthritis
- Intra-articular injury (fracture, meniscal tear, osteonecrosis)
- Metastatic carcinoma

The prevalence of septic arthritis in hospital series of patients with monoarthritis is 8–27%.

If septic arthritis is suspected, arthrocentesis of the joint is mandatory, and the synovial fluid is analysed for Gram stain, white blood cell (WBC) count and differential, and cultured for bacteria. Staphylococci or streptococci cover about 90% of the infections. Gram-negative organisms are more common in older patients and in those who are immunocompromised (table 2). The sensitivity of Gram staining and bacterial cultures of the synovial fluid to detect the infection is, however, limited. The Gram stain is positive in 71% of Gram-positive septic arthritis, 40–50% of cases of Gram-negative septic arthritis, and in <25% of cases of gonococcal septic arthritis (see below) (Garcia-De La Torre and Nava-Zavala, 2009*). Microscopy is positive in only 50% of cases (Mathews et al, 2007). A synovial fluid WBC count of > 50000/cu mm and > 100000/cu mm has been shown to have a positive likelihood ratio of 4.7 (95% CI 2.5 – 8.5) and 13.2 (95% CI 3.6 – 51.1) respectively for septic arthritis in a meta-analysis. (Carpenter et al, 2011). The presentation of septic arthritis may be mimicked by a pseudo-septic pattern in the setting of calcium pyrophosphate deposition disease as the latter can present with fever, turbid, purulent looking synovial fluid, with neutrophilic leukocytosis of > 50000 / cu mm. PCR of the synovial fluid does not offer any advantage compared with microscopy and culture. Laboratory markers of

systemic inflammation (increased WBC count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) have only a limited diagnostic value owing to their low sensitivity. A markedly raised serum CRP (>100 mg/L) increases the likelihood of septic arthritis only slightly by a likelihood ratio of 1.6. Serum procalcitonin has been shown to be a sensitive marker to differentiate septic and non-septic arthritis in the early stages. However, its role in guiding antibiotic therapy needs to be elucidated further. Procalcitonin cut-off for infections with generalized sepsis is generally accepted to be 0.5 ng/ml, while a lower cut-off may have to be used for localized infections. However, caution should be exercised in interpreting the results as diseases like adult onset Still's disease and ANCA associated vasculitis can also have elevated procalcitonin levels. (Shaikh MM et al, 2014). The concentration of WBCs in the synovial fluid is usually increased, and a count of $>50 \times 10^9/L$ with >90% of polymorphonuclear cells increases the likelihood of septic arthritis. Evidence of infection should also be searched for outside the joint (chest X-ray examination, cultures of urine, blood, throat, wounds, skin blisters, etc.) (figure 2).

Table 2 Pre-existing morbidities and their association with infective organisms in septic arthritis

Underlying disorder	Possible infection
Rheumatoid arthritis	<i>Staphylococcus aureus</i>
Osteoarthritis	<i>Staphylococcus aureus</i>
Alcoholism	<i>Klebsiella pneumoniae</i>
Malignancy	Gram-negative bacteria
Use of immunosuppressive drugs	Gram-negative bacteria
Intravenous drug abuse	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i>
Systemic lupus erythematosus	<i>Salmonella</i> , <i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i>
Complement deficiency	Encapsulated microbes
HIV	No major difference from non-HIV patients

Figure 2 The same patient as in figure 1. Septic lesion on right knee.



Radiography of the joint is usually normal, unless there is a pre-existing chronic rheumatic condition such as RA or osteoarthritis; however, radiographic features of underlying chondrocalcinosis and osteomyelitis should be sought, but note that the former can co-exist with septic arthritis. In established septic arthritis radiographs may reveal juxta-articular osteoporosis, diffuse joint space narrowing due to cartilage destruction and erosions in areas of reflection of the synovium onto the bone (figure 3). At a late stage the joint may appear badly destroyed. Musculoskeletal ultrasound may show non-echo-free effusions, characteristic of septic arthritis. Magnetic resonance imaging (MRI) has greater resolution for soft-tissue abnormalities and aids in early diagnosis of septic arthritis.

Figure 3 Septic arthritis of the right hip due to non-typhi salmonella in a 64-year-old-man.



An X-ray examination shows severe joint space loss, demineralisation and geodes in the femoral head and acetabula roof. Despite appropriate antibiotic therapy, the post-treatment course of the patient in figure 3 was not favourable and surgery was therefore undertaken to remove the right femoral head. Antibiotics were continued and a total hip prosthesis was implanted 3 months later.

2.1.1.3 Treatment

A high suspicion of septic arthritis should prompt treatment with parenteral antibiotics without waiting for the results of bacterial cultures, and drainage of the infected joint, which are the cornerstones of treatment. The

decision about treatment can be guided by microscopy and routine analysis of synovial fluid, but a negative Gram stain does not exclude septic arthritis. The choice of antibiotic is primarily empirical and based on the likelihood of the organism involved and comorbidities (table 3). When the culture results are available, antibiotics can then be chosen according to the sensitivity pattern. The duration of the intravenous treatment should be 10–14 days, often followed by oral antibiotics. The total duration of treatment, usually 6 weeks, depends on the infecting microorganism, other concomitant diagnoses and treatment options, as well as the initial response to the treatment.

Table 3 Antibiotic treatment of septic arthritis. (Modified from Mathews et al, *Ann Rheum Dis* 2007;66:440–5; Mathews and Coakley, *Curr Opin Rheumatol* 2008;20:457–62)

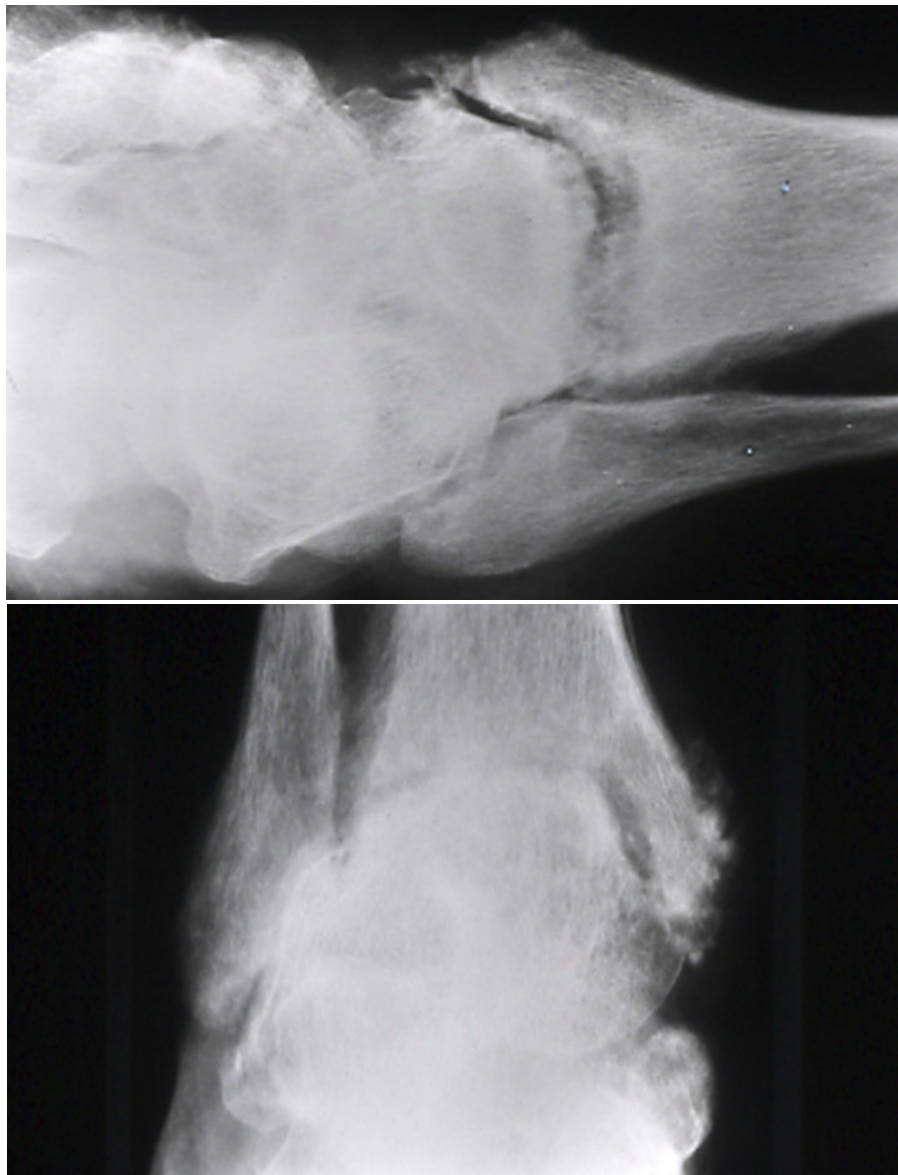
Patient group	Antibiotic choice
No risk factors for atypical organism	Staphylococcal penicillin (eg, cloxacillin or Flucloxacillin) 2 g four times a day IV Fusidic acid 500 mg three times a day by mouth, or gentamicin IV may be added In the case of penicillin allergy, clindamycin 450–600 mg four times a day, or second- or third-generation cephalosporin
High risk of Gram-negative sepsis	Second- or third-generation cephalosporin (eg, cefuroxime 1.5 g three times a day)
MRSA (methicillin-resistant <i>Staphylococcus aureus</i>) risk	Vancomycin 1 g two times a day IV plus second- or third-generation cephalosporin
Suspected gonococcus or meningococcus	Ceftriaxone 1 g once a day (IM or IV) or similar drugs, depending on local policy/resistance
Intravenous drug users	Consult local microbiologist
Patients in the intensive therapy unit, known colonisation of other organs	Consult local microbiologist

Drainage of the inflammatory debris is mandatory for preserving joint function and limiting joint destruction. This can be performed as daily needle aspiration, arthroscopic debridement with lavage, open lavage or arthrotomy with synovectomy. No randomised studies have shown superiority of any of these interventions (Mathews and Coakley, 2008). In practice, if a joint is easily accessible by needle arthrocentesis, this approach can be used. In a complicated case or for a joint with limited access (eg, hip and shoulder joints), arthroscopic or open lavage would probably have a better therapeutic effect. In addition to the above-mentioned treatment options, non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics should be prescribed according to the patient's symptoms. Unloading of the affected joint is recommended until infection is controlled. Physiotherapy to prevent muscular atrophy and contractures should be instituted early, first as manual mobilisation of the joint and isometric contraction of the quadriceps muscle in the case of knee infection. Partial weight bearing can be started later on, with more active mobilisation only when inflammation is suppressed.

2.1.1.4 Outcome

The outcome of septic arthritis varies and seems to depend on the duration of symptoms, type of organism, type of joint drainage, pre-existing joint problems and coexisting osteomyelitis. The functional outcome depends on the presence of degenerative changes in the joint before infection and on the patient's age (figures 4A and B).

Figure 4 (Top) X-ray picture of the ankle of the patient in figure 1 at entry. Notice the destructive lesions in the ankle. (Bottom) X-ray picture of the right ankle 1 year later. Notice the total destruction of talocrural arthritis with periosteal reaction.



2.1.1.5 Rare bacterial infections

More subacute or chronic forms of infectious arthritis with insidious onset and considerable delay in diagnosis may be caused by mycobacteria and brucella species. Clinical suspicion is based on knowledge of host susceptibility, endemic areas of specific organisms and the usual clinical patterns of musculoskeletal involvement.

Mycobacterium tuberculosis arthritis Musculoskeletal manifestations of extra-pulmonary tuberculosis have been described in 10-15% of patients. (Malaviya et al, 2003). The prevalence varies widely with geographical location. -There are many ways in which Mycobacteria can affect the joints –

- a) Direct invasion – septic arthritis
- b) Secondary infection of joints, following inflammatory or degenerative changes
- c) Following intra-articular procedures such as corticosteroid injections or arthroscopies, or in prosthetic joints
- d) Reactive arthritis – Poncet's disease

Musculoskeletal involvement is caused by haematogenous and/or lymphatic spread of tuberculosis bacilli from other lesions, such as a quiescent pulmonary primary localisation or another extraosseous focus. Usually the patient presents with a slow onset monoarthritis of a weightbearing joint (eg, hip, knee), with only mild or no systemic symptoms. In the early stage of the disease, tuberculous arthritis may easily be mistaken for a degenerative condition. The significant delay between the onset of symptoms and definitive diagnosis commonly ranges between 5 and 50 months. The prevalence of prosthetic joint tuberculosis has been steadily rising in endemic areas. Advanced age (>70 years), tuberculosis in the past, and chronic immunosuppression therapy are risk factors for tuberculosis of prosthetic joints. (Kim et al, 2013). Systemic symptoms, frequently absent at the beginning of the joint involvement, may include a low-grade fever, asthenia, decreased appetite, weight loss and night chills. Chest radiographs can be normal. Radiographs of affected joints can show diffuse joint space narrowing and bony erosions. The Phemister's triad of periarticular osteoporosis, peripherally located osseous erosion and gradual reduction of intraosseous space is highly specific for tuberculous arthritis. MRI can clearly determine severity and extent of joint damage. MRI features of rheumatoid arthritis can also mimic those of tuberculous arthritis. Uneven and extensive synovial thickening is pathognomonic of rheumatoid arthritis, whereas, larger bone erosions with rim enhancement and extra-articular cystic mass are more common in tuberculous arthritis. (Choi et al, 2009). Confirmatory diagnosis depends on the isolation of *Mycobacterium tuberculosis*. Ziehl–Nielssen staining of synovial fluid is only positive in 10–20% of cases. Cultures of synovial fluid and synovial tissue are positive in 80% and 94% of cases, respectively, and PCR is being used increasingly to make a more rapid diagnosis. Synovial biopsy is of major interest for articular tuberculosis infection, since

histology can show the chronic caseating granulomatous inflammation long before bacterial cultures become positive.

Poncet's disease, a non-suppurative reactive arthritis (see below), mainly occurs in patients with extrapulmonary tuberculosis. Erythema nodosum is a characteristic feature in these cases. Patients present with asymmetric, oligo-polyarthritis, mostly involving large joints of lower limbs, and sparing the axial skeleton. Arthritis resolves within weeks of initiating anti-tuberculous therapy, and generally there is no tendency for progression to chronic arthritis. (Rueda et al, 2013).

Atypical mycobacterial infection Clinical manifestations of atypical mycobacterial infection resemble those of tuberculosis, but tenosynovitis, bursitis, periarticular discharging sinus and polyarthritis are more common. Non-tuberculous mycobacteria include *Mycobacterium avium*, *Mycobacterium marinum*, *Mycobacterium kansasii*, *Mycobacterium abscessus* and *Mycobacterium chelonae*. The most commonly affected joints are knees, hands and wrists, which are usually infected through direct inoculation. Infection with *Mycobacterium marinum* frequently involves the hands or wrists, most often in association with a history of periarticular trauma or exposure to marine environments. Intra-articular injections are a common route of entry for these organisms. Patients with atypical mycobacterial infection are mostly immunocompromised (e.g., diabetes mellitus, end-stage renal disease, haemodialysis patients, HIV infection).

***Mycobacterium leprae* infection** The prevalence of arthritis in leprosy varies widely, depending on the geographical location, with high rates being reported from countries in Asia and Central America. Patients with lepromatous leprosy have been shown to have a higher prevalence of arthritis. An explosive onset, acute symmetric polyarthritis, involving small joints of hands and feet, and associated with the Lepra reaction is the commonest presentation. Symptoms last for a few weeks and resolve with treatment. Patients can also present with tenosynovitis alone (swollen hands and feet syndrome). Demonstration of acid-fast bacilli in joints is the gold standard for diagnosis. Plain radiographs of extremities reveal periosteal reaction, subarticular cysts, acro-osteolysis, subluxation or complete destruction of joints. The presence of rheumatological manifestations warrants addition of immunosuppression along with multi-drug therapy. (Gupta et al, 2016; Danda D et al, 2001)

Brucellosis This infection is often acquired by ingestion of contaminated milk or dairy products, and manifests as a febrile illness with hepatosplenomegaly, lymphadenopathy and leucopenia or pancytopenia. *Brucella mellitensis* is most often the causative agent, but disease due to *Brucella abortus* and *Brucella suis* also occurs. History of ingestion of infected unpasteurised dairy products or professional exposure is an important clue to the diagnosis, especially in combination with travel to endemic countries. Besides these manifestations, musculoskeletal lesions are present in one-third of patients. Common osteoarticular manifestations of brucellosis are acute unilateral sacroiliitis, or peripheral arthritis involving predominantly the large joints of lower limbs. If brucella infection is suspected, the laboratory should be consulted since this organism requires a

special culture medium and extended culture time for its growth in culture. Even when cultured in special medium, only 50% of synovial fluid cultures are positive. PCR is useful for detection of brucella DNA in synovial fluid or tissue. In the absence of bacteriological confirmation, positive brucella serology (titre >1:160, or a significant rise in brucella antibody titre) might help the diagnosis. However, cross-reactivity in serological testing between brucella and *Yersinia enterocolitica* and salmonellae must be taken into account. Only culture allows differentiation of the different brucella species.

2.1.1.6 Fungal arthritis

The onset of fungal arthritis is usually insidious. Articular infections become symptomatic weeks after an episode of fungaemia and clinical symptoms are often more subtle than in bacterial infections, leading to long delays in diagnosis. Primary fungal infections of lung and skin are common, but dissemination to other organs occurs predominantly in patients with a suppressed immune status or receiving prolonged intravenous antibiotics. Clinical clues include trauma with possible inoculation, travel to endemic areas, failure to identify a causative pathogen on synovial fluid cultures, failure to respond to antibiotic therapy or immunodeficiency.

Especially at risk for invasive candida or aspergillus infections are patients with neutropenia receiving glucocorticoid therapy, with central venous catheters, receiving broad-spectrum antibiotics, with a history of, or current detection of, candidaemia, and intravenous drug abusers. Diagnosis is established by detection of the fungus in synovial fluid or bone tissue, either by direct (histological) techniques or culture.

2.1.2 Gonococcal arthritis

In 0.5–3% of gonorrhoea infection, the pathogen can gain access to the bloodstream from the primary mucosal site of infection and produce disseminated gonococcal infection (DGI). Gonococcal arthritis occurs in about 42–85% of such patients. DGI manifests itself in two major forms, with extensive overlap between them. The disseminated form causes tenosynovitis, dermatitis and fever. The patient may also have myopericarditis, meningitis and full-blown sepsis. The septic arthritis form causes monoarthritis or polyarthritis and fever. Dermatitis is less common than in the bacteraemic form.

2.1.2.1 Occurrence

Gonococcal infection used to be the leading cause of septic arthritis among young adults, but the disease has become rare in Western countries after the introduction of effective control programmes. The incidence is lower in Europe than in North America. In Europe, about 1% of septic arthritis is caused by gonococci (Bardin, 2003). In the USA, gonococcal arthritis is mainly seen in urban ethnic minorities with low socioeconomic status. In Africa, the disease is still prevalent. Gonococcal arthritis is three to four times more common in women than in men. This is probably due to asymptomatic local infection, which is more common in women, and allows spreading of the infection. Other risk factors for gonococcal arthritis are pregnancy, menstruation, multiple

sexual partners, male homosexuality, low socioeconomic status, intravenous drug use, complement deficiency, HIV infection and systemic lupus erythematosus.

2.1.2.2 Clinical symptoms and diagnosis

Patients with the disseminated form often have severe polyarthralgia (but a severe polyarthritis is uncommon), fever and chills. Skin lesions (non-pruritic, tiny papules, pustules or vesicles with an erythematous base) in the trunk or extremities occur in >50% of patients (figure 5). Tenosynovitis occurs also in >50% of patients. Predilection is for the dorsum of hands, fingers and feet, wrist and ankles. The septic form is less common. A purulent monoarthritis or oligoarthritis is the major feature. Joint fluid cultures may be positive, but blood cultures are not.

Figure 5 Gonococcal pustules in a patient with disseminated gonococcal infection. (Courtesy of Seattle STD/HIV Prevention Training Centre, University of Washington, WA, USA. Source: Negusse Ocbamichael.)



The diagnosis is based on the clinical picture of DGI supplemented with evidence of gonococcal infection. Gonococcal cultures of the urethra/cervix, rectum and oropharynx should be performed and are positive in about 80% of cases. Blood culture is positive in <50% of patients. Joint aspiration is positive in about 50% of the cases; bacterial cultures of the skin lesions are usually negative. Contact tracing and cultures from partners can help in the diagnosis (Bardin, 2003).

Patients with gonococcal arthritis can have raised WBC in the blood, as well as raised ESR and CRP. Synovial fluid shows an inflammatory pattern. Ligase chain reaction and polymerase chain reaction (PCR) are available for the detection of nucleic acid sequences specific for *N. gonorrhoea* in urogenital samples, first-void urine, prostatic

massage fluid or synovial samples. Cultures are preferred because the microbial sensitivity pattern can also be determined. Serological tests perform less well.

2.1.2.3 Treatment

Initial treatment (depending on local resistance) is a third-generation cephalosporin, e.g. ceftriaxone 1 g once a day (table 3). If the microbe is sensitive to penicillin, the treatment can be switched to G-penicillin 10^6 IU/day intravenously (IV) in divided doses. In cases of penicillin allergy, spectinomycin 2 g IV twice a day can be given. The arthritis responds very quickly to antibiotic treatment. This can be used even as a diagnostic test in a patient with a typical clinical picture and negative cultures. Parenteral antibiotics should be continued for 1–3 days after resolution of the symptoms. Thereafter, oral treatment (cefixime 400 mg twice a day, ciprofloxacin 500 mg twice a day or amoxicillin 500 mg three times a day) can be continued for 7–10 days to complete the treatment. After the treatment, microbial cultures from foci which were positive before antimicrobial therapy should be re-examined. Patients should be screened for other sexually transmitted diseases. A co-infection with *Chlamydia trachomatis* can also be the cause of the arthritis in the patient. Contact tracing and treatment is part of health policy. Other treatment procedures are similar to those described above for non-gonococcal septic arthritis. The joints in the patient with DGI are usually very painful, and need NSAIDs or analgesics. Physiotherapy should be started as in non-gonococcal arthritis.

2.1.2.4 Outcome

The prognosis of both forms of gonococcal arthritis is usually good, provided that antibiotic therapy is started in due time. Sometimes, gonococcal infection appears to be associated with a more prolonged form of sterile arthritis, mimicking reactive arthritis. Usually such an event is associated with a co-infection with *Chlamydia trachomatis*.

2.2 Prosthetic joint infections

The rate of prosthetic joint infections ranges from 0.5% to 1% for hip and knee replacements, the most important risk factor being a revision arthroplasty. Early-onset infections are usually the result of perioperative wound contamination and are most often caused by coagulase-negative staphylococci. Infections that begin later than 3 months after the surgical procedure are more often due to *Staphylococcus aureus*, streptococci or Gram-negative bacilli through haematogenous dissemination.

Clinical features of infections within the first few months of surgery are pain, erythema and drainage at the wound site. By contrast, late-onset infections present with gradually progressive joint pain without fever or other signs of infection. Radiological evidence of joint loosening is often present but does not differentiate mechanical from septic loosening.

If prosthetic joint infection is suspected, synovial fluid must be aspirated for bacterial analysis, under strict aseptic conditions. Treatment usually requires the surgical removal of all the prosthetic components. Rarely, early-onset infections can be eradicated by debridement and a long course of parenteral antibiotics. Patients with late-onset infection will most often require removal of the prosthesis, extensive debridement and a later replacement arthroplasty. Patients at high risk or those refusing replacement arthroplasty are treated with long-term antibiotics.

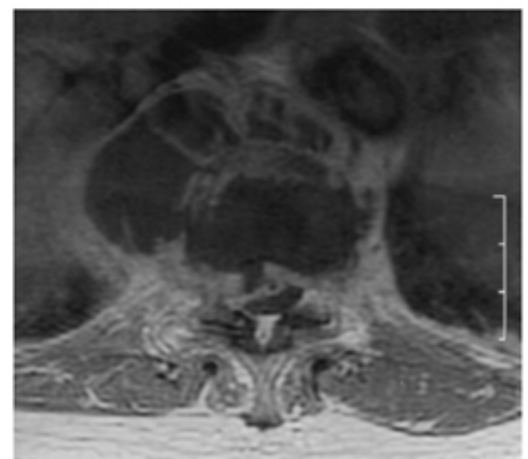
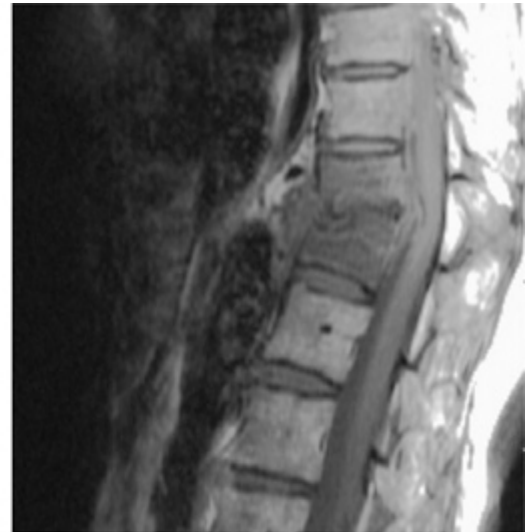
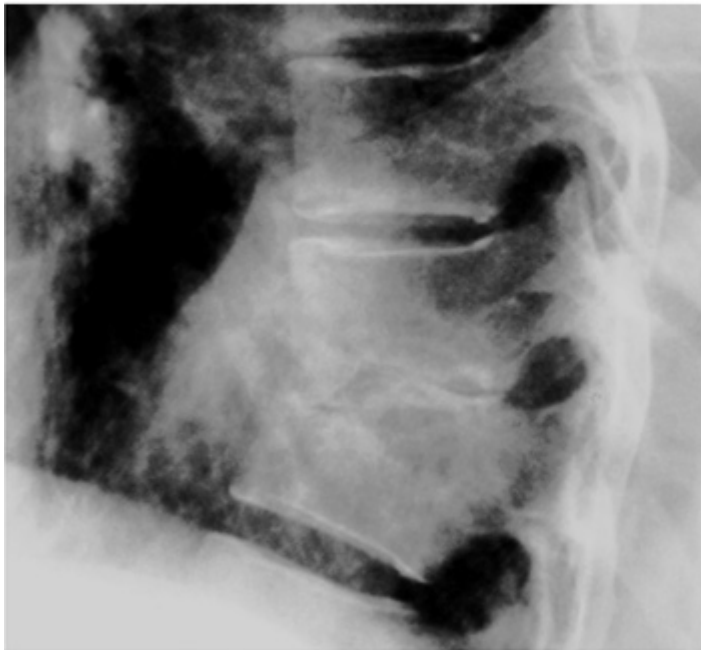
2.3 Spondylodiscitis

Estimates of its prevalence range from 4 to 24 per million a year in developed countries. Most often pathogens infect the spine by haematogenous spread, rarely through direct inoculation or spread from contiguous tissues. Overall, the pathogens responsible for spondylodiscitis are the same as those for septic arthritis (bacteria in the majority of cases, namely *Staphylococcus aureus*, streptococci, enterobacteriaceae, etc.), but the prevalence of tuberculosis is also high, accounting for 10–40% of spondylodiscitis. Infections due to fungi are rare. Pyogenic spondylodiscitis affects preferentially the lumbar spine, followed by the thoracic and cervical spine. In contrast, tuberculosis most often affects the thoracic spine, and more often involves several vertebral bodies. Clinical features of pyogenic spondylodiscitis include moderate to severe back pain progressing over a short period of time, which is typically present or worse at night, and sometimes associated with fever. Patients with tuberculosis spondylodiscitis usually present with slow-onset back pain with weight loss, aesthenia and night sweats. In both the scenarios, neurological symptoms may be present, depending on extension of the infectious process into the spinal cord or spinal nerve roots.

On clinical examination, a marked stiffness of the spine in the frontal and sagittal planes is usual. Imaging features of spondylodiscitis are subchondral radiolucency, erosions and loss of definition of the endplate and loss of disc height. A paravertebral soft tissue mass, particularly within the psoas muscle, is frequently seen with tuberculous spondylodiscitis. MRI is the preferred choice for radiological diagnosis of spondylodiscitis because it provides anatomical information particularly relating to the epidural space and spinal cord. The characteristic changes consist of decreased signal intensity from disc and adjacent vertebral bodies on T1-weighted images with gadolinium enhancement, and increased signal intensity on T2-weighted images. Presence of large paraspinal abscesses is highly suggestive of tuberculosis infection (figure 6). Microbiological investigations include blood cultures and above all a percutaneous biopsy for culture and histology of the infected disc or vertebral body. The principles of treatment for septic spondylodiscitis are identical to those for septic arthritis i.e, appropriate antibiotic therapy, initially parenterally (except for tuberculosis) and then orally, for a total duration of 8–12 weeks. The treatment regimen for tuberculosis is isoniazid and rifampicin, with pyrazinamide and ethambutol for the first 2 months, followed by isoniazid and rifampicin for a total duration of 10–12 months. Whatever the pathogen, bed rest for about 2 weeks is important to prevent spinal deformity, which should be

followed by immobilisation in a corset. Search for a portal entry is of course mandatory. Indication for surgical intervention is mainly based on the presence of compression of neural elements.

Figure 6 Tuberculous spondylodiscitis in a 28-year-old man. X-Ray and MRI of the spine (T1-weighted images). Collapse of a vertebral body with marked erosive changes involving anterior and inferior portion of adjacent bodies. MRI shows discitis associated with epiduritis and soft tissue masses.



2.4 Reactive arthritis (ReA)

Classical ReA belongs to the family of spondyloarthritides, which share features such as inflammatory low back pain, oligoarthritis and extra-articular symptoms. There is no universal agreement on the classification and diagnostic criteria for reactive arthritis. The disease was originally defined as arthritis developing soon after, or during an infection elsewhere in the body, without microorganism entering the joint as viable bacteria. Though the presence of microbial antigenic material, even replicating microbes, has been demonstrated in the joints of some patients with typical ReA microbial cultures are negative. The term 'Reiter's syndrome', an old synonym for ReA, was removed for historical reasons. In 1999, the 4th International Workshop on ReA discussed the use of the term ReA and proposed that it should be used only if the clinical picture and the microbes involved are associated with HLA-B27 and spondyloarthritis, whereas the term 'infection-related arthritis' is used for all other

arthritis related to, or associated with, infections (Braun et al, 2000). Preliminary classification criteria were proposed by the workshop (box 3). These criteria can be used in decision-making, although their use in clinical practice is limited by practical problems in acquiring synovial tissue samples for immunohistology and PCR.

Box 3 Preliminary classification criteria for reactive arthritis

Major criteria

1. Arthritis, with two of three of the following findings
 - Asymmetric
 - Monoarthritis or oligoarthritis
 - Affecting predominantly the lower limbs
2. Preceding symptomatic infection, with one or two of the following findings
 - Enteritis (diarrhoea for at least 1 day, 3 days to 6 weeks before the onset of arthritis)
 - Urethritis (dysuria or discharge for at least 1 day, 3 days to 6 weeks before the onset of arthritis)

Minor criteria, at least one of the following

1. Evidence of triggering infection
 - Positive urine ligase reaction or urethral/cervical swab for *Chlamydia trachomatis*
 - Positive stool culture for enteric pathogens associated with reactive arthritis
2. Evidence of persistent synovial infection (positive immunohistology or PCR for *Chlamydia*)

Exclusion criteria

- Other causes for acute arthritis

Definition of reactive arthritis

- Definite reactive arthritis: both major criteria and a relevant minor criterion
- Probable reactive arthritis: both major criteria, but no relevant minor criteria

or

- Major criteria 1 and one or more of the minor criteria

Modified from Braun et al, *J Rheumatol* 2000;**27**:2185–92.

2.4.1 Triggering infections

Microbes associated with reactive arthritis are usually Gram-negative bacteria, mostly facultative or obligatory intracellular organisms. The primary focus of infection is through the mucosal membrane, usually in the gut or in the urogenital tract (box 4).

Box 4 Microbial infections associated with the development of reactive arthritis**Enteric bacteria**

- *Salmonella** (various serovars)
 - *S. typhimurium*
 - *S. enteritidis*
- *Shigella**
 - *S. flexneri*
 - *S. dysenteriae*
 - *S. sonnei*
- *Yersinia**
 - *Y. enterocolitica* (especially O:3 and O:9)
 - *Y. pseudotuberculosis*
- *Campylobacter**
 - *C. jejuni*
 - *C. coli*
 - *C. lari*
 - *C. fetus*
- *Clostridium difficile* *
- *Giardia lamblia*
- *Escherichia coli* O157

Bacteria causing urethritis

- *Chlamydia trachomatis* *
- *Mycoplasma genitalium* #
- *Ureaplasma urealyticum* #
- *E. coli*

Bacteria causing respiratory infection

- *Chlamydia pneumoniae*
- *Campylobacter pneumonia*

* HLA B27 associated. #Cause urethritis, but the role in reactive arthritis still being discussed

The classic microbes in the gastrointestinal tract causing ReA include yersinia, salmonella, shigella and Campylobacter jejuni. Originally, Shigella flexneri was the only shigella species known to be associated with reactive arthritis, but according to a large epidemiological survey, all species of shigella can trigger reactive arthritis (Hannu et al, 2006*). Other less frequently diagnosed infections in association with reactive arthritis include Campylobacter lari, Chlamydia psittacii and Clostridium difficile. Chlamydia pneumoniae, a respiratory pathogen, may be involved in about 10% of patients with reactive arthritis. Bacteria belonging to the normal gut flora (such as Escherichia coli) have only occasionally been connected with reactive arthritis. However, enteritis caused by enterotoxigenic E. coli O157 has been increasingly implicated with the development of reactive arthritis (Townes et al, 2008; Rohekar and Pope, 2009).

Chlamydia trachomatis is by far the most common cause of genital infection and also the most common triggering infection for reactive arthritis. Of the other microbes causing urethritis, *Neisseria gonorrhoea* probably does not trigger true reactive arthritis, though the infection is well known to cause bacteraemic and septic arthritis (see above). Infection with *Mycoplasma genitalium* and *Ureaplasma urealyticum* is connected with urethritis, but their role as an independent trigger for ReA (in the absence of chlamydia infection) is still discussed.

2.4.2 Epidemiology of reactive arthritis

The annual incidence of reactive arthritis varies from country to country, but in epidemiological studies, it has been reported as 1–30/100 000, *Chlamydia trachomatis* and enterobacteriaceae playing an equal aetiological role. *Campylobacter* has recently been recognised as one of the most important infections to cause gastroenteritis in the Western world, where shigella infections are uncommon and usually imported from the developing world. (Hannu et al, 2006*; Townes et al, 2008).

2.4.3 Genetic component in reactive arthritis

Genetic factors influencing susceptibility partially explain the reason why only 1–15% of infected subjects develop reactive arthritis. In hospital-based series, about 60–80% of patients have HLA-B27, the presence of which is associated with a more severe arthritis and occurrence of extra-articular features. It also predicts a prolonged disease. In studies of defined outbreaks or in epidemiological surveys at population level, the picture is different. The disease is usually mild, oligoarticular or polyarticular, and there is only a slight or no increased frequency of HLA-B27 (Leirisalo-Repo, 2005a).

2.4.4 Pathogenesis of reactive arthritis

The classic bacteria capable of triggering reactive arthritis are Gram-negative obligate or facultative intracellular aerobic bacteria with a lipopolysaccharide-containing outer membrane. They are invasive and cause primary infection of gastrointestinal mucosa (enteric pathogens) or urogenital mucosa (*Chlamydia trachomatis*). The invasiveness of the bacteria is probably not contributed to by host genetic factors (HLA-B27), but there is abundance of evidence in favour of the hypothesis of an impaired elimination of the microbes in the infected host. In patients with reactive arthritis, bacterial antigens seem to disseminate in the body, and chlamydia, yersinia, salmonella and shigella antigens have been detected in the synovial fluid or in synovial tissue. Yersinia DNA and RNA as well as chlamydial DNA and RNA have been detected by sensitive techniques in the joints, but also in some asymptomatic control subjects. There is increasing evidence that *Chlamydia trachomatis* can persist in the host for years. Furthermore, recent studies have shown that patients with chronic seronegative oligoarthritis/polyarthritis, with a diagnosis of chronic spondyloarthritis, harbour chlamydia antigens in synovial

tissue and peripheral blood at a higher frequency than in control subjects with osteoarthritis (Carter et al, 2009*).

After invasion via the mucosal route, the microbes persist either in the epithelium or within associated lymphoid tissues, liver and spleen. The viable organisms or bacterial antigens are disseminated to the joint, causing a local inflammatory response. A CD4+ T-cell response to the invading micro-organism is readily detected in the joint and may drive the arthritic process, supported probably also by a CD8+ T cell response. It is possible that the acquired immune response to the organism may be inadequate in ReA, and favour the persistence of the microbes/microbial antigens and contribute to the poor elimination of the antigens in the host (Gaston and Lillicrap, 2003*).

While HLA-B27 is not required for the development of reactive arthritis, its presence contributes to the severity and chronicity of the disease. The role of HLA-B27 in this process has been discussed, and one of the early hypotheses was a cross-reaction between microbial structures and HLA-B27 – “molecular mimicry”, or that HLA-B27 itself might be a target of the immune response. Currently the molecular mimicry hypothesis has not been proven, and not found when specifically sought, but remains a possibility. Alternatively, the persistence of microbial structures in the host might be explained by an impaired elimination of the microbes by deficient cytokine production which might in turn be related to unusual characteristics of HLA-B27. These views assume that the role of HLA-B27 in ReA is similar to its role in ankylosing spondylitis.

2.4.5 Clinical symptoms and diagnosis

2.4.5.1 Symptoms

There is usually a delay of 1–6 weeks from the start of infection to the onset of arthritis. In about 10–25% of cases, the triggering infection can be asymptomatic. This is especially observed with *Chlamydia trachomatis*. Individuals who are HLA-B27+ have a higher risk of contracting ReA following a triggering infection, but the incidence of B27 positivity amongst individuals who develop ReA after particular infections (e.g. outbreaks of gastrointestinal infection due to contaminated foodstuffs), varies widely. The patients are usually young adults, with a mean age of 30–40 years; in children the disease is uncommon and usually associated with gastroenteritis. Male and female patients have a similar risk for the development of reactive arthritis induced by gastrointestinal infection, while reactive arthritis triggered by *Chlamydia trachomatis* is more frequently diagnosed in male patients.

Patients typically have asymmetrical oligoarthritis, often in large joints of the lower extremities (figure 7). However, about 50% of patients have arthritis also in upper limbs. The disease can also manifest as a mild polyarticular form of arthritis in small joints. Besides arthritis, patients may have dactylitis (figure 8). Patients often have extra-articular inflammatory symptoms and signs (table 4). Enthesitis or bursitis can occur as well as

other extra-articular features, common to other spondyloarthritides. They include eye symptoms (conjunctivitis, and less commonly acute anterior uveitis), various skin symptoms (figure 9), and occasionally onycholysis in prolonged or chronic cases, resembling that seen in psoriasis (figure 10). Carditis is rare, but heart conduction disturbances can be seen occasionally. Urethritis can be a manifestation of infection, especially due to *Chlamydia trachomatis*, but it can also be sterile and occur in reactive arthritides triggered by enteric pathogens. *Salmonella* can also be isolated from urine, although this is very uncommon. About 30% of patients have acute inflammatory low back pain, typically worse during the night, radiating to the buttocks (Leirisalo-Repo, 2005a).

Figure 7 Reactive arthritis involving left ankle, along with dactylitis of the 5th toe. (Source: Cofer, <http://www.lecofer.org>.)



Figure 8 Dactylitis of the left fourth toe. (Courtesy of CRI (Club Rhumatismes et inflammation, <http://www.cri-net.com>). Collected by Professor Daniel Welding and Professor René-Marc Flipo.)



Figure 9 Keratoderma blenorrhagica. (Courtesy of CRI (Club Rheumatismes et inflammation, <http://www.cri-net.com>). Collected by Professor Daniel Welding and Professor René-Marc Flipo.)



Figure 10 Nail changes (onycholysis) in a patient with chronic reactive arthritis.**Table 4 Clinical features of acute reactive arthritis in a hospital series**

Clinical features	Range*
Number of joints, range	1–24
Low back pain, range (%)	2–67
X-ray sacroiliitis, range (%)	11–20
Urethritis, mean, range (%)	4–93
Conjunctivitis, range (%)	6–78
Iritis, range (%)	6–17
Skin lesions, range (%)	4–14
- Erythema nodosum	
- Pustules	
- Keratoderma	
- Circinate balanitis	
Heart conduction disturbances	<1%
Duration of arthritis, range (months)	1–30
Chronic course (>12 months), range (%)	0–30
HLA-B27+, range (%)	0–94

*Range from several studies reported in the literature.

2.4.5.2 Laboratory diagnosis

The diagnosis of reactive arthritis relies, besides the typical clinical picture, on demonstration of the triggering infection, such as isolation of the microbe or demonstration of antibodies against the microbes. During the acute phase of enteric infections, isolation is usually possible from the stools. However, by the time arthritic complications appear, the patient may have already recovered from the gastroenteritis and the microbe may no longer be detectable, though stool cultures can be positive for up to a month after acute infection. The

laboratory diagnosis is sometimes dependent on serodiagnosis, but unfortunately, there are no international standards for such tests, and the techniques used vary greatly (Hannu et al, 2006*).

Urethritis can be a sign of local infection or an inflammatory, 'reactive' symptom. Genital infections are frequently asymptomatic. Therefore, a high degree of suspicion for chlamydia is relevant for the diagnosis of reactive arthritis and should prompt Chlamydia trachomatis detection in the urogenital tract. Search for chlamydia in the first portion of the morning urine by PCR is currently the preferred test. It is more convenient than a urogenital swab and the results are comparable.

The use of serology for the diagnosis of infections with Chlamydia trachomatis is hampered by a relatively high prevalence of positive antibodies among normal subjects and by a possible cross-reactivity with antibodies directed against Chlamydia pneumoniae. Determination of IgG antibodies is not sufficient, but this should be combined with tests for IgM and IgA antibodies. Positive serology alone without a history of a urogenital tract infection does not suffice to make a definite diagnosis of chlamydia-induced reactive arthritis.

In about 60% of patients with a typical clinical picture of reactive arthritis, evidence of previous infection can be detected either by serology or by cultures from urogenital or stool samples.

Based on hospital series, the occurrence of HLA-B27 has been reported to be as high as 90% but is considerably lower or not raised at all in patients with mild arthritis. Therefore, the use of HLA-B27 as a diagnostic tool is not recommended. If the clinical picture does not strongly favour reactive arthritis, the post-test probability of the diagnosis, conferred by HLA-B27 detection is low.

ESR and CRP are usually raised. Synovial fluid leucocyte count is between 2 and $60 \times 10^9/L$. Other rheumatic conditions, such as Lyme arthritis, gout, early RA starting exceptionally as arthritis of a large joint, viral arthritides and even osteoarthritis, should be excluded on the basis of the clinical picture and/or by relevant laboratory tests.

2.4.6 Treatment

2.4.6.1 Treatment of the triggering infection

All patients with acute Chlamydia trachomatis infection should have routine treatment (eg, azithromycin 2 g as single dose treatment, with partners also treated concurrently). Uncomplicated enteritis preceding reactive arthritis is not an indication for treatment with antimicrobial agents. However, if a patient has had reactive arthritis previously, the option for treatment of uncomplicated enteritis may be clinically justified. Prolonged treatment with antibiotics does not shorten the duration of continuing reactive arthritis triggered by enteric infection. In a prospective, double blind clinical trial comparing duration of doxycycline for Chlamydia trachomatis-induced ReA, prolonged treatment with a 4-month regime was not superior to a short-term 10 days

therapy. (Putschky N, et al 2006). In patients with acute reactive arthritis triggered by *Chlamydia trachomatis*, a 3-month course of tetracyclines may be of benefit. Interestingly, prolonged (6 months) administration of a combination of oral antibiotics (azithromycin + rifampicin or doxycycline + rifampicin for 6 months) in the treatment of chronic arthritis in patients with evidence of persisting chlamydia infection has recently been shown to be effective (Carter et al, 2010*).

2.4.6.2 Treatment of arthritis

The use of NSAIDs, often in full dose, is usually of major benefit. Local glucocorticoid injections can be given and are usually also of benefit in patients with monoarticular or oligoarticular disease, as is usually the case. Enthesopathy also responds to local glucocorticoid injections. Systemic use of glucocorticoids is indicated if the patient is bedridden due to severe polyarthritis, there is high systemic inflammation, the patient is febrile, or, in the rare case of the patient having carditis/atrioventricular conduction disturbances. The patients often need a prednisone/prednisolone dose of 20–40 mg/daily at the start. For spinal pain, NSAIDs with long half-life are preferred by the patient. As the arthritis usually affects joints of the lower extremities, physiotherapy is important to reduce pain, prevent muscular atrophy and prevent loss of range of motion. This is especially important in the case of knee synovitis. Early mobilisation, muscle isometric contractions and partial weight bearing can be started immediately, followed later by active exercise.

Effect of antibiotics on the development of acute arthritis. Although no controlled studies exist, early treatment of the infection with antibiotics, before the arthritis has had time to develop, might prevent the arthritis. However, once arthritis is established, the introduction of antibiotics, except possibly in the case of chlamydia-induced arthritis, does not modify the course of the disease.

When are disease modifying antirheumatic drugs indicated? Methotrexate is useful in peripheral arthritis, especially when the symptoms tend to become subacute or chronic. Sulfasalazine in a dose of 2000mg per day has been shown to be significantly effective as compared to placebo in patients with ReA unresponsive to NSAID therapy (Clegg et al 1996). Sulfasalazine is also effective in chronic reactive arthritis. Biological agents are a new class of drugs shown to be effective in chronic HLA-B27-associated diseases such as in ankylosing spondylitis, chronic spondyloarthritis and psoriatic arthritis. They have been used in single cases of reactive arthritis with severe acute or chronic disease resistant to conventional treatments, with major responses and without any evidence of relapse of the background infection.

2.4.7 Outcome

About 50% of patients recover from reactive arthritis within the first 6 months with the above-mentioned treatments. The outcome is usually good. A prolonged (>1 year) extension of the acute arthritis occurs in 15–20% of patients. After the acute episode, mild joint pain or enthesopathy is common. Also, one-third of patients

have occasional attacks of low back pain. During the following 10–20 years, depending on the triggering infection and on the follow-up time, chronic arthritis is seen in 2–18%, sacroiliitis in 14–49%, and ankylosing spondylitis in 12–26% (Hannu et al, 2006*). Patients with reactive arthritis triggered by urogenital infection seem to be more vulnerable to recurrent urethritides and, consequently recurrent episodes of arthritides. The development of ankylosing spondylitis is more common in such patients than in those with previous reactive arthritis triggered by enteric infections.

2.5 Acute rheumatic fever and post-streptococcal arthritis

Streptococcal sore throat (caused by group A β -haemolytic streptococci) can be complicated by the development of acute rheumatic fever, one of the five major manifestations of which is migratory polyarthritis. The diagnostic criteria of rheumatic fever (the Jones criteria) were last updated in 1992 (Guidelines for the diagnosis of rheumatic fever, 1992) (table 5). According to these criteria, a patient with streptococcal infection followed by arthritis as the only major manifestation, should have at least two other minor manifestations for the diagnosis. Acute rheumatic fever is nowadays a rare disease in developed countries, but is still a ~~major~~ concern in the developing countries.

Table 5 Revised Jones criteria for acute rheumatic fever (Reproduced with permission from Guidelines for the diagnosis of rheumatic fever, JAMA 1992;268:2069–73)

Major manifestations	Minor manifestations	Laboratory findings
Carditis Polyarthritis	Fever Arthralgia	Raised acute-phase reactants: (a) C-reactive protein (b) Erythrocyte sedimentation rate
Chorea	Previous rheumatic fever or rheumatic heart disease	Prolonged P–R interval in ECG
Erythema marginatum Subcutaneous nodules		Supporting evidence of preceding streptococcal infection: (a) Increased ASLO or other streptococcal antibodies (b) Positive throat culture for group A-haemolytic streptococci (c) Recent scarlet fever

Acute rheumatic fever can be suspected in the presence of two major manifestations, or one major and two minor manifestations, if the patient has evidence of preceding streptococcal infection, and other causes of acute arthritis have been ruled out.

Post-streptococcal reactive arthritis In some patients acute monoarthritis or oligoarthritis is preceded by group A streptococcal pharyngitis as the only manifestation without other features of rheumatic fever. This usually develops within 14 days after streptococcal pharyngitis; fever and scarlatiniform rash are often present during the acute phase of pharyngitis, but are absent by the time the arthritis appears. There is a bimodal age

distribution, with a peak at 8-14 years and another at 21-37 years. Contrary to the arthritis of acute rheumatic fever, which is migratory and responds rapidly to acetyl salicylic acid, the arthritis in the post-streptococcal reactive form is prolonged. The patients lack other manifestations of acute rheumatic fever. Some studies have shown that during a later follow-up, some of the patients with post-streptococcal arthritis have had signs of chronic rheumatic heart disease, making the diagnosis of the acute phase questionable. However, a study from the Netherlands showed no increased risk for valvular heart disease during a median follow-up of 8.9 years (van Bommel et al, 2009). Evidently, post-streptococcal reactive arthritis is not a single entity but a spectrum of heterogeneous group of diseases with varying manifestations ranging from acute rheumatic fever like-illness to a form which is simply a post-infectious arthritis A, without satisfying other criteria for acute rheumatic fever. Post streptococcal arthritis is not associated with HLA-B27, does not have the typical extra-articular features of ReA, and is not therefore a true ReA in the spondyloarthritis spectrum.

The treatment of post-streptococcal reactive arthritis consists of eradication of the streptococcus from the throat (with, for example, penicillin as used in the treatment of acute streptococcal tonsillitis) for 10 days. A prolonged use of antibiotics is not of major help and is not recommended, unlike in rheumatic fever, although no controlled studies are available to prove this recommendation. The arthritis can be managed with NSAIDs, and in the case of observed synovitis, intra-articular glucocorticoid injections can be used. If the patient has a severe polyarticular disease, use of prednisone/prednisolone orally, starting with 20–40 mg/day and tapering the dose according to the clinical response is usually sufficient.

2.6 Lyme arthritis

2.6.1 Epidemiology of Lyme disease

Lyme disease (Lyme borreliosis) is a tick-borne infectious disease causing complex clinical symptoms. The infection is caused by *Borrelia burgdorferi* (most prevalent in the USA), *B. garinii* and *B. afzelii*. The risk of infection is variable in geographically different areas, depending on the density of infected ticks, their feeding habits and animal hosts. In Europe, Lyme borreliosis is most common in forests. It has spread into the whole of Europe, except for the warmest and dry areas in the south and the coldest areas in the north. The annual incidence of Lyme disease in the USA is 8/100 000 and in central Europe and in Scandinavia varies from 0.3 to 155/100 000 (Schnarr et al, 2006*).

2.6.2 Clinical features of Lyme disease

The clinical features of Lyme disease are usually divided according to the duration of the disease (acute vs chronic). This difference is often arbitrary. History and clinical symptoms—for example, skin changes, might help in the diagnostic investigation of a patient with musculoskeletal symptoms (table 6). The distribution of clinical features is slightly different between patients from North America and from Europe. Neuroborreliosis is more

common in European patients, while severe and chronic arthritis is more frequently described in North American patients. This is probably due to differences in the bacterial species (see table 6).

Erythema migrans (figure 11) is the hallmark of the primary infection, and is the most common finding, in 70% of patients. Erythema migrans is the only manifestation of Lyme borreliosis that can be reliably diagnosed by clinical examination. About half of patients develop also signs and symptoms of systemic infection (malaise, fatigue, headache, arthralgia, myalgia, low-grade fever and lymphadenopathy). The infection is also readily disseminated, at least in the North American patients.

Acute neuroborreliosis develops in about 15% of patients within weeks to months after the primary infection. Acute carditis is uncommon (occurring in 5% of patients) but it might be the presenting symptom. Borrelia infection can also cause eye inflammation (conjunctivitis and uveitis, most commonly posterior uveitis).

If untreated, borrelia infection may persist for months to years. It can manifest in the skin as chronic atrophic changes (acrodermatitis chronica atrophicans, figure 12), occurring in European patients and caused by *B. afzelii*. The patient may also have neuropathic pain and arthritis in the affected areas. Chronic neuroborreliosis is rare. It can manifest as chronic encephalitis, encephalomyelitis, peripheral neuropathy or cerebral vasculitis. Cognitive disturbances, radicular pain and distal paraesthesia may occur.

Figure 11 Erythema migrans after a tick bite. Copyright Dr Raimo Suhonen (© R Suhonen, <http://www.ihotauti.net>).



Table 6 Clinical features of borreliosis with respect to geographical areas. (Adapted from Schnarr et al, Best Pract Res Clin Rheumatol 2006;20:1099–118*)

Organ system	Clinical symptom	Europe and Asia (<i>B. afzelii</i> , <i>B. garinii</i> , <i>B. burgdorferi</i> ss)	North America (<i>B. burgdorferi</i> ss)
Skin:			
Acute phase	Erythema migrans	Spreading slowly, less inflammation, haematogenous dissemination less common	Local distinct inflammation, systemic symptoms common, possibly frequent haematogenous dissemination
	Lymphocytoma	Rare, predominantly in children	Not reported
Chronic phase	Acrodermatitis chronica atrophicans	Caused primarily by <i>B. afzelii</i>	Rare
Nervous system:			
Acute phase	Meningopolyradiculoneuritis Cranial nerve palsy	Severe radicular pain, meningitis, caused primarily by <i>B. garinii</i>	Meningitis, less prominent radiculoneuritis
Chronic phase	Encephalitis Encephalomyelitis Cerebral vasculitis Peripheral neuropathy	Subtle sensory neuropathy within areas of acrodermatitis Severe encephalomyelitis, spasticity, cognitive abnormalities	Subtle sensory neuropathy without acrodermatitis Encephalopathy, cognitive disturbance
Heart:			
Acute phase	Carditis	Atrioventricular block and subtle myocarditis	Atrioventricular block and subtle myocarditis
Chronic phase	Dilated cardiomyopathy	Described	Not reported
Musculoskeletal:			
Acute phase	Arthritis	Oligoarthritis (less frequent) Less intense joint inflammation	Oligoarthritis (more frequent) More intense joint inflammation
Chronic phase	Arthritis	Persisting arthritis less frequent	Treatment-resistant arthritis in about 10% of patients
	Myositis		
	Bursitis		

Figure 12 Atrophic skin changes in the right hand (Acrodermatitis atrophicans) in a patient with previous borrelia infection. Copyright Dr Raimo Suhonen (© R Suhonen, <http://www.ihotauti.net>).



2.6.2.1 Lyme arthritis

In the USA, where *B. burgdorferi sensu stricto* (ss) is the main infecting agent, arthritis is the most common manifestation of borreliosis. Arthritis can occur early or late after the infection. It is usually monoarticular or oligoarticular, affects large joints (knee, ankle, elbow) and runs a fluctuating course with remissions and relapses. Dactylitis and bursitis have been occasionally described, but sacroiliitis is not a feature. Signs of systemic inflammation are usually mild, and rheumatoid factor is usually absent. Synovial fluid shows active inflammation with WBC counts up to $100 \times 10^9/L$. Polymorphonuclear cells are predominant.

The prognosis of Lyme arthritis is usually good; even when untreated, about 10% of patients recover each year. Erosions are rare. After appropriate antibiotic therapy, 90% of patients recover. A small proportion of patients do not respond to antibiotic therapy. In the USA, about 10% of patients belong to this group. Among European patients, there are fewer such cases.

2.6.2.2 Diagnosis of Lyme disease

Patient history and clinical signs and symptoms, especially the occurrence of erythema migrans are important in the clinical diagnosis. Serology does help in the decision-making in more complicated disease. Borrelia antibodies of IgM class start to rise 2–4 weeks after infection, peak within 6–8 weeks and then production is

switched to IgG class. IgM and IgG class antibodies can persist in some patients for many years, even after treatment. A highly sensitive ELISA test should be used in screening, and if the result is positive or borderline, the result should be confirmed by a specific immunoblot test. Especially in European patients, the test should cover all the relevant species (*B. burgdorferi* ss, *B. afzelii*, and *B. garinii*). After clinically successful treatment, there is no need to control the antibody levels.

Culture of borrelia in skin biopsy specimens and in plasma can be performed; culture of the synovial fluid is rarely successful. Borrelia DNA has been detected by PCR in skin biopsy specimens, cerebrospinal fluid, synovial fluid, blood and urine. It is not a routine method, but can be used as an aid in the differential diagnosis of synovitis. The detection of borrelia by PCR is highly specific, but sensitivity in the synovial fluid at best ~85%.

2.6.2.3 Treatment of Lyme arthritis

Lyme borreliosis is treated with antibiotics, tailored to the clinical picture of the disease. Positive antibodies in an asymptomatic subject are not an indication for antibiotics. Erythema migrans can be treated with amoxicillin 500–1000 mg three times/day or with doxycycline 200 mg/day for 14–21 days. For a child or a pregnant patient, amoxicillin (500–1000 mg three times/day), azithromycin (first day 1000 mg, then 500 mg/day for 5–10 days), or cefuroxime axetil (500 mg twice a day for 14–21 days) (Schnarr et al, 2006*; Hytönen et al, 2008) are recommended. The prognosis of erythema migrans is good.

For facial palsy, the drug of choice is doxycycline, and alternative options are ceftriaxone, cefotaxime or penicillin G, as above. For other forms of neuroborreliosis, carditis or other organ involvements, the first choice is ceftriaxone 2 g/day for 14 days. Alternative drugs are cefotaxime and penicillin G (Schnarr et al, 2006*). For the treatment of European patients with neuroborreliosis, oral doxycycline has been shown to be as efficient as intravenous ceftriaxone.

For arthritis or acrodermatitis, the treatment options vary. Ceftriaxone 2 g/day for 14–21 days or doxycycline 200 mg/day for 1–2 months can be used (Schnarr et al, 2006*; Hytönen et al, 2008). An alternative choice is amoxicillin as above, cefotaxime 2 g three times a day IV or penicillin G 5×10^6 IV four times a day, for 14–21 days (Schnarr et al, 2006*). The arthritis often settles within 3 months from the onset of treatment. If the arthritis persists, another course with unrelated antibiotics can be used (Puéchal and Sibilia, 2009). Besides antibiotics, patients need analgesics and anti-inflammatory drugs. The administration of systemic or intra-articular glucocorticoids is controversial, because they may impair the eradication of the spirochete (Steere and Angelis, 2006). Physiotherapy is often of benefit, especially for knee synovitis. If the arthritis persists after adequate antibiotic therapy, synovectomy can be considered. Use of disease-modifying antirheumatic drugs, such as hydroxychloroquine, sulfasalazine and methotrexate, is an option in a resistant case with active joint inflammation (Franssila and Hedman, 2006*). A consensus has emerged that repeated courses of antibiotic therapy are not indicated for persistent subjective symptoms, such as musculoskeletal pain following Lyme

disease (Puéchal and Sibilia, 2009). The patient should be thoroughly examined for other medical conditions that might explain the symptoms, and treated accordingly.

3 Viral causes of arthritis

A large number of viruses are well-recognised causes of inflammatory arthritis. Acute onset polyarthritis should always raise the suspicion for viral arthritis. Over the past few years the epidemiology of viral arthritis has swiftly changed, with several epidemics of arbovirus related arthritis being increasingly recognized in different parts of the globe. With increase in the frequency of trans-continental travel, these viruses have transcended geographical boundaries and have affected various populations.

3.1 Parvovirus

Human parvovirus B19 is a small non-enveloped single-stranded DNA virus, which ~~only~~ generally replicates in erythrocyte precursors. Transmission of infection occurs via a respiratory route, through blood products, and vertically from mother to foetus. About half of the infections are asymptomatic. Parvovirus B19 is a common viral infection affecting predominantly children, in whom it causes erythema infectiosum ('Fifth disease'), a febrile exanthema characterised by a 'slapped cheek' rash with or without joint symptoms. The rash is typical, and can be easily diagnosed. In adults, its manifestations are more protean, including symptoms such as aplastic anaemia, thrombocytopenia, pancytopenia, hepatitis, myocarditis, myositis and symptoms of the central nervous system. Arthritis or arthralgia occurs in about 8% of juvenile and 60% of young adult patients (Franssila and Hedman, 2006*). During pregnancy, the infection can cause hydrops fetalis and death of the foetus.

3.1.1 Clinical picture and diagnosis of parvovirus arthritis

Children generally present with an asymmetric large-joint oligoarthritis, commonly the knee. Adults have a rheumatoid arthritis like symmetrical, small joint predominant arthritis involving the small joints of hands. (Marks et al, 2016). The arthritis is more common in female than in male patients. It is transient and usually subsides within 3 weeks, without permanent damage. In about 20% of patients, usually women, the arthritis/arthralgia persists for months. Chronic inflammatory arthritis is rarely seen with parvovirus arthritis. (Danda et al. 2010).

The diagnosis of parvovirus infection is made by serology, where the presence of IgM class parvovirus antibodies indicates an infection within 3 months. As most people have acquired parvovirus infection in childhood, the presence of IgG class antibodies is common and, in the absence of IgM class antibodies, is not of diagnostic aid. The patients can be transiently seropositive for rheumatoid factor, antineutrophil cytoplasmic antibodies and have various autoantibodies, which can make the differential diagnosis between parvovirus arthritis and other arthritides complicated. Sometimes, patients may also have thrombocytopenia, thus resembling systemic lupus erythematosus. The clinical picture of systemic lupus erythematosus and parvovirus infection can be very

similar; furthermore, non-specific anti-parvovirus antibodies can be produced by a patient with established lupus. Parvovirus infection is a rare cause of the development or flare-up of systemic lupus erythematosus. Other autoimmune diseases like rheumatoid arthritis, systemic sclerosis, myositis, vasculitis, juvenile idiopathic arthritis and chronic fatigue syndrome have been described to be triggered by or associated with parvovirus B19 infection, but these ideas lack strong supporting evidence.

Parvoviral B19 DNA has been detected in synovial fluid samples in some patients with early synovitis or with chronic RA. The role of parvovirus in triggering chronic arthritis or autoimmune disease has been discussed for years. It seems, however, that the progression of parvovirus arthritis to chronic RA, systemic lupus erythematosus or vasculitis is extremely rare (Franssila and Hedman, 2006*).

3.1.2 Treatment of parvovirus arthritis

Erythema infectiosum does not usually require any treatment. The arthralgia/arthritis can be treated with NSAIDs, if severe. The prognosis is usually good.

Interestingly, about 50% of both juvenile and adult patients with various rheumatic diseases and positive antiphospholipid antibodies have evidence of persisting parvovirus B19 infection. There are reports of a small number of patients with juvenile arthritis resistant to all previous drugs where the use of intravenous gammaglobulin therapy resulted in loss of parvovirus B19 viraemia and good clinical response.

3.2 Rubella

Rubella virus is a single-stranded RNA-containing virus. The most common manifestation of the infection is rash, preceded about 6 days previously by lymphadenopathy.

3.2.1 Clinical picture and diagnosis of rubella arthritis

Arthritis and arthralgia are uncommon in children and in men, but occur in about 50% of women, soon after the onset of the rash. Symmetrical polyarthritis involving the metacarpophalangeal and proximal interphalangeal joints of hands, followed by wrists, knees, ankles and elbows is common. The arthritis is self-limiting, usually lasting for a maximum of 3 weeks. Sometimes, a prolonged or relapsing course can occur. Rubella infection can be prevented by vaccination with attenuated living rubella vaccines. Vaccination can also induce a similar form of arthritis in women, thought to be due to immune complexes (Franssila and Hedman, 2006*).

The routine laboratory diagnosis is based on the detection of antirubella antibodies in the serum. Detection of antirubella IgM in combination with IgG seroconversion or detection of a rise in rubella-specific IgG in paired serum samples indicates acute infection. Recent primary rubella, remote rubella infection, reinfection and persistent rubella IgM reactivity may be differentiated by measuring rubella-specific IgG avidity (Franssila and Hedman, 2006*).

3.2.2 Treatment of rubella arthritis

Rubella arthritis is usually short-lived and can be managed by symptomatic drugs—for example, NSAIDs. In the rare case of persistent rubella arthropathy, intravenous immunoglobulin therapy may be effective.

3.3 Hepatitis B

HBV is a double stranded DNA virus belonging to Hepadnaviridae family, and well known for its extra-hepatic association. Following transmission vertically, sexually, or through blood-borne contact, about 95% of adults mount an immune response resulting in clearance of the virus. Arthritis in HBV, seen both in the prodromal phase and chronic infection, occurs as a result of formation and deposition of immune complexes containing viral antigens.

3.3.1 Clinical picture and diagnosis

In the acute phase arthritis can be the only presenting feature, occurring as part of serum sickness. Symmetrical polyarthritis, resembling rheumatoid arthritis, affecting small and large joints is the usual manifestation in prodromal phase of infection. Arthritis lasts for days to months, resolving with the onset of jaundice. A quarter of patients with chronic infection complain of joint symptoms, though severe joint damage is uncommon. Association of immune complex deposition syndromes like cryoglobulinaemia and polyarteritis nodosa should be considered in patients presenting with chronic arthritis. Serologic tests for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) IgM are required for diagnosing acute hepatitis B infection. Liver function tests including liver enzymes, direct serum bilirubin, albumin and measurement of international normalized ratio (INR) should be done in all patients. Quantification of HBV DNA gives an estimate of level of infectivity. Chronic active HBV infection is categorized into HBeAg positive and HBeAg negative disease. Rheumatoid factor can be positive in 25% of patients, while C3 and C4 may be low in around 40% of patients due to immune-complex mediated process.

3.3.2 Treatment

A detail discussion on this topic is not within the purview of this chapter. Anti-viral therapies like lamivudine, adefovir, tenofovir and entecavir, and recombinant interferon-alpha and its pegylated form, are the commonly used therapies, which cause suppression of HBV replication. Use of non-biologic DMARDs in HBsAg positive or negative and anti-HBc positive patients may increase the risk of reactivation. In patients with low risk of reactivation non-biologic DMARD usage is relatively safe. Risk of reactivation of HBV during therapy with biologic DMARDs increases. Anti-viral prophylaxis should be considered in patients requiring DMARDs or corticosteroids. (Felis-Giemza et al, 2015). According to the 2012 update of 2008 ACR recommendations for treatment of RA none of the biologic therapies are recommended in untreated chronic hepatitis B or those with treated chronic hepatitis B with Child Pugh class B and higher. (Singh et al, 2012)

3.4 Hepatitis C

HCV is a linear, small size, single stranded RNA virus belonging to the family of *Flaviviridae*. It is a blood-borne virus, which usually gets transmitted as a result of poor sterilization of medical devices and unscreened blood products. Vertical and sexual transmission is also described. HCV is a hepato- and lymphotropic agent, which leads to chronic infection in 70-80% of affected patients. HCV causes arthritis by direct invasion of synovium, autoimmune response to virus in the synovium and immune complex or cryoglobulin deposition.

3.4.1 Clinical picture and diagnosis

Rheumatological manifestations are one of the most frequent extra-hepatic manifestations of HCV. There has been a renewed interest of late in association of HCV with autoimmune diseases like SLE, Sjögren's syndrome, rheumatoid arthritis, polyarteritis nodosa and antiphospholipid syndrome. Arthralgia (mono-, oligo- and polyarticular) is a frequent symptom. HCV related arthritis can have similar presentation as rheumatoid arthritis, thus making it difficult to distinguish both. RF positivity has been noted in 54-80% of patients with HCV-related arthritis, often in high titres. The course of arthritis, however, is less aggressive in HCV patients as compared to RA. Other manifestations include paraesthesia, myalgia, pruritus, sicca symptoms and fibromyalgia. Presence of HCV in a patient with arthritis should raise suspicion of HCV related arthropathy. Serological tests to detect HCV antibodies and molecular tests to quantify HCV RNA remain the mainstay of diagnosis. Identifying the genotype is useful for predicting response and determining duration of interferon therapy.

3.4.2 Treatment

Conservative management with analgesics and NSAIDs is recommended for patients with mild arthritis. Patients not responding to NSAIDs may be initiated on low dose steroid therapy. As there are no consensus treatment guidelines to treat HCV with arthritis, management should be individualized. Ironically, interferon alpha is known to precipitate autoimmune diseases.

HCV infection with concomitant RA

Use of DMARDs is indicated in patients with RA and concomitant HCV infection. A step-wise approach, starting with non-biologic DMARDs, followed by biologic DMARDs in those unresponsive to initial therapy is preferred practice. According to the 2012 ACR update of 2008 recommendations for the use of DMARDs in RA, Etanercept is the recommended biologic for RA with concomitant HCV infection. Methotrexate is contraindicated in all patients with Child-Pugh class A, B or C; Sulphasalazine is contraindicated in patients with Child-Pugh class B or C and Hydroxychloroquine is contraindicated in patients with Child-Pugh class C.

HCV infection with cryoglobulinaemia

A combination of pegylated interferon and ribavirin is the current standard antiviral treatment in this situation. Patients with severe disease seem to benefit with antiviral therapy along with Rituximab. Plasma exchange is useful for rapidly removing cryoglobulins and immune complexes.

HTLV-1 associated arthritis

HTLV-1 is a retrovirus known to cause peripheral, symmetric, polyarthritis involving small and large joints, akin to rheumatoid arthritis. Rheumatoid factor can be positive in these patients. Patients are predisposed to T cell leukaemia.

3.5 Alphavirus arthritis

Alphaviruses belong to a group of arboviruses and share the common feature of transmission by arthropod vectors. Alphaviruses are spherical small RNA-containing viruses with a potential to induce arthritis, fever, fatigue and rash. The spectrum of clinical symptoms associated with alphavirus infections is wide, from severe haemorrhagic symptoms to paraesthesia and glomerulonephritis (table 7).

Table 7 Viruses related to articular symptoms. (Modified from Laine et al, J Int Med 2004;256:457–71)

Virus	Clinical features	Epidemiological area
Chikungunya	Fever, rash, myalgia, arthralgia/arthritis, chronic joint pain, haemorrhagic symptoms, paraesthesias	Africa, India, South East Asia, West Pacific, sporadic in Europe, USA
Mayaro	Fever, rash, myalgia, arthralgia/arthritis, chronic joint pain, haemorrhagic symptoms	South America
O'nyong-nyong	Fever, rash, myalgia, arthralgia/arthritis, chronic joint pain, haemorrhagic symptoms, paraesthesias	Central and East Africa
Barmah Forest	Fever, rash, myalgia, arthralgia/arthritis	Australia
Igbo Ora	Fever, rash, myalgia, arthralgia	Ivory Coast
Ross River	Fever, rash, polyarthritis, chronic arthralgia, paraesthesias, glomerulonephritis	Australia, West Pacific
Sindbis	Fever, rash, arthralgia/arthritis, paraesthesias	Europe, Africa, Australia, Asia, Philippines
- Ockelbo	Fever, rash, arthralgia/arthritis, chronic joint pain, paraesthesias	Sweden, Norway
- Pogosta	Fever, rash, arthralgia/arthritis, chronic arthritis	Finland
- Karelian fever	Fever, rash, arthralgia	Russia
- Dengue	Fever, rash, severe myalgia, polyarthralgia, haemorrhagic symptoms	India, South East Asia, Africa, Latin America
- Zika	Fever, maculopapular rash, muscle aches, arthralgia	Africa, South East Asia, Americas

In Northern Europe, milder forms of disease induced by alphaviruses belonging to the Sindbis group have been described in several countries. In Finland, this mosquito-borne viral disease is called Pogosta disease, in Sweden, Ockelbo disease, and in Russian Karelia it is called Karelian fever.

3.5.1 Chikungunya virus

The most severe form of arbovirus-induced arthritis is caused by Chikungunya virus (CHIKV), belonging to the family *Togaviridae*. Following its initial isolation in Tanzania in 1952 the virus was locally confined and of low intensity. Since 2005, it has caused a large outbreak in the southwest Indian Ocean islands and the infection has spread to India, causing a large epidemic with more than 1.5 million people infected (Taubitz et al, 2007). As tourism is expanding, European and US travellers returning home from these areas have been described with severe arthritis and tenosynovitis caused by the Chikungunya virus (Taubitz et al, 2007). The first cases of CHIKV in the Americas were described in 2013. Chikungunya arthritis has also been described in Europe in patients who have not travelled. CHIKV is globally distributed in over 60 countries and continues to be endemic in Africa, India and several Southeast Asian countries and Latin America.

3.5.1.1 Clinical picture and diagnosis of CHIKV

The clinical picture of Chikungunya virus infection is biphasic. Acute infection (< 10 days) manifests as fever, arthralgia, back pain and headache. Less common clinical features include skin rashes, oral ulcerations, hyperpigmentation and exfoliative dermatitis. Low to high-grade fever lasts for 3-5 days. Symmetrical polyarthralgia involving distal joints, hands, wrists and ankles develops 2-5 days following onset of fever. Peri-articular oedema or swelling can be seen in 32-95% of patients. Oedema of the face and periauricular tissues is characteristic. Generally acute CHIKV infection resolves without any sequelae. Chronic rheumatologic manifestations, including polyarthralgia or arthritis, multiple tendinitis, tenosynovitis, enthesopathies, carpal tunnel syndrome, classical rheumatoid arthritis, cryoglobulinaemia and psoriatic arthritis, however, can occur in a small group of patients. Detection of viral antigen, viral nucleic acid, anti-CHIKV IgM and IgG antibodies and viral culture continue to be the mainstay of diagnostic tests. Anti-CHIKV IgM are elevated after 10 days of infection and remain elevated for 3-6 months. Reverse transcription polymerase chain reaction (RT-PCR) and real time loop-mediated isothermal amplification (RT-LAMP) methods aid in early diagnosis of CHIKV infection. (Mathew AJ et al, 2016)

3.5.1.2 Treatment

Treatment of acute infection is mainly conservative, with analgesics, antipyretics and NSAIDs. After the initial viraemic febrile period is over, low dose steroid with rapid tapering and withdrawal by 4-6 weeks is effective and safe for acute CHIKV infection. Hydroxychloroquine (HCQ) has been reported in few studies to be effective in acute infections. HCQ also has anti-viral properties. However, anti-inflammatory action of HCQ takes months

to act, and hence, its use in such self-limiting disease is controversial. Development of vaccines is still in infancy, and requires testing in clinical trials. DMARDs have been tried in chronic infections, with varied success.

3.5.2 Other alphaviruses

Sindbis virus-induced diseases in Northern Europe typically occur in late summer or early autumn. The incubation time is short (2–10 days), after which the onset of arthritis is usually sudden. The arthritis in Pogosta disease is often oligoarticular (ankle, knee, wrist, fingers, especially metacarpophalangeal joints) and occurs usually in the summer and early autumn. Other features are fatigue and maculopapular rash, often itchy, present in the majority of patients. The rash appears 3–4 days after the onset of illness, and disappears after a few days. Other systemic symptoms include fever, muscle pain, malaise, headache, nausea, and retro-orbital pain. Symptoms common to all alphavirus infections include rhinorrhoea, sore throat, marked lethargy and backache. The arthritis is usually transient with migratory arthralgia in the small joints of hands, feet, wrists and ankles, often accompanied by generalised myalgia. In about half of patients the recovery from arthritis can take more than 1 month, even more than 12 months in few cases, but a complete recovery is the rule (Laine et al, 2004). Men and women are affected with similar frequency. Clinical disease is less common in children, who often have subclinical infection. Some alphavirus infections affecting populations outside Europe (see table 7) can induce petechiae, bleeding and neurological symptoms, but the European Sindbis virus infections are milder.

The diagnosis of alphavirus infection is based on history (travelling in tropical areas, walking in forests in summer/early autumn) or on clinical picture (rash and arthritis) and is confirmed by serology.

Treatment is symptomatic, but acetyl salicylic acid is to be avoided if there is a suspicion of a haemorrhagic disease. Prevention is important by the use of mosquito repellents, mosquito nets in the tropics and appropriate clothing.

3.4 HIV and arthritis

Patients infected with HIV have an increased frequency of musculoskeletal complaints (Reveille and Williams, 2006*). In the pathogenesis of arthritides, direct spreading of HIV to the joints, immune response of the host to the infection and infection of the host with pathogens known to be capable of triggering reactive arthritis, especially in HLA-B27-positive subjects (chlamydia, salmonella, yersinia, shigella, campylobacter), contribute to the development of arthritis in this setting.

There are definite geographical variations in the prevalence and clinical spectrum of musculoskeletal manifestations of HIV infection in reports from different centres. This has been thought to be probably secondary to several factors, such as patient selection, ethnic background, risk factors, stage of HIV infection, use of specific highly active antiretroviral therapy (HAART), among others. Arthralgia occurs in 5% of patients with HIV infection. The musculoskeletal symptoms can be divided into three subgroups: those associated directly

with the HIV infection, those occurring more frequently in HIV-positive individuals, at least partially associated with increased risk of infection, and those as a result of HIV treatment.

Septic arthritis due to the usual infectious agents is not increased in patients with HIV, but musculoskeletal infections due to atypical mycobacteria are increased. Mycobacteria most frequently causing septic arthritis or osteomyelitis include *Mycobacterium avium intracellulare*, *M. kansasii*, *M. haemophilum*, *M. terrae* and *M. fortuitum* (Reveille and Williams, 2006*). These induce systemic infection, and often, infection of several joints or skeletal sites. Cutaneous lesions (nodules, ulcers, draining sinus tracts) occur frequently. These infections occur late in the course of HIV, as do fungal infections, which also can cause septic arthritis. A patient with joints infected with opportunistic infection should be examined for the presence of HIV antibodies.

3.4.1 HIV arthritis

HIV infection can present with a wide variety of musculoskeletal manifestations including arthralgia, painful articular syndrome (self-limiting syndrome lasting less than 24 hours), HIV associated oligoarthritis and ReA like presentation. Acute HIV infection is associated with arthritis, which resembles other viral arthritides. Infective joint complications are also frequently seen in the African patients with AIDS, in whom AIDS is the leading cause of aseptic arthritis (60% of the cases). The disease does not meet the classification criteria for spondyloarthritis. It is typically oligoarticular, predominantly in the lower extremities, and lasts for <6 weeks. Synovial fluid, if obtained for analysis, is non-inflammatory and sterile for bacteria. There is no increased association with HLA-B27, mainly because this HLA type is not present in many African populations. The arthritis is usually self-limiting, and can be treated with NSAIDs. In the more severe forms, low-dose glucocorticoids, hydroxychloroquine or sulfasalazine can be used. Previously, HIV-infected patients often developed spondyloarthritis or severe psoriasis-like skin disease and also psoriatic arthritis. The use of HAART is effective in the treatment of HIV infection and also the associated psoriasis and arthritis.

3.4.2 Reactive arthritis in HIV-infected patients

Reactive arthritis is observed in 5–10%, psoriatic arthritis in 1–6% and undifferentiated spondyloarthritis in 3–11% of patients with AIDS. Clinical features in the phenotypes of arthritides differ between African and Western patients, those in the West having more typical reactive arthritis. The clinical picture is classical of reactive arthritis and spondyloarthritis with oligoarticular pattern, enthesitis and sausage toes/fingers. Mucocutaneous complications (keratoderma blenorrhagica and circinate balanitis) are common. The disease is associated with HLA-B27. Treatment is similar to that for reactive arthritis in general, starting with NSAIDs. In more severe or prolonged disease, sulfasalazine is the recommended drug, but hydroxychloroquine can also be tried. Methotrexate and cyclosporine, owing to their immunosuppressive effect, theoretically might enhance the HIV load, but can be used if the viral load and the number of CD4+ cells are monitored. Skin lesions in reactive arthritis and psoriatic arthritis respond also to etretinate (Reveille and Williams, 2006*). Although biological

drugs are not officially recommended and not indicated for HIV-related diseases, there are some case reports of the use of tumour necrosis factor (TNF)-blocking agents in a patient with severe arthritis/skin disease, with good clinical response and without any major increase in the risk of infections or progression of immunosuppression in the short term.

3.4.3 Arthritis in the HAART era

The availability of HAART has made a great change in the well-being and prognosis of patients infected with HIV. While the complications of HIV infection are effectively suppressed by the treatment, the return of immunocompetent cells has been associated with de novo appearing autoimmune phenomena. A new non-infectious immune reconstitution syndrome has been described in patients receiving HAART. Patients with this syndrome develop an autoimmune disease, mostly presenting as sarcoidosis or systemic lupus erythematosus-like disease, or a non-systemic autoimmune syndrome, usually thyroid disease (Calabrese et al, 2005).

Several other musculoskeletal symptoms are commonly noted. Diffuse myopathy, muscular pain, raised muscle enzyme levels, even rhabdomyolysis, systemic lupus erythematosus, sarcoidosis, osteopenia and osteoporosis, and avascular necrosis of bone have been reported with increasing frequency in patients treated with antiviral drugs. These adverse events have been linked to various treatments, especially protease inhibitors. At the same time, there has been a great shift in the spectrum of associated diseases as compared to patients who have never received HAART. The development of reactive arthritis, psoriasis arthritis and mono/oligo/polyarthritis and myositis have been definitely declining in patients receiving HAART (Calabrese et al, 2005).

4 Role of infections in the aetiology of chronic rheumatic diseases

4.1 Whipple's disease

Whipple's disease is rare, with protean manifestations ranging from arthralgia and malabsorption to neurological symptoms. If untreated, the disease can be fatal. Whipple's disease was first described by George Whipple in 1907 but the first successful culture of the causative bacterium (classified as an actinomycete), *Tropheryma whippelii*, took place nearly 100 years later in 2000. The organism was initially named *Trophynema whippelii* but the name was subsequently changed to *Tropheryma whippelii*. The name comes from Greek words *troph*i (food) and *eryma* (barrier) referring to the malabsorption which is often associated with the disease.

4.1.1 Pathogenesis

There are no valid estimates of the prevalence of Whipple's disease. Only about 1000 cases have been reported, mostly in middle-aged white men, but considering the assumed ubiquitous prevalence of the causative organism and the difficulty of diagnosis, the true prevalence might be higher. In post mortem studies the prevalence has been described as <0.1%. The pathogenic bacteria *T. whippelii* appears to be present ubiquitously in the

environment but its exact source is not established. The presence of *T. whipplei* has been demonstrated by PCR in human stool, and an association with *Giardia lamblia* infection has been reported. It has been suggested that transmission of *T. whipplei* takes place through faecal-oral transmission and it is possible that significantly more people are exposed to *T. whipplei* than those who actually develop the disease. Thus, genetic factors and undefined subtle defects in cellular immunity, perhaps specific for *T. whipplei*, may play a role in its pathogenesis (Marth and Raoult, 2003; Fenollar et al, 2007*).

4.1.2 Clinical picture

The typical patient is a middle-aged white man who presents with joint symptoms, malabsorption and wasting. The disease can, however, occur at all ages and it should be noted that about 15% of patients do not have the classic signs and symptoms. In those cases the diagnosis may be difficult. Whipple's disease has two stages: the prodromal stage and the steady state. The prodromal stage is characterised by protean, non-specific manifestations—in particular, arthralgia and arthritis. Weight loss and diarrhoea are characteristic of the steady state but several other symptoms can also occur. The length of the prodromal stage can be quite long, with an average duration of 6 years. It is noteworthy that if the patient has received immunosuppressive therapy, such as glucocorticoids or anti-TNF blockers, the progression of the disease may be faster.

Joint involvement is common and has been reported in 65–90% of patients with classic Whipple's disease. Arthropathy is also commonly the first manifestation of Whipple's disease. The most common form of arthropathy is a migratory intermittent non-destructive oligoarthritis or polyarthritis. Destructive arthritis resembling seronegative RA can also occur but it is rarer. In rare cases spondyloarthropathy and hypertrophic osteoarthropathy have been described. In a middle-aged man with unexplained intermittent polyarthritis, Whipple's disease should be considered as a possibility.

The most common gastrointestinal manifestation is weight loss (90% of patients), which may be associated with diarrhoea. Occult bleeding from the intestinal tract has been reported in 20–30% of patients. In addition, abdominal pain, hepatosplenomegaly and hepatitis may be seen.

Neurological symptoms occur relatively commonly in association with Whipple's disease. They have been reported in 6–63% of patients with classic Whipple's disease, but in a small series of 11 patients' central nervous system involvement was described in 10, based on autopsy findings. The neurological manifestations vary and range from commonly occurring cognitive changes to dementia. Depression and personality changes are seen in about half of patients who have neurological involvement. Supranuclear ophthalmoplegia, myoclonus and hypothalamic involvement have been described. The prognosis of patients who have neurological involvement is poor with significant mortality and presence of persistent neurological sequelae.

Cardiac involvement is also relatively common. Cardiac murmurs, insufficiency of aortic or mitral valve as well as blood culture negative endocarditis have been described.

Other commonly (>30% of cases) occurring symptoms include fever, lymphadenopathy, hyperpigmentation, peripheral oedema and hypotension.

4.1.3 *Diagnosis*

As the manifestations of the disease vary a high degree of suspicion is required to make the diagnosis. Symptoms, such as malabsorption, wasting and abdominal symptoms occurring in association with atypical seronegative arthritis should suggest a diagnosis of Whipple's disease. Histological examination and periodic acid–Schiff (PAS) staining of biopsy samples from the duodenum or jejunum should be obtained to confirm the diagnosis. PCR can be used to complement the PAS staining. PCR can also be used to detect *T. whipplei* in other body tissues and fluids. Humoral response cannot be used as a diagnostic tool in Whipple's disease.

4.1.4 *Treatment*

Initiation of antibiotic treatment leads to rapid resolution of symptoms in many patients. Diarrhoea and fever may resolve in 1 week and arthropathy in a few weeks. Tetracycline was previously used as a first-line treatment, but the relapse rates were high. Thus, antibiotics which can effectively cross the blood–brain barrier are favoured these days for treatment. Recommended treatment is to use the combination of trimethoprim (160 mg) with sulfamethoxazole (800 mg) twice a day for 1–2 years. The oral treatment should be preceded, especially in severely ill patients, by parenteral administration of a 2-week course of ceftriaxone (2 g daily) or streptomycin (1 g/day) combined with penicillin G (1.2×10^6 U/day). However, lack of clinical response as well as relapses have been reported also with this regimen (Marth and Raoult, 2003; Fenollar et al, 2007*).

4.2 **Fungal arthritis**

Fungal causes of arthritis are very uncommon. Haematogenous dissemination or direct inoculation following injury, surgery and intra-articular injections are the common modes of spread. Presentation can be acute mono- or polyarticular in 60% of patients or indolent. Large, weight-bearing joints are commonly affected. Isolation of the organism, along with imaging and bone scan is the preferred method of diagnosis. Early diagnosis of such arthritis has been attempted by PCR.

4.3 **Is RA caused by infection?**

In addition to genetic susceptibility, environmental factors have been suggested to play a role in the development of RA. Among those, infections have been widely suspected, though a definite association is lacking. Epstein Barr virus, Parvovirus and rubella have been commonly suspected viral candidates. The suspected mechanisms range from direct infection by mycobacteria, streptococcus or mycoplasma to

immunological cross-reactivity between bacterial antigens (eg, *Porphyromonas gingivalis*, a bacterium associated with periodontal disease) and the host. In about 20% of patients with early RA, there is serological evidence of some recent infection. There is not a single putative microbe, but several microbes may be able to induce joint disease in a susceptible patient.

4.3.1 Epstein–Barr virus infection

Epstein–Barr virus (EBV) is a tumorigenic herpesvirus that infects over 90% of the adult population world-wide. The virus persists for a person's entire lifetime without causing overt disease, and the persistence is sustained by a fine balance between the host immune system and the virus. This common infection has been one of the infectious candidates for RA for several years. The virus affects B cell immunity inducing polyclonal activation of B cells and production of autoantibodies, including rheumatoid factor, anti-DNA antibodies, antiphospholipid antibodies and anti-cyclic citrullinated peptide antibodies. EBV can directly infect synovial cells. Patients with chronic RA have higher levels of anti-EBV antibodies than healthy controls. In addition, EBV-specific cytotoxic T cell function, which is needed for the control of chronic infection, is defective in patients; this probably causes the observed increase in viral load (Leirisalo Repo, 2005a). Although there is no good evidence in favour of the primary infection as a trigger of subsequent RA, based on the above-mentioned immune aberrations, EBV would be a good candidate to trigger chronic immune complex disease.

EBV, cytomegalovirus and parvovirus B19 have been found to persist in a latent form in the synovial fluid/synovial tissue of patients with RA and psoriatic arthritis, but less frequently in those with reactive arthritis. This can be interpreted either as evidence of the primary role of these viruses in autoimmune arthritis or as indicating that the circulating inflammatory cells harbouring the viral DNA of persisting viruses migrate as innocent bystanders to the inflamed synovium.

In summary, there is some epidemiological evidence referring to the possibility that patients who develop first manifestations of RA might have had various infections close to the onset of arthritis. The role of persisting viral infections as a cause of RA needs further confirmation.

4.4 Is ankylosing spondylitis caused by infection?

4.4.1 Bacteria and ankylosing spondylitis

There is indirect evidence that previous bacterial infection can be associated with the later development of ankylosing spondylitis. This is based on the fact that a minority of patients with acute reactive arthritis, especially if they possess HLA-B27 develop the disease 10–20 years after the initial infection. Furthermore, there is increasing evidence for the role of the gut microbiota in the maintenance of joint symptoms in patients with chronic spondyloarthritides or ankylosing spondylitis.

About 10–20% of patients with chronic inflammatory bowel disease (IBD) develop a peripheral arthritis at some time during the course of their disease, and ankylosing spondylitis has been reported in between 5% and 10% of patients with IBD. HLA-B27-positive patients with IBD have an especially high risk of developing ankylosing spondylitis. Although no specific microbes have been shown to be responsible, altered gut microbiota or dysbiosis, such as reported in patients with IBD, might be involved. *Klebsiella*, a microbe belonging to normal gut flora, has been previously suspected, especially in association with peripheral arthritis, but current evidence does not support this idea. Previous infection with *Chlamydia trachomatis* has also been linked to the subsequent development of sacroiliitis and ankylosing spondylitis. Also, flares of established ankylosing spondylitis, especially if there is acute peripheral arthritis, can be due to superimposed acute reactive arthritis associated with enteric and urogenital infections.

Urogenital infections may also contribute to chronic spondyloarthritis. Prostatitis has been shown to support the continuing joint/axial inflammation in chronic reactive arthritis and ankylosing spondylitis. These associations suggest a more thorough search is needed for microbes in patients with active ankylosing spondylitis—notably, in gut microbiota.

Environmental factors (most probably infections) have also been suggested to have a role in the severity and age of onset of ankylosing spondylitis. There are some reports that ankylosing spondylitis and related diseases are more severe in lower social classes with poorer hygiene.

In Mexico and China, ankylosing spondylitis starts at an earlier age and follows a more severe course than in Western Europe. In both the countries repeated bacterial infections of the gastrointestinal tract starting at a young age are frequent, especially in the lower socioeconomic strata. This indicates that persistent or repeated infection, most probably of the gut, may be an important contributor to the pathogenesis and also to the severity of ankylosing spondylitis.

In conclusion, the aetiology of ankylosing spondylitis is not known. The role of infectious agent(s) as a possible cause of ankylosing spondylitis has been suspected during the past 30–40 years. Indirect evidence for the role of infection comes from the following: (1) a proportion (20–35%) of patients with reactive arthritis, followed up prospectively for 20–25 years, developed sacroiliitis and ankylosing spondylitis; (2) chronic bacterial prostatitis has been associated with active ankylosing spondylitis, with treatment of the infection also suppressing the inflammatory back pain; (3) patients with active ankylosing spondylitis have a higher titre of IgA class antibodies than patients with low disease activity and (4) sacroiliitis and ankylosing spondylitis occur in patients with chronic IBD, such as ulcerative colitis and Crohn's disease.

4.5 Are other spondyloarthritides caused by infection?

Most patients with reactive arthritis recover, but about 15% continue to have chronic arthritis. Recurrent attacks of acute reactive arthritis occur in about 10–20% of patients with previous yersinia or salmonella arthritis, and are especially common in those with previous Chlamydia trachomatis induced arthritis. Factors determining the progression of acute reactive arthritis to chronic spondyloarthritis are incompletely understood, but persistent or recurrent urogenital infection or a chronic inflammatory focus in the gut may be a good explanation. The presence of yersinia and salmonella antigens has been demonstrated in synovial fluid cells or in synovial tissue of patients with reactive arthritis. Furthermore, yersinia structures have been shown to persist in submucosa of the gut, in lymph nodes and in the synovial fluid of patients with prolonged or chronic yersinia arthritis. Chlamydia trachomatis also persist in the infected host for months or even years. Reactive arthritis is the acute form of spondyloarthritis, whereas ankylosing spondylitis is at the other end of the spectrum. In reactive arthritis, infection has a definite triggering role, and for ankylosing spondylitis, the role of infection as one of the initiating factors or as a contributory factor in the flare-up has already been discussed. Most patients with chronic spondyloarthritis have no preceding known infection, but based on the similarities with other diseases of the same family, infection might have a role, at least in some patients. The finding of chlamydia antigens in the synovial tissue and/or peripheral blood mononuclear cells of some patients with chronic spondyloarthritis may suggest that chronic infection has a role in the development of chronic rheumatic disease (Carter et al, 2009*). Thus, infection has a definite role in the aetiology of acute reactive arthritis and probably contributes to the clinical activity or to the exacerbation of spondyloarthritides, in general.

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SUMMARY POINTS

- Direct infection of a joint (septic arthritis) should be suspected in a patient with acute monoarthritis, usually in the lower limbs. Most patients have a contributing factor for the infection. The affected joint should be aspirated and the fluid should be analysed with Gram stain, bacterial culture and white blood cell count with differential. Bacterial cultures of blood, mucosa, wounds and skin lesions should be performed. Treatment with an intravenous antibiotic should be started immediately without waiting for microbiological verification.
- Reactive arthritis is characterised by oligoarthritis in a young or young adult patient, often preceded by enteritis or urethritis/cervicitis, often associated with extra-articular inflammatory signs and symptoms. Treatment is based on non-steroidal anti-inflammatory drugs and physiotherapy. Local glucocorticoid injections or systemic glucocorticoids can be used in severe cases. Antibiotics do not modify the course of the continuing arthritis. Most patients recover within the first 6 months, and 85% within 1 year.
- Lyme arthritis should be suspected in a patient with a history of a tick bite, especially if followed by erythema migrans. Arthritis is usually monoarticular, with predilection for the knee. The arthritis has a naturally waxing and waning course. The diagnosis of borreliosis can be confirmed by serology followed by immunoblot. Synovial fluid can be examined for borrelia by PCR. For treatment, antibiotics are used, usually doxycycline 200 mg/day for 1–2 months, or intravenous ceftriaxone for 14–21 days.
- Arthritis/arthritis is associated with several virus infections. The most important are parvovirus and rubella infections. Alphaviruses are a large family of viruses spread around the world capable of causing protean symptoms, including acute arthritis and prolonged joint pain. Diagnosis is based on clinical features supplemented by serology. Treatment is symptomatic and outcome is good.
- Patients with HIV infection may have septic or reactive forms of arthritis, and an increased frequency of psoriatic arthritis and spondyloarthritis. Increased load of infections, immunosuppression by HIV and direct effect of the HIV infection can contribute to the symptoms. With highly active antiretroviral therapy (HAART), patients have fewer opportunistic infections, but musculoskeletal symptoms are still often present.
- Whipple's disease is a rare chronic infection which manifests with generalised arthralgia and arthritis followed by a chronic phase, with diarrhoea, malabsorption, neurological and cardiac symptoms. The diagnosis is based on high clinical suspicion, and histological analysis of biopsy specimens from the duodenum or jejunum with PAS staining or PCR. Treatment is with long-term antibiotics.
- The role of various infections (especially Epstein–Barr virus, cytomegalovirus and parvovirus B19) as triggers of rheumatoid arthritis has been discussed for decades, with no clear positive answer.
- The aetiology of ankylosing spondylitis is not known, but chronic gut inflammation has been shown in a significant proportion of patients, leading to suspicion that altered gut microbiota play a part.

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Infection and arthritis. Reactive arthritis - Lyme - Whipple - HIV - Viral arthritis - Septic arthritis

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IN-DEPTH DISCUSSION I

**Reactive arthritis – treatment of acute and
prolonged/chronic arthritis**

Patients with acute reactive arthritis are most often treated with non-steroidal anti-inflammatory drugs as a first line-therapy, of which they often need high doses. Most patients have oligoarticular disease with arthritis predominantly affecting large joints of the lower limbs. Intra-articular injections with glucocorticoids are usually effective. In the case of a patient with fever, low back pain, hip/knee arthritis insufficiently responding to the above-mentioned therapeutic interventions, systemic use of prednisone/prednisolone is indicated. Compared with patients with rheumatoid arthritis, who usually respond to very low doses, patients with reactive arthritis need higher doses, eg. 40 mg prednisolone as starting dose. Physiotherapy, local cold, and use of appliances (crutches to alleviate pressure of inflamed hip/knee/ankle) are part of the routine treatment in severe cases.

Extra-articular symptoms are usually mild and disappear with time. There are no controlled studies concerning various treatment modalities. Enthesopathy and dactylitis respond to local corticosteroid injections. Keratoderma responds to topical glucocorticoids, but if the patient has systemic symptoms (fever), systemic glucocorticoids can be used. If the patient has balanitis, Chlamydia and Candida infections should be searched for and treated appropriately. If there is no infection, mild topical glucocorticoid ointment can be used for short periods of time. Conjunctivitis can be a sign of reactive arthritis but does not normally require treatment but, if symptomatic, topical vasoconstrictors may be used. About 5% of patients with reactive arthritis have more serious eye symptoms, usually acute anterior uveitis, but also keratitis or posterior uveitis have been described. Acute anterior uveitis is usually affecting only one eye, and the eye is painful, red, and the patient has photophobia. Such a patient should be referred immediately to an ophthalmologist to be treated with local glucocorticoids and mydriates.

The use of antibiotics to treat acute reactive arthritis has been extensively studied, and the results have been largely negative. The use of antibiotics is indicated in the case of symptomatic infection, eg. positive stool culture for salmonella, campylobacter, yersinia or shigella: for salmonella and yersinia infections, ciprofloxacin 750 mg twice a day for 10 days; for Shigella dysenteriae norfloxacin 400 mg twice a day or ciprofloxacin 500 mg twice a day for 5-10 days, and for campylobacter a macrolide antibiotic e.g. roxithromycin 150 mg twice a day for 10 days.

The use of antibiotics in reactive arthritis triggered by gastroenteritis does not shorten the duration of the arthritis. For Chlamydia trachomatis infection, both the patient and the sexual partner(s) should be treated with antibiotics (azithromycin 1 g as a single dose) irrespective of arthritis. For Chlamydia trachomatis induced arthritis, there is limited evidence that a prolonged use of tetracyclines might be effective for the arthritis (1).

The prognosis of a patient with reactive arthritis is usually good. In a previous Finnish study, the average duration of arthritis was 3-5 months, and about 15 % of patients developed chronic sequels or proceeded into chronic spondyloarthritis (2). Often, after objective recovery and with normal laboratory markers of

inflammation and absence of arthritis, the patients continue to have pain in the involved areas. Part of this pain can be explained to be due to enthesopathy, and part due to muscle wasting during the acute phase. Therefore, physiotherapy and encouragement of the patient for exercises are part of the therapeutic process.

About 15% of the patients proceed into a chronic spondyloarthritis. In some of them, the chronicity is a sequel of recurrent acute arthritides. In such patients, treatment with DMARDs has been tried, with varying effect. There is only limited information of the efficacy of such an approach. Sulfasalazine has been shown to be effective when used in chronic reactive arthritis (3). Methotrexate and leflunomide have also been used, but they are only of limited efficacy, analogous to what is seen in the peripheral arthritis of ankylosing spondylitis (4, 5). Biologicals are a new class of drugs shown to be effective in chronic HLA-B27 associated diseases such as in ankylosing spondylitis (6), chronic spondyloarthritis (7), psoriatic arthritis (8, 9). Interestingly, case reports of patients with severe acute reactive arthritis and chronic reactive arthritis have shown a rapid efficacy of infliximab in the patients (10, 11, 12), without any evidence of relapse of infection. Of the eye inflammatory symptoms, acute anterior uveitis usually heals within 3 months, but can recur, and some patients proceed into chronic eye inflammation, and can develop glaucoma or cataract either due to recurrent inflammation or to glucocorticoid therapies (13).

Antibiotics, especially tetracyclines have also been used for months in the very severe chronic cases, without any large controlled study. Carter et al. (14) reported a beneficial effect of a combination treatment with doxycycline and rifampicin or with roxithromycin and rifampicin, used for 6 months on patients with chronic spondyloarthritis (duration of the disease for 10 years) with evidence of persisting chlamydia in the body, compared with doxycycline as a single treatment.

As many of the patients with chronic spondyloarthritis proceed to ankylosing spondylitis, the therapy can be followed according the treatment options suggested for ankylosing spondylitis.

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11

module

Infection and arthritis. Reactive arthritis - Lyme - Whipple - HIV - Viral arthritis - Septic arthritis

Ashish J Mathew, Debashish Danda, Hill Gaston

A previous version was coauthored by Maxime Breban, Riita Koivuniemi, Marjatta Leirisalo-Repo, Ben A. Dijkmans, Kari K. Eklund and Janneke Tekstra.

IN-DEPTH DISCUSSION II

Diagnosis and treatment of Lyme arthritis

Diagnosis of borrelia infection

As joint symptoms are common in the population, and ticks (and ticks infected with borrelia) are widely distributed, the patient history focussing on the previous tick bites, and possible erythema migrans are important in the clinical diagnosis. A travelling history is important, as in Europe, Lyme borreliosis is primarily caused by the three species (*Borrelia burgdorferi sensu stricto*, *B. afzelii* and *garinii*), while *B. burgdorferi sensu stricto* is the only human pathogenic species in the US (1). The clinical spectrum is different in patients infected with different borrelia species.

Erythema migrans develops in about 70% of the patients at the site of the tick bite. A red papule developing immediately at the site of the bite is not an indication of borrelia infection. The infection has an incubation time of a few days to one month, after which the skin lesion develops, starting as a red macula or papule that slowly expands. However, as indicated above, the skin manifestation is lacking in one third of the patients. Erythema migrans is so typical that its presence can be taken as an indication of borreliosis. In those who do not develop erythema migrans, antibody detection methods can be used. Detection of the causative agent by culture isolation and PCR is confined to special situations.

Serology The serological examination consists of a serological screening assay (a sensitive ELISA assay), supplemented in the event of positive or equivocal result, by a confirmatory assay (immunoblot). As the borrelia species differ between US and European infections, the US serological, immunoblot or PCR tests cannot be used in European patients. Recently various recombinant antigens for better accuracy in ELISA tests have been developed (2). For optimal diagnostics, a close collaboration and discussion between the clinician and the local laboratory is recommended. The frequency of positive serology depends on the detection methods used by the local laboratory, and on the timing of the infection. Borrelia antibodies of IgM class start to rise 2-4 weeks after infection, peak within 6-8 weeks after which the production is switched to IgG class. In early localized disease, the sensitivity of positive antibody response is 20-50%, and most of the antibodies are of IgM class. If borreliosis is strongly suspected, serological follow-up is recommended. In early disseminated disease, the sensitivity rises to 70-90%. The majority of patients with short disease duration have IgM class antibodies, while in those with long disease duration, the IgG class of antibodies predominant.

Patients with late disease (e.g. arthritis or acrodermatitis) are nearly always seropositive with IgG class antibodies (see 2). Thus, a positive IgM antibody and negative IgG antibody result speaks against late disease. IgM and IgG class antibodies can persist in some patients for many years, even after therapy. Serology cannot be used as an indication of the effect of antibiotic therapy. Furthermore, after clinically successful therapy, there is no need to treat raised antibody levels.

For confirmation of the preceding infection by immunoblot, use of recombinant antigens is recommended (2). There are differences between different tests with respect to the antibody binding patterns. Here, as with antibody tests, the tests used in the US and Europe differ and the European tests should be used for European patients. Patients with early disease have immune response restricted to only a few proteins, but patients with late disease (e.g. arthritis) have IgG antibodies to a broad spectrum of antigens.

Antigen detection Culture of borrelia is a time consuming method and has a low sensitivity, especially in body fluids. For synovial fluid, PCR is positive in 50-70% of the patients, while culture is very seldom positive (2).

Treatment of Lyme arthritis

In the US, arthritis is the most frequent manifestation of disseminated and chronic borreliosis, about 60% of the patients developing joint manifestations months to years after the tick bite (3). However, a survey among German physicians showed that about 25% of patients with Lyme borreliosis had arthritis (4). There are no internationally accepted guidelines on how to treat Lyme arthritis. Some experts use parenteral antibiotics (ceftriaxone 1 g twice a day for 14-21 days) as the first-line therapy. However, Schnarr et al. recommend as first choice doxycycline 200 mg/day for 30 days. An alternative choice is amoxicillin 500-750 mg three times/day for a child or a pregnant patient. In the case of failure of previous treatment, ceftriaxone 1 g twice a day i.v. for 14-21 days is recommended. Alternative choices are cefotaxime 2 g 3 times a day i.v. or penicillin G 5 million units 4 times a day, for 14-21 days (3).

The arthritis often resolves within 3 months of the onset of treatment. In resistant cases, antibiotics have been used for up to 3 months. Besides antibiotics, patients need analgesics and anti-inflammatory drugs. The administration of systemic or intra-articular corticosteroids is controversial, because the treatment may impair the eradication of the spirochete (5). Physiotherapy is often of benefit, especially in the case of knee synovitis. The prognosis of arthritis is usually good, about 10% of untreated patients with arthritis recover per year. The majority of the patients respond to the antibiotic treatment (6). If the arthritis persists after adequate antibiotic therapy, synovectomy can be considered. Use of disease-modifying antirheumatic drugs is an option in the resistant case with active joint inflammation.

What to do, if the arthritis continues?

If the objective symptoms and signs persist for more than 1 year after adequate antibiotic therapy, the patient is considered to have treatment-resistant Lyme disease (3). However care must be taken in these cases to re-evaluate the evidence for Lyme disease to ensure that there is some certainty about the diagnosis and hence that the condition is definitely treatment-resistant. If persistent infection (positive PCR in the synovial fluid/synovial membrane, or in rare cases, positive borrelia culture) is demonstrated, the recommendation is to aim at eradication of the microbe (3). This includes switching from oral to parenteral antibiotics. There are

no controlled studies and the treatment options are usually based on case reports or on small open series of treated patients. Based on experience on 135 US patients with Lyme arthritis treated with various protocols, Steere and Angelis (5) propose a step-wise approach to the diagnosis and treatment of the patients with antibiotic-refractory arthritis (Figure 1).

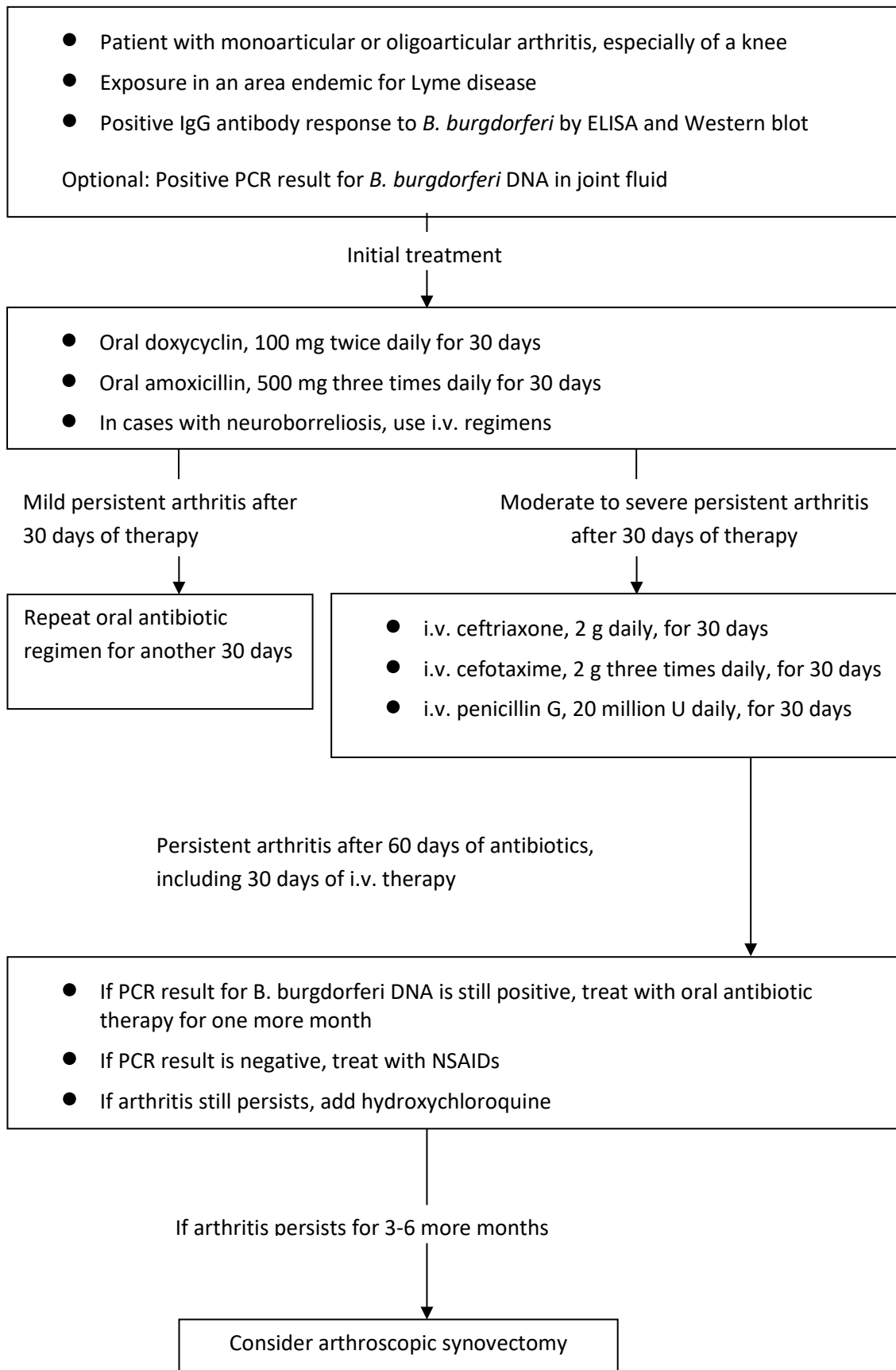
Post-Lyme syndrome

Some patients proceed to have continuous subjective symptoms (such as fatigue, musculoskeletal aches, neurocognitive dysfunction) without objective arthritis. Two controlled studies showed minor or no benefit with antibiotics in such cases. However, the discussion continues with pro (7) and con (8) views for prolonged use of antibiotics for the Post-Lyme syndrome; the situation is complicated by the fact that the symptoms in many patients following their Lyme disease may stem from anxiety or have a psychological basis. The current opinion is that taking into consideration the adverse effects of prolonged antibiotics, such therapy can be hazardous to the patient and is not recommended (3, 9).

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Figure 1. Algorithm for the diagnosis and treatment of Lyme arthritis (Steere and Angelis 2006)





EULAR on-line course on Rheumatic Diseases

Crystal arthropathies

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A previous version was co-authored by Franco Schiavon, Eliseo Pascual, Thomas Bardin and Pascal Richette

1. GOUT

LEARNING OUTCOMES

- Recognise by the clinical presentation those patients with a disease consistent with gout
- Plan the diagnostic investigation, recognising the limitations of a clinical approach
- Be aware that crystal identification in synovial fluid or in an aspirate of a tophus provides an unequivocal aetiological diagnosis
- Be aware that urate crystal deposition—causative of gout—is fully reversible by reducing serum urate levels to normal; after crystals have fully dissolved, features of crystal deposition disappear and gout can be taken as cured as long as uricaemia is maintained at a normal level. Urate crystal dissolution is the main aim in gout treatment
- Manage an acute attack of gout when it does occur
- Recognise the conditions associated with gout, particularly the growing evidence that gout increases the risk of cardiovascular diseases

1.1 Introduction

Gout is an inflammatory disease caused by the deposition of monosodium urate (MSU) crystals in joints and other tissues. The formation of the crystals is the consequence of hyperuricaemia, a condition so called when serum uric acid (SUA) levels are >6.0 mg/dL (360 μ mol/L) (Bardin and Richette, 2014). However, it is important to underline that most patients with hyperuricaemia do not have clinical gout (Richette and Bardin, 2010).

Gout is the most common form of inflammatory arthritis in men and its incidence and prevalence are rising in postmenopausal women. In Western countries, gout affects about 1–2% of adults, with a prevalence increasing with age, being 7% in men over 65 years and 3% in women over 85 years (Roddy and Doherty, 2010). In the UK, the overall prevalence of gout is 2.49% according to a cohort study nested within the Clinical Practice Research Database (CPRD) (Kuo, 2015)

Gout is not a minor disease since it may induce disability and severe nephropathy and increases cardiovascular risk. It is also associated with significant impairment in Health Related Quality of Life (Chandratre et al, 2013).

Deposits of MSU crystals known as tophi may form usually in and around joints but also elsewhere; emerging data suggest that gout is a deposition disease from the first attack or even earlier. Identification of MSU crystals in synovial fluid (SF) obtained during the attacks (McCarty and Hollander, 1961), from previously

inflamed asymptomatic joints of untreated subjects during intercritical periods (Pascual et al, 1999*) or in an aspirate from a tophus is simple and allows immediate unequivocal diagnosis. Ultrasound studies have demonstrated deposition of MSU crystals in patients with asymptomatic hyperuricaemia who have not yet developed clinical manifestations of gout (Pineda et al, 2011; Puig et al, 2008; De Miguel et al, 2012). The disease generally presents with episodes of joint inflammation that in most occasions can be easily treated or avoided. Renal lithiasis and formation of tophi in internal organs and other structures may also occur. Of importance, the crystals slowly dissolve and finally disappear when SUA levels are lowered below a certain threshold (Pascual and Sivera, 2007). Effective and well-tolerated drugs are available for this purpose. Finally, in an important proportion of patients hyperuricaemia is part of the metabolic syndrome and the presence of gout should alert the physician to this problem and its associated morbidities, which may require modification of dietary and lifestyle habits and often drugs. Gout has also been found to be an independent risk factor for atherosclerotic cardiovascular disease (Krishnan et al, 2006). The guidelines on gout diagnosis and management published by the European League Against Rheumatism (EULAR) (Richette and Bardin, 2010*; Bardin and Richette, 2014) and more recently, by the American College of Rheumatology (ACR) (Khanna et al, 2012a*; Khanna et al, 2012b*), outline the current interest in gout.

1.2 Why do crystals form?

Gout is a MSU crystal deposition disease. The formation of the crystals requires (1) raised SUA levels and (2) some local conditions, which are starting to be understood.

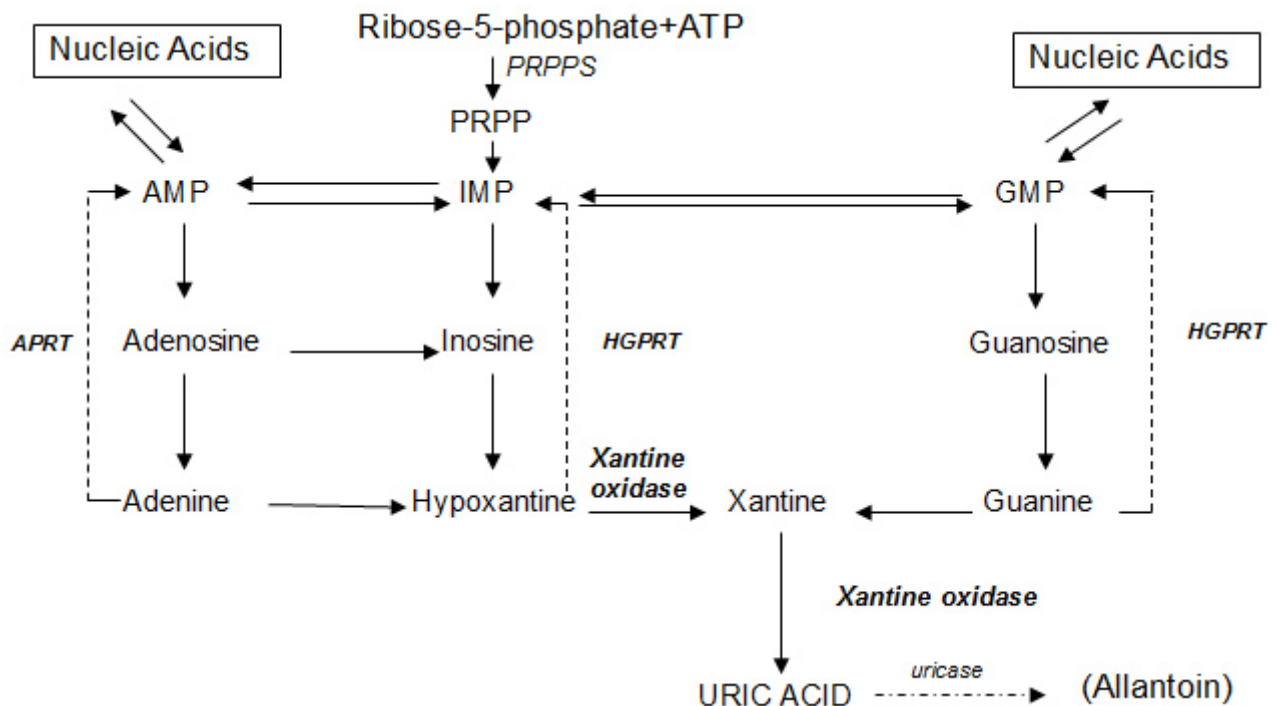
1.2.1 Hyperuricaemia

Uric acid is the final metabolite of purine metabolism in man. Purines are heterocyclic aromatic organic compounds, consisting of a pyrimidine ring fused to an imidazole ring. Uric acid is a weak acid with a pKa of 5.75 (the pH at which uric acid and urate concentrations are equal). At a physiological pH of 7.4 in the extracellular compartment, 98% of uric acid is in the ionised form of urate. Because of the high concentration of sodium in the extracellular compartment, urate is largely present as MSU, with a low solubility limit of about 380 µmol/L (Richette and Bardin, 2010*). So, when urate concentrations exceed this limit, the risk of MSU crystal formation and precipitation increases.

The levels of SUA depend on the balance between purine ingestion, synthesis and degradation. The ingestion of purine and/or urate is very limited, contributing about 10% of the total pool of urate in the body. The main site of the synthesis is the liver. Since purines are difficult to synthesise, during their degradation there are salvage pathways aimed at their reutilisation. The salvage pathways are a major source of nucleotides for synthesis of DNA, RNA and enzyme cofactors. The enzymes most involved in these salvage pathways are adenosine phosphoribosyltransferase and hypoxanthine-guanine phosphoribosyltransferase (HGPRT). At the

distal end of the purine pathway there is the enzyme xanthine oxidase that catalyses the oxidation of hypoxanthine to xanthine, and xanthine to uric acid (figure 1).

Figure 1 Uric acid synthesis.



The starting point of uric acid synthesis is the ribose-5-phosphate, a pentose derived from glycolytic metabolism, converted to phosphoribosyl pyrophosphate (PRPP) and then to phosphoribosilamine, that will be transformed into inosine monophosphate (IMP). From this intermediate compound are derived adenosine monophosphate (AMP) and guanosine monophosphate (GMP), the purinic nucleotides useful for DNA and RNA synthesis, and inosine that will be degraded into hypoxanthine and xanthine and finally, into uric acid by the enzyme xanthine oxidase. Hypoxanthine and guanine may enter in a salvage pathway, using HGPRT, an enzyme that reconverts these purines bases into their respective nucleotides. In a similar salvage pathway, adenine phosphoribosyltransferase (APRT) converts adenosine to AMP.

In humans and other primates, urate oxidase (uricase), a hepatic enzyme, is inactive as a result of a non-sense mutation. So, only animals which possess uricase can transform uric acid in a more soluble and more eliminable molecule: allantoin.

Defects of the enzymes involved in the salvage pathways may cause severe diseases, as in the case of partial or total deficiency of HGPRT, which causes Lesch–Nyhan disease in boys. Another cause of secondary hyperuricaemia is the raised activity of phosphoribosyl pyrophosphate synthetase, in which hyperuricaemia and gout are associated with renal over excretion of uric acid and lithiasis. However, these genetic defects

account for the minority of cases of gout associated with raised production and excretion of uric acid and frequently with urinary lithiasis.

In mammals, the final product of purine degradation is allantoin, which is derived from uric acid by the action of uricase, an enzyme that is lacking in humans and higher primates, owing to mutations affecting uricase (Oda et al, 2002).

SUA levels depend on gender and age. Prepubertal children of either sex have low SUA levels. At puberty SUA levels rise to the levels that will be maintained throughout life owing to a decrease in the renal clearance of urate, at least in women (Roddy and Doherty, 2010); in men these levels rise slightly with age. Oestrogens are uricosuric so that uricaemia will be lower in women up to the menopause or end of hormonal substitution treatment (McCarty and Hollander, 1961; Pascual et al, 1999*). This explains why children do not have gout, with the exception of boys with very unusual enzymatic defects, and of children affected by familial hyperuricaemic nephropathy, an inherited kidney disease with low urinary urate excretion. It also explains why in men the risk of gout starts soon after puberty, while in women gout is exceptional before the menopause. All these aspects were observed by Hippocrates (469–399 BD) who in his aphorisms suggested that women do not have gout while they have their menses, nor do boys before they initiate sexual activity.

Excess uric acid may result from an increase in the amount of purines being degraded, either endogenously from tumours, or haematological conditions like leukaemia or lymphomas, especially when treated, or in psoriasis, or exogenously owing to raised ingestion of purines from food or drinks—in particular, beer or fructose-rich beverages (McCarty and Hollander, 1961; Choi et al, 2004; Choi et al, 2010). For haematological diseases, only patients with chronic conditions develop gout, owing to the time necessary for MSU crystal deposition.

Decreased urate clearance results in raised SUA levels and is the most common cause of gout. In humans, only 5–10% of the filtered urate is finally excreted by the kidneys, the largest part being reabsorbed in the tubules (Hediger et al, 2005). Urate is poorly soluble and has to be transported across cell membranes. Different urate transporters have now been identified: URAT (urate transporter/channel) 1, and GLUT (glucose transporter) 9, two members of the family of organic anion transporters (OAT1 and OAT3) related to tubular secretion of urate and the main protein responsible for tubular reabsorption of urate (Gibson, 2012). The defect in increasing uricuria when uricaemia increases, which characterises most primary hyperuricaemic patients most probably reflects particular polymorphisms of the genes involved in the tubular transport of urate. The calculation of urate clearance is cumbersome and susceptible to errors in a 24 h urine collection. It can be substituted by the calculation of the fractional excretion of urate, which is the relation between urate and creatinine (Cr) clearance and is reported as a percentage. The normal fractional excretion of urate is 7–10%, which represents the percentage of the filtered urate which is finally excreted. The fractional excretion of

urate can be simply calculated on simultaneous spot urine and blood samples (urine uric acid (UA) \times serum Cr/serum UA \times urine Cr) (McCarty and Hollander, 1961; Pascual et al, 1999*). Decreased fractional excretion of urate causes the raised SUA levels which accompany the metabolic syndrome (Pascual and Sivera, 2007)—which is correctable by changing to a low caloric diet (Krishnan et al, 2006)—essential hypertension (Tykarski et al, 1991), decompensated heart failure (Ochiai et al, 2005), saturnine gout—which is correctable by lead chelation (Lin et al, 2001)—and alcohol consumption. Some drugs such as cyclosporine (Lin et al, 1989), low-dose aspirin (Caspi et al, 2000) and diuretics also produce hyperuricaemia by reducing the fractional excretion of urate (Pascual, 1998; Gibson, 2012).

Although the influence of the intestinal excretion of uric acid in SUA levels has not been well evaluated, it seems responsible for about a third of the excretion of uric acid produced daily. Reduced intestinal excretion of urate has been recently shown to be a possible cause of hyperuricaemia (Ichida et al, 2012).

1.2.2 Local conditions for MSU crystal formation

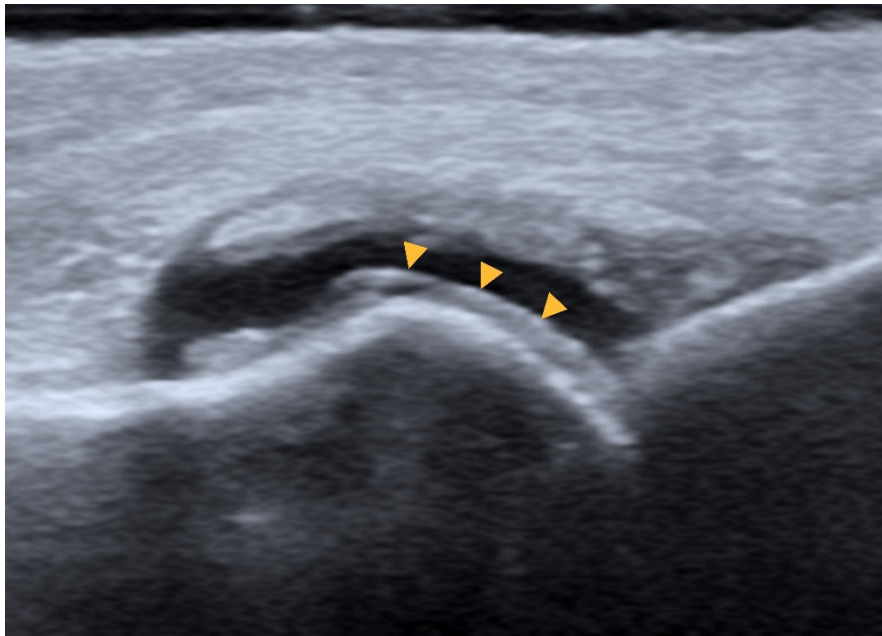
The formation of MSU depends on several factors, including mainly the local concentration of urate. However, its solubility may be influenced by the articular hydration state, temperature, pH, concentrations of cation and the presence of extracellular matrix proteins such as proteoglycans, collagen and chondroitin sulphate.

Variations in these factors may influence the occurrence and the localisation of gout. Although gout may occur in different joints, the disease has a preference for those of the lower extremities such as those in the feet, ankle or knee, where the disease generally starts and the attacks occur more often. The orderly arrangement of MSU crystals on small detached cartilage fragments recovered along SF samples obtained from asymptomatic gouty knees suggests epitaxial formation of the crystals (Pascual et al, 1998). The association between gout and osteoarthritis (OA) in the same joint (Mikkelsen et al, 1965) suggests that cartilage damage related to OA may help to expose collagen fibres which may act as templates for epitaxial formation, prompting MSU crystal nucleation and growth. Sites of deposition of both monosodium urate (MSU) and calcium pyrophosphate crystals have been shown to correlate closely with degenerative lesions in articular cartilage (Muehleman et al, 2008). A clinical diagnosis can be made with reasonable confidence after careful history-taking and examination (tenderness to touch, with subsequent complete resolution affecting the first metatarsophalangeal joint) (Zhang et al, 2006b). Ultrasonography can be used to facilitate arthrocentesis in difficult locations and may reveal or confirm the diagnosis of gout (Punzi and Oliviero 2009). Sonographic studies indicate that MSU crystals form on the surface of the joint cartilage (figure 2), whereas calcium pyrophosphate dihydrate crystals form within its interior (Hall et al, 1967). A decreased permeability of the synovial membrane for urate may facilitate concentration of urate in the joint cavity and enhance crystal nucleation (Choi et al, 2004); also, colder temperature may facilitate formation of tophi in distal joints and in the helix of the ear.

1.3 What triggers the attacks?

Although MSU was identified in gout in the 1700s and shown to be the causative agent in 1899, the mechanisms by which MSU crystals trigger acute inflammation have only recently begun to be understood. After McCarty and Hollander (1961) published their observations that the crystals found in the SF were composed of MSU, these crystals were injected into healthy canine and human joints triggering attacks of gout. From this observation it was implied that the trigger for gouty attacks was the ‘injection’ or shedding of MSU crystals into the joint cavity from surrounding tissues.

Figure 2 Sonography of the first metatarsophalangeal joint: the metatarsal head cartilage is covered by a white line produced by the monosodium urate crystals deposited at its surface. A joint effusion is seen as a dark space. The crystals are bathed by SF explaining their constant presence in SF samples from affected joints, symptomatic or asymptomatic. SF, synovial fluid. (Image provided by Dr Agustín Martínez.)



The inflammation stimulated by MSU crystals is one of the most powerful seen in man. The sequence of events following MSU precipitation concern their physical contact with cells and the interaction with both surface and intracellular receptors that finally leads to the activation of specific inflammatory pathways. Early in the development of the attack, MSU crystals activate monocytes and macrophages with the production of chemotactic substances causing a massive infiltration of neutrophils in the joint fluid and synovial membrane. MSU crystals induce the secretion of a variety of cytokines, prostanoids, chemotactic factors and other proteins, which amplify the inflammatory process through the recruitment of inflammatory cells, the upregulation of adhesion molecules and the stimulation of the acute-phase response (Choi et al, 2005; Lioté and Ea, 2006).

One of the most important advances in the understanding of gout over the past 10 years has been the observation that MSU crystals can activate the NLRP3-inflammasome, a multimolecular intracellular complex

that converts pro-interleukin (IL)-1 and pro-IL-18 into their active forms (Martinon et al, 2006), leading to the concept that gout inflammation involves similar pathways to those of autoinflammatory syndromes (Punzi et al, 2012). The observation that MSU crystals activate the inflammasome places IL-1 β , in particular, at the centre of the gouty inflammatory response (Punzi and So, 2013). Another interesting but unclear aspect is the self-limiting nature of the acute gout attack. It has been suggested that among the various possible causes one of the most relevant might be linked to the differentiation state of the MSU crystal-recruited monocyte population which along their differentiation path into macrophages switch from producing proinflammatory cytokines to producing the anti-inflammatory cytokine transforming growth factor 1 in response to MSU crystal stimulation (Chen et al, 2011; Scanu et al, 2012).

It is important to underline that MSU crystals are regularly found in SF samples from asymptomatic gouty joints of untreated patients, as demonstrated by sonographic studies, showing that the crystals deposit at the surface of the joint cartilage, directly bathed by SF and in an area of contact and friction, explaining their constant presence in joint fluid. In the SF of asymptomatic gouty joints the crystals and white cells interact (as shown by crystal phagocytosis (Pascual and Jovaní, 1995)), resulting in a mild subclinical inflammation (Rouault et al, 1982; Pascual, 1991).

The drop in SUA after the initiation of SUA-lowering drugs is the best characterised trigger of gouty attacks (McCarty and Hollander, 1961); the attacks that frequently accompany severe disease or surgery also can result from the drop in SUA owing to a higher renal clearance which occurs in these circumstances. Also some patients find that overindulgence or ingestion of some foods may trigger attacks. We do not have a conclusive explanation for this.

1.4 Clinical features

The natural history of gout was classically composed of three periods: asymptomatic hyperuricaemia, acute attacks with asymptomatic intervals and chronic gout. However, recent sonographic evidence on the presence of intra-articular microtophi in patients with 'asymptomatic hyperuricaemia', has allowed some authors to suggest the addition of an additional phase 'asymptomatic MSU deposits' after asymptomatic hyperuricaemia and before the acute attack or intermittent flares (Bardin and Richette, 2014).

The classic presentation of acute gout is characterised by a typical rapid development of severe pain, swelling, with overlying erythema and tenderness that reaches its maximum within 6–12 h, often starting at night or in the early morning (Zhang et al, 2006b*).

Most often gout presents as acute monoarthritis and usually it involves a single joint in the lower extremity—in particular, the first metatarsophalangeal joint (podagra), which has been considered as a hallmark of the disease (Bolamaski and Schumacher, 1984). Less often, the disease starts in other joints: tarsal and subtalar

joints, ankle, knee, wrist, metacarpophalangeal or interphalangeal joints of the hand are frequently affected. Inflammation at the Achilles tendon insertion, of the olecranon bursae or patellar tendon is also common (Canoso and Yood, 1979). In about 10% of cases, gout may have an oligoarticular presentation (Lawry et al, 1988). In some cases, the attack of acute gout may involve more joints, in a polyarticular manner, as seen in the elderly, especially women, and in patients who have had a transplant (Meyers and Monteagudo, 1985). In these patients, gout may affect some unusual locations, such as shoulders, hips and small joints of the hands, and may be associated with particular features, such as pitting oedema (puffy hands). Patients with polyarticular gout tend to be older and more often women than those with monoarticular attacks (Meyers and Monteagudo, 1985; De Leonardis et al, 2007). It may occur that patients with gout are seen late after the onset, in a chronic phase, and so it is sometimes difficult to distinguish gout from other chronic arthritis, such as rheumatoid arthritis, psoriatic arthritis or OA (Lally et al, 1989).

Factors that might trigger acute attacks include alcohol intake, heavy meals rich in animal purines, fasting, trauma, infection and surgery (Richette and Bardin, 2010*). Different drugs can also precipitate acute gout by raising or lowering SUA concentrations, such as diuretics and urate-lowering therapy (ULT) shortly after initiation.

Gouty inflammation tends to be very intense and painful. It is characteristic of the disease that the maximal inflammation is reached within a few hours. When peripheral joints or bursa are stricken—such as the first metatarsophalangeal, tarsal, metacarpophalangeal joints, wrist, ankle or the olecranon or Achilles bursa—erythema is common and its intensity appears to be related to the intensity of the inflammation and also to the proximity of the affected structure to the skin (figure 3). Erythematous skin can desquamate after some days. With intense inflammation, regional swelling and erythema are common, such as in the hand with wrist arthritis or in the foot with tarsal arthritis. In deeply seated joints, such as in the knee and frequently ankle, arthritis is often unaccompanied by skin changes and clinically manifests only as pain and swelling. When affecting large joints or if polyarticular it can produce fever and be taken for a septic process. Most often, neglected gout has an episodic nature in which gouty attacks alternate with long intercritical periods, during which the patients are free from symptoms.

Figure 3 Gout attack striking a tarsus which is erythematous and very painful.



As the disease progresses without treatment, gouty attacks tend to be more frequent, affect additional joints and become more polyarticular and persistent, leading to chronic gout. Then, palpable tophi can appear. Gouty inflammation can be less acute and low-grade chronic arthritis also occurs. In older subjects receiving diuretics, gout may result in modest inflammation and simulate or occur at Heberden and Bouchard's nodes (Lally et al, 1989). Gout at prosthetic joints has been reported (Williamson et al, 1994).

Tophi are nodules of a palpable size generally placed near joints and may be the initial clinical feature of gout, but are usually seen in longstanding undiagnosed or improperly treated gout. Tophaceous gout is not a different type of gout; large crystal accumulation just indicates delayed diagnosis or poor treatment. Tophi are often easily seen and can be palpated (figure 4), usually close to joints, and their white content is often seen through the skin (figure 5). When abundant, tophi can result in joint deformation (figure 6). They can also form in the subcutaneous tissue, skin, and their formation along the outer border of the helix is quite characteristic. Also tophi present inside joints can limit movement (Yu et al, 2004). Tophi can be found presenting as masses in many different body locations, resulting in different clinical problems which are finally understood when the mass is sampled and analysed. Aspiration with a needle of a tophus yields a snow white chalky material which is very suggestive of the nature of the nodule, though for an unequivocal diagnosis, the material should be examined by a polarised microscope for definitive identification of the crystals.

Figure 4 Tophus at the olecranon bursa, a common location.



Figure 5 White monosodium urate deposits in a tophus seen through the skin.



Figure 6 Extensive tophaceous gout as seen in a hand. Tophi can be much more extensive than those shown here.



Chronic urate arthropathy is a late feature of neglected gout and is generally associated with palpable tophi. This destructive arthropathy, due to urate infiltration of joints, is responsible for mechanical pain and permanent disability, interspaced with acute or subacute inflammatory episodes. In radiographs, intraosseous tophi and bone erosion by adjacent tophi result in subchondral bone radiolucencies (Dalbeth et al, 2009), often associated with adjacent bone formation, particularly at the erosion edges (bridging osteophytes). Narrowing of cartilage space is characteristically a late event. The association of subchondral bone erosions, osteophytes and long preserved cartilage space is very suggestive of urate arthropathy.

1.5 Diagnosis

Identification of MSU crystals in SF samples drawn from joints undergoing gouty attacks or from tophi allows an unequivocal definitive diagnosis of gout (Zhang et al, 2006b*). It is important to underline that MSU crystals may be found in asymptomatic joints also during the intercritical period, so arthrocentesis should be

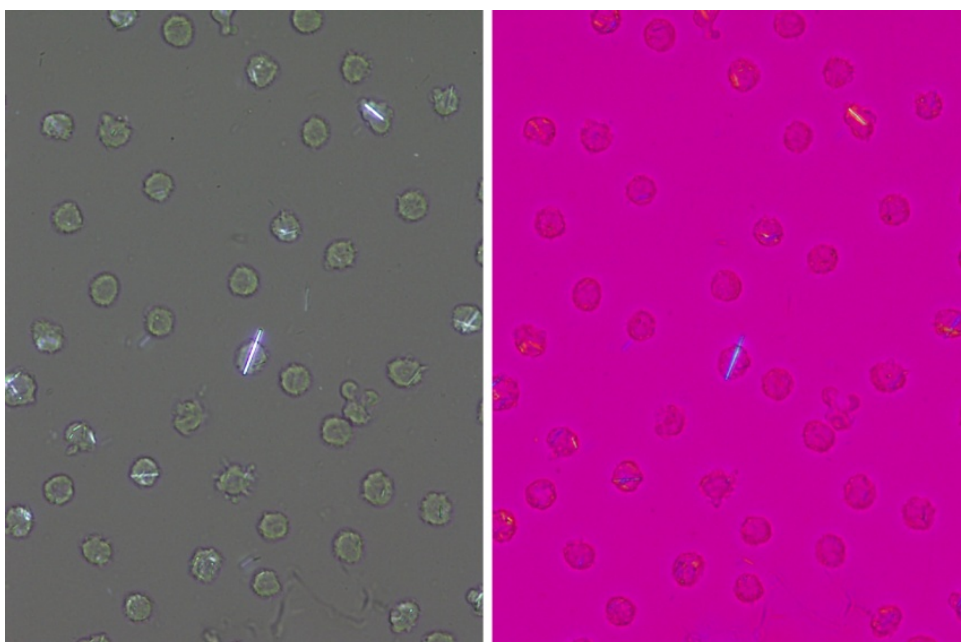
performed even in patients referred when the acute attack is resolved (McCarty and Hollander, 1961; Zhang et al, 2006b*).

Thus, joint aspiration is useful and even mandatory in the diagnosis of gout or when there is a suspicion of gout. Owing to the importance of SF analysis for crystal identification, ultrasonography should be used to facilitate arthrocentesis in difficult locations; furthermore, ultrasonography may be useful in revealing or confirming the presence of crystals in SF before arthrocentesis (Punzi and Oliviero, 2009).

MSU crystals dissolve during SUA-lowering therapy and in treated patients finally disappear; the time needed for disappearance relates to the duration of gout (Pascual et al, 1999*).

The technique of crystal detection and identification in SF (described in 'In depth Discussion I') is a simple and reproducible procedure (Pascual et al, 1989); an ordinary microscope allows detection and identification of MSU (figure 7) and calcium pyrophosphate crystals and is good for initiation into the technique of SF analysis for crystals (Lumbreras et al, 2005*) but a compensated polarised microscope remains the standard tool. Recommendations published by EULAR on the diagnosis of gout (Zhang et al, 2006b*) and outcome measures by Outcome Measures in Rheumatology (Schumacher et al, 2005)—and also the 1977 preliminary criteria for classification of the acute arthritis of primary gout (Wallace et al, 1977)—highlight the accuracy of definitive diagnosis by MSU crystal identification. An appropriate microscope is not expensive and must be available in all rheumatology units. It must be kept in mind that when an infectious arthritis occurs at a joint containing MSU or calcium pyrophosphate crystals, the crystals will be present—and identified if searched for—in the SF. So when a joint infection appears possible, the presence of crystals should not deter from culturing the SF.

Figure 7 Monosodium urate crystals in a synovial effusion ×400. Left: simple polarised microscopy; right: compensated polarised microscopy.



1.5.1 Limitations of clinical diagnosis

In general the clinical manifestations of gout are considered to be sufficiently characteristic to allow diagnosis of the disease, and diagnosing gout on clinical grounds remains a widespread practice among rheumatologists and many other physicians. This approach appears to be supported by the use for diagnosis of the 1977 ACR classification criteria of the acute arthritis of primary gout (Wallace et al, 1977) and by tradition; these criteria have been recently validated against MSU crystal identification and have been found to have poor sensitivity and specificity (Malik et al, 2009; Janssens et al, 2010). In very typical presentations (such as recurrent acute podagra in a patient with hyperuricaemia), gout is by far the most likely diagnosis (and alternate diagnoses unlikely), and clinical diagnosis is reasonable (Zhang et al, 2006b). Absence of podagra, oligoarticular or polyarticular gout, gout in women, less acute or less painful attacks, gout in unusual or very unusual locations, unusually placed tophi, gouty attacks with normal SUA levels and simply, acutely inflamed joints of uncertain (and consistent with an infectious) aetiology are not uncommon presentations. Gout in these settings is only diagnosed if MSU crystals are routinely searched for in all SF samples from all unclassified arthritides, as it should be done according to the EULAR recommendations for gout diagnosis (Zhang et al, 2006b*). Many physicians appear to be happy diagnosing gout on clinical grounds when they feel that it is 'typical', but they are likely to consult a rheumatologist to evaluate patients with less evident disease and in whom they feel that the possibilities of misjudgement and error are not acceptable. Rheumatologists should then be prepared to provide a sound definitive diagnosis based on joint aspiration and crystal identification.

When hyperuricaemia accompanies consistent clinical features it makes the diagnosis more likely, but to use hyperuricaemia as an aid to the diagnosis of gout has important limitations. Hyperuricaemia most frequently is asymptomatic and must not be confused with clinical gout, even if US studies have shown that a large proportion of asymptomatic hyperuricaemic subjects have asymptomatic deposits. Only 0.9 people per 1000/year among those whose SUA is between 7 and 7.9 mg/dL (0.42–0.47 mmol/L) will present with gout. The proportion rises to 4.1 per 1000/year when the SUA is between 8 and 8.9 mg/dL (0.48–0.53 mmol/L) and to 49 per 1000/year with SUA concentrations >9 mg/dL (0.54 mmol/L) (Campion et al, 1987). About 7% of adult men have SUA levels above normal. Any clinical feature in these subjects consistent with gout may easily be taken as gout. On the other hand, SUA levels tend to decrease during gouty attacks (Urano et al, 2002; Park et al, 2003); it can be normal at that time and the diagnosis missed. Sensitivity and specificity of SUA levels are too low to be applied as a diagnostic test.

Tophi are formed by MSU crystals and can be the first manifestation of gout, but tophi should be differentiated from other nodular lesions. If a white content is perceived through the skin the chance of a nodule being a tophus is high, but again in unclassified patients confirmation that the presumed tophus contains MSU crystals should be undertaken by needling and polarisation microscopy.

Although gout can result in rather characteristic radiological images, these only form after a sufficiently long period of evolution of gout and so are only present in a small percentage of undiagnosed patients. Additionally, gout can be misdiagnosed if the diagnosis is based on radiological features (Rappaport et al, 1976; Talbott et al, 1978). Radiological changes have never been critically evaluated for their diagnostic value in gout.

MSU crystal deposits can be detected by sonography, which shows crystals deposited along the surface of the joint cartilage, and also in synovial tissue and tendons. MSU crystals floating in SF are shown by sonography as small echoic aggregates (Grassi et al, 2006*). Subcutaneous or periarticular tophi are also visualised well (Wright et al, 2007). The possibility of using sonography to diagnose gout has received consideration (Thiele and Schlesinger, 2007). Although this is an appealing possibility, studies to determine sensitivity—mostly at the time of the first gouty attack when MSU deposits are likely to be small—and specificity of MSU crystal identification are required before adopting this technique for diagnosis (Chowalloor and Keen, 2013).

1.6 Hyperuricaemia, gout and comorbidities

Gout may be classified as primary or secondary, depending on the presence or absence of an identified cause of hyperuricaemia (Bardin and Richette, 2014). Frequently primary gout may be accompanied or associated with other conditions, including obesity, alcohol consumption, hypertension, type 2 diabetes mellitus, obstructive sleep apnoea and hypertriglyceridaemia (Roddy and Choi, 2014; Zhang et al, 2015). Secondary gout may be the consequence of specific drugs, mainly diuretics, and drugs used in organ transplantation, in particular cyclosporine and tacrolimus; and to a lesser extent low-dose aspirin.

Nephropathy is often found in association with gout. The presence of kidney stones is most common, occurring in 10–40% of patients, with a risk twofold higher than for subjects without gout. Furthermore, an association between hyperuricaemia and renal dysfunction has been observed, independently of urate crystal formation (Bardin and Richette, 2014).

Patients with hyperuricaemia and/or gout should be carefully assessed for the presence of metabolic syndrome, since its prevalence may be very high, up to 60–70%. The presence of metabolic syndrome may explain the presence of an increased cardiovascular risk in patients with hyperuricaemia and mainly, with gout (Pascual and Sivera, 2007). Moreover, studies have shown that gout is an independent risk factor for cardiovascular risk and also for increased all-cause mortality (Krishnan et al, 2006).

1.7 Treatment

1.7.1 Aims of treatment

The management of gout may include different approaches depending on the type of disease presentation and individual patient characteristics. However, the main aims of treatment are the treatment of acute attacks and the cure and/or the prevention of chronic disease, by achieving dissolution of the pathogenic MSU crystals.

So, when planning to treat a patient with gout, several aims have to be independently considered:

1. Gout is a reversible MSU crystal deposition disease; the reduction of SUA to normal levels results in the dissolution of the crystals. The final aim of the treatment of gout is to eliminate the urate crystals; without crystals the possibility of joint inflammation ceases and the disease can be taken as 'cured' (Richette et al, 2016) (although SUA needs to be maintained in the normal range indefinitely to avoid formation of new crystals and the return of gout).
2. Avoidance of inflammatory episodes in joints still containing MSU crystals by appropriate prophylactic treatment.
3. Treatment of the crystal-associated inflammation, which occurs at the initial stage of gout or may recur after the start of urate-lowering treatment, often triggered by dose increases.
4. Finally, causes of gout should be looked for, and other conditions associated with gout, of which the most common is metabolic syndrome, should be recognised and treated.

1.7.2 Acute attack

Owing to the intensity of the inflammation during the acute attack, acute treatment is directed towards reducing inflammation rather than eliminating crystals. Standard treatment includes non-pharmacological treatment, such as rest and application of ice to the affected joints and mainly, pharmacological modalities. According to the pathogenesis of the attack, drugs should be able to combat inflammation and subsequently induce a rapid relief of the symptoms. The most appropriate drugs for this are anti-inflammatory substances, which include traditional drugs such as colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, and innovative drugs, such as the biological drugs acting as IL-1 inhibitors, in patients with inadequate response or contraindication/intolerance to standard drugs. Overall, all anti-inflammatory drugs work much better when given early after the onset of gouty flares.

As already noted by Hippocrates, gouty attacks subside spontaneously after a short period; drugs with anti-inflammatory properties hasten the process and most often result in a rapid relief of the symptoms. It is accepted that treatment early after the start of an attack results in faster resolution.

All drugs indicated for an acute attack may be used alone or in combination with each other. The treatment can be maintained after subsidence to avoid rebounds, generally at lower, prophylaxis doses of a single drug.

1.7.2.1 Colchicine

EULAR and ACR guidelines (Richette et al, 2016; Khanna et al, 2012b*) recommend low doses of colchicine for the treatment of an acute attack, given early after the attack onset, at a loading dose of 1 mg followed 1 h later by 0.5 mg on day 1 (Richette et al, 2016; Khanna et al, 2012b*).

Colchicine is an alkaloid derived from a plant, the *Colchicum autumnale*, which has a long tradition in the treatment of gout. However, there are some concerns about its frequent side effects, especially abdominal complaints, diarrhoea and vomiting, which, however, are generally quickly reversible. In a placebo-controlled trial of high-dose colchicine (1 mg immediately followed by 0.5mg every 2 hours, although colchicine was effective, every patient in the colchicine group experienced diarrhoea and/or vomiting (Ahern et al, 1987). Hence, such high-dose regimes are best avoided.”

A recent trial has shown that, when given in the first 12 h, a lower-dose regimen (two 0.6 mg tablets followed in 1 h by one 0.6 mg tablet) was equally effective for acute gout but with fewer side effects than a higher dose (two 0.6 mg followed by 6-hourly doses of 0.6 mg) (Terkeltaub et al, 2010*). However, other low-dose regimes such as 0.5mg two to four times daily are not uncommon in clinical practice yet have not been evaluated in randomised trials (Roddy and Doherty, 2010 ; British National Formulary). Continuation of a lower dose of colchicine (0.5 mg twice a day) is usually needed for 1–2 weeks to treat the attack, and for several months if a urate-lowering drug is introduced to prevent ultra-low-dose (ULT)-induced flares. Colchicine can be used in combination with other anti-inflammatory drugs in acute gouty attacks, possibly in doses lower than when used alone.

A true severe toxicity, with myelotoxicity and myotoxicity, is uncommon and usually related to very high doses and/or to prolonged use, most often in older patients with renal, hepatic or other comorbidities. Colchicine dose reduction or non-prescription is recommended in these patients and in those taking lipid-lowering drugs and drug inhibitors of cytochrome P450 3A4 and P-glycoprotein, such as clarithromycin, erythromycin, cyclosporine and disulfiram.

1.7.2.2 NSAIDs

All NSAIDs given to treat acute attacks of gout have shown efficacy. NSAIDs are considered a convenient and well-accepted therapeutic option (Richette et al, 2016; Khanna et al, 2012b*); the choice of a specific NSAID is largely a matter of personal preference (Bardin and Richette, 2014). It appears advantageous to use full doses of the selected drug unless contraindications are present. Among NSAIDs, indomethacin has traditionally been considered to be a particularly effective agent, however, there is no evidence to support its effectiveness over

any other NSAID and it is best avoided in view of frequent toxicity (Roddy and Mallen, 2013). Cyclo-oxygenase 2 (Cox-2) inhibitors are an option in patients with gastrointestinal contraindications or intolerance to NSAIDs. Major limitations of the conventional NSAIDs are the well-known side effects of the group—gastrointestinal, cardiovascular and renal—and the possibility of interactions with other drugs taken by the patient. Gouty attacks often strike aged patients with comorbidities, in whom NSAIDs can be hazardous, especially in elderly patients taking oral anticoagulants. Although distressing and painful, gouty attacks only exceptionally constitute a major health problem so effective therapeutic alternatives to NSAIDs should be seriously considered.

1.7.2.3 Glucocorticoids

A short course of systemic glucocorticoids (such as 30–35 mg of prednisone for 3–5 days with a rapid tapering off) (Groff et al, 1990; Janssens et al, 2008) has been found effective. Recent ACR guidelines recommend starting treatment with oral prednisone 0.5 mg/kg per day with a duration of 5–10 days or 2–5 days at full doses, then tapering for 7–10 days and then stopping (Khanna et al, 2012b*). However, short courses of glucocorticoids can be followed by a rebound attack of gout. To avoid this, co-administration of prophylactic doses of colchicine (0.5–1.5 mg/day) from the start of the glucocorticoid treatment may help.

Intra-articular glucocorticoids, even in small doses (Fernández et al, 1997), are effective especially when large joints are affected and may minimise the systemic effects of these drugs and are safe if joint infection has been excluded. As suggested above, intra-articular treatment could be used in combination with oral glucocorticoid, colchicine or an NSAID (Khanna et al, 2012b*).

A few studies support the rapid effectiveness of parenteral adrenocorticotrophic hormone, which is considered by ACR recommendations (Khanna et al, 2012b*) for patients unable to take oral anti-inflammatory drugs (Fernández et al, 1997).

1.7.2.4 Off-label therapy: the interleukin-1 blockade

Refractory gouty attacks have not been critically defined and the approach to the treatment of 'refractory' gouty inflammation has only received anecdotal attention. However, this might, in some cases, be a serious problem. Owing to the role of IL-1 β in gouty inflammation, some authors have proposed the use, in refractory cases, of agents which can block this cytokine. At present three such agents are available. Two of these, canakinumab and rilonacept (also known as IL-Trap) are Food and Drug Administration (FDA) and EMA approved for cryopyrin-associated periodic fever syndromes. Anakinra is FDA and European Medicines Agency (EMA) approved for rheumatoid arthritis. Each of these agents has recently been investigated in refractory gout, with promising results in both acute attack and prophylaxis. The most important difference in clinical use among these three agents is their half-life, the longest being canakinumab (21–28 days), followed by

rilonacept (34–57 h) and anakinra, which is the shortest-acting IL-1 β antagonist, with a half-life of 4–6 h. Anakinra, a recombinant IL-1 receptor antagonist was the first of these agents to demonstrate efficacy in an open-label trial in 10 patients with acute gout (So et al, 2007). Another study provided a positive signal to suggest that rilonacept may offer a well-tolerated approach for reducing pain in patients with chronic active difficult gouty arthritis not adequately managed with other treatments (Terkeltaub et al, 2009). Two recent randomised, multicentre, double-blind trials showed that treatment with canakinumab provided significant pain and inflammation relief and reduced the risk of new flares in patients with acute gouty arthritis (Schlesinger et al, 2012), leading to recent EMA approval.

These preliminary results support the hypothesis that IL-1 blockade may be a useful and selective treatment strategy for the growing population of patients with gout, including chronic, refractory gouty arthritis, who cannot tolerate standard treatments such as NSAIDs, colchicine or glucocorticoids. Obviously, as for rheumatoid arthritis, current infection is a contraindication to the use of IL-1 blockers.

1.7.3 Urate-lowering therapy

Because hyperuricaemia is the absolute prerequisite of gout, the primary objective of SUA-lowering therapy is to maintain urate concentration below the saturation point for MSU. This treatment dissolves crystal deposits and cures gout while it is maintained. EULAR and ACR guidelines recommend that plasma or serum urate should be maintained at a concentration of <6 mg/dL (360 μ mol/L) (Richette et al, 2016; Khanna et al, 2012a*). However, this target serum level can be lowered to <5 mg/dL (300 μ mol/L) in the presence of severe tophaceous gout (Khanna et al, 2012a*). Lower SUA levels result in faster reduction of the size of tophi (Perez-Ruiz et al, 2002b) and the same presumably occurs with crystals deposited in joints. However, whilst it appears rationale to recommend reducing SUA levels as much as reasonably possible, particularly in patients with long-standing tophaceous or polyarticular gout, a cautionary note has been introduced by the observation that hyperuricaemia may be protective against the incidence and progression of neurodegenerative disease (Acherio et al, 2009 ; Eusar et al, 2009; Auinger et al, 2010 ; Paganoni et al, 2012 ; Jain et al, 2011). The implications of this for lowering SUA in the context of treating gout are unknown, however, the revised EULAR management guideline advises against maintaining very low SUA levels in the long-term (Richette et al, 2016). In patients with gout of longer duration, the time of disappearance of MSU crystals from signal joints induced by normalisation of SUA levels has been shown to be longer (Perez-Ruiz and Liote, 2007*).

There is no general agreement about the right time for starting SUA-lowering therapy (ULT). Suggestions vary from very early initiation after the initial attacks to not starting this treatment unless the patient has several attacks per year, or develops chronic arthritis or tophi, radiological lesions or uric acid renal calculi. However, early treatment may be advantageous because the aim of SUA-lowering therapy is to dissolve all MSU crystals and this takes less time when gout is more recent. Furthermore, gout has been identified as an independent

risk factor for atherosclerotic cardiovascular disease, the level of this association rising with the severity of gout, also in women (De Vera et al, 2010). Crystal disappearance might lead to the diminution or disappearance of this risk factor. Finally, SUA levels should be maintained within normal values after elimination of the MSU crystals from the joints, otherwise crystals will form again and with them gouty inflammation returns (Bull and Scott, 1989; van Lieshout-Zuidema and Breedveld, 1993). Therefore after the crystals have dissolved, unless dietary and lifestyle modifications are sufficient to reduce SUA to normal levels, SUA-lowering therapy should continue. The best method of ascertaining that MSU crystals have disappeared from the joints remains undetermined, although sonography seems to be useful (Chowalloor and Keen, 2013). In any case, if SUA levels are to be kept within normal values indefinitely, the need to ascertain the disappearance of crystals has limited clinical value.

For all SUA-lowering drugs it is an often accepted rule that they should not be started until the gouty attack has fully resolved; furthermore, it must be kept in mind that the initiation or increase in dosage of SUA-lowering therapy in patients with gout frequently results in a gouty attack if prophylactic colchicine is not co-administered—for example, at 0.5–1 mg/day.

The ULT could be started during an acute attack, provided that the anti-inflammatory therapy has been instituted and is effective. The dose of drug used in ULT should initially be low and progressively increased until the achievement of the target serum urate level. It is important to monitor SUA levels during ULT titration, approximately every 2–4 weeks.

Three classes of drugs are approved for ULT: xanthine oxidase inhibitors, uricosuric agents and uricase agents. Xanthine oxidase inhibitors block the synthesis of uric acid.

1.7.3.1 Allopurinol

Since its introduction, allopurinol has become the mainstay urate-lowering drug and so it is used as first-line ULT. It has been used extensively, is inexpensive and for most patients with gout it is a safe and effective option. Allopurinol is a purine analogue that competitively inhibits xanthine oxidase, the enzyme responsible for the degradation of hypoxanthine and xanthine to uric acid, reducing the total amount of uric acid formed. The starting dose of allopurinol should be no greater than 100 mg/day, consistent with EULAR and ACR guidelines (Richette et al, 2016; Khanna et al, 2012a*), and should be increased progressively until a target uric acid concentration or maximum dose is achieved. This low dosage could reduce the early gout flares after ULT initiation, and the risk of a rare but severe hypersensitivity reaction to allopurinol. Cutaneous intolerance to allopurinol occurs early (in the first 3 months) of allopurinol introduction or dose increase and should prohibit any further allopurinol use. In patients with healthy renal function, daily doses can be raised to 300–600 mg, and even to 900 mg/day in rare cases.

Data drawn from different series show that in a substantial percentage of allopurinol-treated patients the SUA levels attained are insufficient for crystal dissolution, but this probably relates to the widespread use of 300 mg/day as a fixed dose.

The allopurinol dose needs correction according to renal function, since levels of oxypurinol, the main metabolite of allopurinol, are related to the glomerular filtration rate (Emmerson et al, 1987). Published standards for quality care recommend dose reductions of allopurinol and avoidance of NSAIDs in patients with Cr clearance <50 mL/min (Mikuls et al, 2004). Allopurinol dose adjustment to renal function is also recommended by the EULAR and ACR guidelines (Richette et al, 2016; Khanna et al, 2012a*), to avoid toxicity. For many years, dose adjustment has followed the recommendations by Hande et al based on the maximum permitted allopurinol dose per level of renal impairment (Hande et al, 1984). More recently, a regime based on the starting dose of allopurinol has been shown to reduce the incidence of allopurinol hypersensitivity syndrome (Stamp et al, 2012). Of importance, reduction of SUA has been found to improve renal function in both non-gouty (Siu et al, 2006) and gouty patients with renal insufficiency (Perez-Ruiz et al, 2000).

Azathioprine is metabolised also by xanthine oxidase; allopurinol interferes in its metabolism and their co-administration results in higher levels of azathioprine, risking marrow suppression. Coadministration is therefore not recommended, although a regime for adjustment of the dose of azathioprine exists (Witte, Allen, 2008). In kidney transplant recipients with gouty arthritis, mycophenolate mofetil may be substituted for azathioprine (Jacobs et al, 1997), allowing a safer use of xanthine oxidase inhibitors.

The allopurinol hypersensitivity syndrome remains a serious and potentially lethal hazard, which can develop within the 3 first months of allopurinol introduction or titration (Jacobs et al, 1997). Severe allopurinol-induced toxic effects arise in <1% of patients but can be life threatening, with a mortality rate of about 20% (Gutierrez-Macias et al, 2005; Bardin and Richette, 2014).

For mild cases of the allopurinol hypersensitivity syndrome desensitisation may be an option (Fam et al, 1992), but it is hazardous in more severe cases. An association of severe hypersensitivity reaction with human leucocyte antigen (HLA-B*5801) has been observed in Chinese and Korean patients, so HLA testing should be considered in these populations before starting allopurinol treatment (Khanna et al, 2012a*).

The general approach to both allopurinol hypersensitivity and refractoriness, generally, is to apply alternative drugs.

1.7.3.2 Non-purine inhibitor of xanthine oxidase: febuxostat

Febuxostat is a non-purine selective inhibitor of xanthine oxidase, approved for the management of gout in the USA and in the European Union. The doses of 80 mg/day and 120 mg/day, which have been approved in Europe, have shown better efficacy than 300 mg/day allopurinol in controlled studies (Becker et al, 2005a;

Becker et al, 2005b). Since metabolism occurs in the liver via glucuronide formation and oxidation, with about 50% of the drug excreted in stool and 50% in the urine, febuxostat dose adjustments are not needed in patients with mild to moderate renal failure (Mayer et al, 2005). Febuxostat provides an advantageous alternative for patients in whom allopurinol cannot be used at appropriate doses because of renal insufficiency or intolerance. Febuxostat is not recommended for patients with severe heart disease. With regard to severe cutaneous reactions, in one study, 12 of 13 patients with gout and previously documented severe allopurinol adverse events tolerated subsequent febuxostat treatment safely. However, the development in one case of a hypersensitivity-type cutaneous vasculitis, probably but not definitively febuxostat-related, mandates caution, careful dose escalation and close monitoring when febuxostat is considered for allopurinol-intolerant patients (Chohan, 2011).

1.7.3.3 Uricosuric drugs

Uricosuric drugs work by raising the renal clearance of urate. The most used are probenecid, sulfinpyrazone and benzbromarone. They are valid options as second-line therapy especially if use of allopurinol is problematic. Treatment with uricosuric drugs makes sense since the majority of patients with gout have impaired renal excretion of uric acid (Perez-Ruiz et al, 2002a; Pascual and Perdiguero, 2006) which can be normalised by these drugs. Since uricosuric drugs are associated with a high risk of urolithiasis, they are contraindicated in patients with a history of urolithiasis. Furthermore, fluid intake should be increased and urine pH maintained above 6 to prevent development of uric acid stones (Richette and Bardin, 2010*).

Benzbromarone remains available in some European countries, although with restricted use, but not in the USA. It is mainly indicated in the treatment of patients refractory or intolerant to allopurinol (Kumar et al, 2005). It can be used in patients with moderate renal insufficiency (Pérez-Ruiz et al, 1999), and has been a successful option for transplanted patients with gout (Zürcher et al, 1994; Marcén et al, 1995). In Europe the drug was discontinued because of rare cases of fatal liver toxicity, but a review has shown that deaths are no more frequent with benzbromarone than with allopurinol or colchicine (Jansen et al, 2004). A typical starting dose of benzbromarone would be 50 mg daily, to be increased in steps of 50 mg to the maintenance dose (often 100–200 mg day) required to reach the SUA target, whilst carefully monitoring liver function (Lee et al, 2008).

The recent ACR recommendations suggest that probenecid should be preferred as first choice among uricosuric drugs available in the USA (Khanna et al, 2012a*), and underline that uricosuric drugs have to be used cautiously, at the same time as alkalinising the urine and raising the ingestion of fluids, but only if there is no other rational option available. For difficult cases of patients refractory to allopurinol the combined use of allopurinol, which decreases the total amount of urate formed, and a uricosuric drug, which by raising the renal urate clearance decreases the SUA levels further, often works well and is worth trying.

1.7.3.4 Uricase

In all mammals, except man and higher primates, who lost uricase through mutations (Oda et al, 2002), uricase degrades uric acid to allantoin which is soluble and can be easily disposed. In humans uricase is a very effective means of preventing and treating tumour lysis syndrome and SUA levels as low as 0.78 ± 0.4 mg/dL (0.05 mmol/L) after 4 h of administration can be achieved (Goldman et al, 2001). Rasburicase, a recombinant uricase, has been now successfully used in unusually severe cases of gout (Vogt, 2005; Richette and Bardin, 2006). At present, a pegylated (to increase the half-life of the drug) uricase has been approved by the FDA and EMA for the treatment of severe refractory gout (Becker et al, 2013). These drugs appear to be able to deplete urate deposits faster than other available drugs and could be used if considered especially convenient. Their proper place in the management of gout will become established as we gain experience with them.

1.7.3.5 Other drugs

Losartan, calcium pump inhibitors, statins and clofibrate are uricosuric and have a SUA level reducing effect. The effect of losartan has been found sometimes to be transient, but fenofibrate has a long-lasting effect. They can be useful adjuvants in the management of patients with gout, who can also benefit from their effect in reducing blood pressure and lowering lipids.

1.7.4 Prophylaxis of ULT-induced gouty attacks

Urate lowering frequently induces mobilisation of persisting urate crystals, resulting in the occurrence of acute flares when ULT are started. This should be explained to the patient and prevented as such flares can make the patient stop taking the ULT. The daily administration of 0.5–1.5 mg colchicine avoids in most cases such ULT-induced attacks of inflammation (Yu, 1992). Prophylaxis is recommended during the first 6 months (Borstad et al, 2004). In any case, after initiation of SUA-lowering therapy, gouty attacks may still occur until the joint is free of crystals, and for complete avoidance of attacks, colchicine therapy should be maintained until their complete dissolution. The initiation and increase in dose of SUA-lowering therapy often results in an attack of gout if prophylaxis is not co-administered. It has been noted that after prolonged successful SUA-lowering therapy gouty attacks became less frequent (Sarawate et al, 2006); this may be related to the decrease in the concentration of MSU crystals in joints as a result of the SUA-lowering therapy, already apparent at 3 months after its initiation (Roddy and Doherty, 2010). For the few patients who are intolerant even to small daily doses of colchicine, an every other day schedule can be tried. A small dose of a NSAID, such as naproxen 250mg daily, or oral prednisolone 5-7.5mg daily, can be an appropriate alternative if colchicine cannot be tolerated. A minority of patients usually with longstanding poorly treated gout have attacks when starting SUA-lowering drugs even if given prophylaxis with a proper dose of colchicine. For these patients it is worth giving, in addition to an incremental progressive increase in SUA-lowering treatment (as allopurinol given in 100 mg increments), a more complete prophylaxis including colchicine and a small dose of an NSAID. Occasionally,

patients need the addition of prednisone 5–7.5 mg/day to colchicine for 1–3 months to allow an uneventful start of SUA-lowering treatment. For patients with especially difficult prophylaxis, IL-1 blocking by canakinumab or anakinra may be an alternative to consider. In the long term the best prophylaxis is to implement proper SUA-lowering treatment and dissolve all MSU crystals, since in their absence gout does not occur.

1.7.5 Dietary and lifestyle factors, medication

The popular association of gout and other diseases with the overindulgence in alcohol and food associated with wealth predates modern medicine. Hyperuricaemia and gout are now considered as elements of the metabolic syndrome, where hyperuricaemia results mainly as a consequence of a decreased renal clearance of urate. In these subjects a hypocaloric diet decreases SUA levels by increasing urate clearance (Tirahones et al, 1997) and, if the diet is also low in fat, it is also beneficial for the often coexisting obesity, hypertension and hyperlipidaemia (Miller et al, 2006). The increasing prevalence of gout, in general, has been related to dietary changes. Gout associated with the metabolic syndrome shares the comorbidities of the group, mostly related to atherosclerosis. Gout has now been independently associated with myocardial infarction, the level of this association rising with the severity of gout (Krishnan et al, 2006). No doubt the benefits of appropriate lifestyle changes go far beyond their effect on gout (Choi and Curhan, 2005). The attention to comorbid conditions is considered as a key issue in recently published recommendations on gout management (Richette et al, 2016; Khanna et al, 2012a*). The relation of lifestyle changes and diet with gout has been extensively reviewed (Choi and Curhan, 2005; Fam, 2005; Lee et al, 2006; Saag and Choi, 2006; Choi et al, 2008). In addition to reduced intake of food rich in purine (such as anchovies, herring and animal organs) and alcohol, sugar-sweetened soft drink consumption should also be kept to a minimum, as the latter also is associated with hyperuricaemia, in contrast to diet soft drinks (Choi and Curhan, 2008; Choi et al, 2008).

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2. Calcium pyrophosphate crystal deposition disease

LEARNING OUTCOMES

- ➔ To outline the terminology recommended by the EULAR
- ➔ To describe and explain the epidemiology and the various aetiologies of the disease
- ➔ To describe and explain the pathophysiology of calcium pyrophosphate (CPP) crystal deposition and of CPP crystal-induced inflammation
- ➔ To describe the multiple clinical presentations of CPP
- ➔ To outline the links between osteoarthritis and CPP crystal deposition
- ➔ To diagnose CPP crystal deposition disease, according to the EULAR recommendations
- ➔ To manage CPP crystal deposition disease, according to the EULAR recommendations

2.1 Introduction

Three types of calcium-containing crystals can be observed in and/or around joints (table 1). Calcium oxalate crystal deposits are very rare and occur almost exclusively in patients with primary or secondary oxalosis who are undergoing dialysis. Basic calcium phosphate deposition is the main cause of calcific tendinitis/bursitis. Calcium pyrophosphate (CPP) dihydrate crystals are commonly found in the joints of the elderly and can occasionally be observed in periarticular tissue. These three types of calcium-containing crystals are associated with a variety of clinical features but are frequently asymptomatic. This paper focuses on CPP dihydrate crystal deposition disease.

Table 1 Intra-articular and periarticular calcium crystal deposits

	Intra-articular	Periarticular
CPPD	+++	+
BCP	+	+++
Ca Oxalate	++	++

BCP, basic calcium phosphate; CPPD, calcium pyrophosphate deposition.

2.2 Terminology

To simplify a terminology which has been variable and confusing, EULAR has recently issued recommendations (Zhang et al, 2010), according to which CPP dihydrate crystal is abbreviated as CPP crystal. CPP deposition (CPPD) stands as the umbrella term for the conditions related to this disorder, including acute CPP crystal

arthritis (formerly frequently called ‘pseudo-gout’), osteoarthritis (OA) with CPPD (formerly ‘pseudo-OA’) and chronic CPP crystal inflammatory arthritis (formerly ‘pseudo-rheumatoid arthritis (RA)’). Chondrocalcinosis (CC) is cartilage calcification, most commonly due to CPPD and detected by imaging or histological examination.

2.3 Epidemiology

CPPD is mainly a disease of the elderly (Richette et al, 2009). Prevalence of radiological CC in Caucasians is very low before 55–60 years of age but subsequently increases: 15% between 65 and 74 years; 36% between 75 and 84 years and 44% in those aged ≥ 85 years according to one study (Wilkins et al, 1983). One community study in the UK confirmed an increased prevalence of CC with age: from 3.7% for those aged 55–59 years to 17.5% for those aged 80–84 years (Neame et al, 2003). Prevalence may be lower in Chinese people (Zhang et al, 2006). Most patients with early CPPD have familial or secondary disease.

2.4 Classification

CPPD can be a familial disease, which is most frequently recognised as an early onset severe disease but has also been identified in the elderly with the usual clinical presentations (Fernandez Dapica and Gomez-Reino, 1986; Reginato et al, 1995). CPPD can also be secondary to a number of metabolic diseases (table 2) (Jones et al, 1992; Richette, et al, 2009), including primary hyperparathyroidism (Rynes and Merzig, 1978), haemochromatosis (Pawlotsky et al, 1999) and hypomagnesaemia (Richette et al, 2007), some of which can also be familial. CC can also develop in operated or traumatised joints (Doherty et al, 1982; De Lange and Keats, 1985). CC has also been reported to associate with low cortical bone mineral density (Abhishek et al, 2014). Most patients with CPPD have no familial or predisposing disease. This idiopathic or sporadic CPPD particularly involves the elderly.

Table 2 Conditions associated with calcium pyrophosphate deposition

Definite associations	Possible associations
Hypophosphatasia	Gout
Primary hyperparathyroidism	Ochronosis
Familial hypercalciuric hypercalcaemia	Wilson’s disease
Haemochromatosis	Hypophosphataemic rickets
Hypomagnesaemia	Brachydactyly and epiphyseal dysplasias
	Acromegaly

2.5 Pathophysiology

CPP deposits occur mainly in the mid-zone of articular cartilage and in fibrocartilage of joints (figure 1) and are believed to be due to a locally excessive $[Ca \times PP]$ product. Early studies have shown that pyrophosphate (PPi) concentrations are normal in the serum (except for patients with hypophosphatasia) but elevated in the synovial fluid (SF) of patients with CPPD or in patients affected by a metabolic disease which predisposes to CPPD (Doherty et al, 1991). PPi is abundantly produced by cells, following the metabolism of ATP during synthetic processes, but intracellular PPi cannot passively cross intact cell membranes. Two mechanisms are known to release PPi outside the cells (figure 2). The ecto-enzyme plasma cell glycoprotein 1 (PC1) hydrolyses extracellular nucleotide triphosphate, resulting in PPi release outside the cell. A PPi transporter, ankylosis human (ANKH), allows intracellular PPi to be excreted across the cell membrane (Ho et al, 2000; Netter et al, 2004). A second ectoenzyme, alkaline phosphatase metabolises extracellular PPi to orthophosphate, explaining the increased PPi concentration and CPPD incidence in hypophosphatasia (Chuck et al, 1989). Activating mutations of the ANKH gene have been identified in some, but not all, patients with familial CC (Pendleton et al, 2002). ANKH activity can be increased by cytokines such as transforming growth factor β , and this, together with some polymorphisms of the gene (Zhang et al, 2005), might be an explanation for idiopathic (sporadic) CC. Magnesium is a coenzyme to alkaline phosphatase and increases CPP solubility, explaining the link between CPPD and hypomagnesaemia (Richette et al, 2007). Hypercalcaemia due to familial primary hyperparathyroidism or hypocalciuric hypercalcaemia increases the $[Ca \times PPi]$ product. In addition cartilage damage is also likely to play a role in CPPD as suggested by the association of CPPD with previous traumatic or surgical trauma of the involved joint (Doherty et al, 1982; De Lange and Keats, 1985).

Figure 1 Radiograph of an anatomical slice of the knee joint showing calcium pyrophosphate deposition within the femur cartilage (FC), tibial cartilage (TC) and the meniscus.

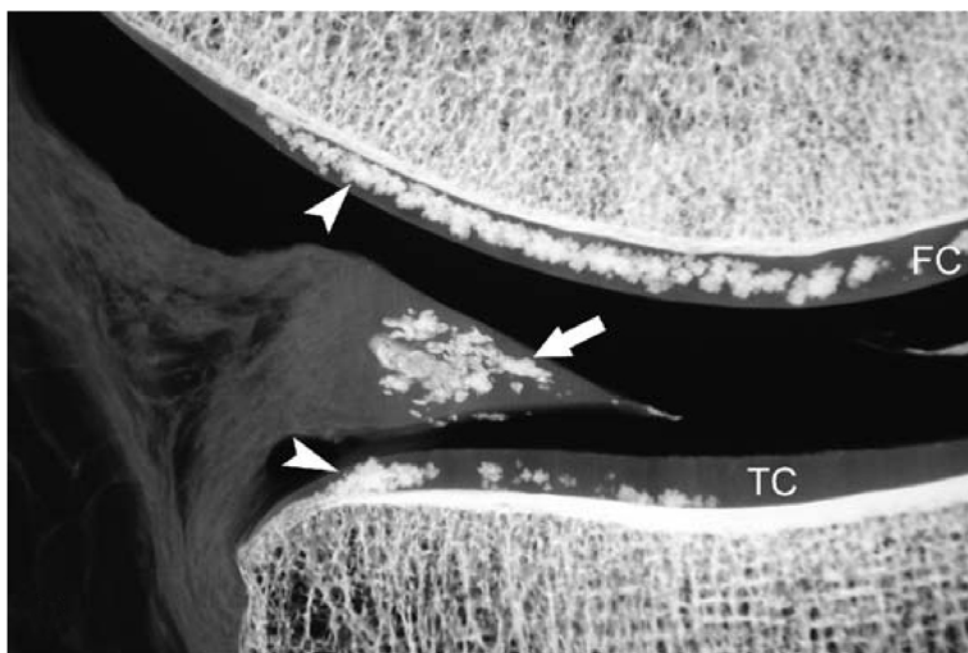
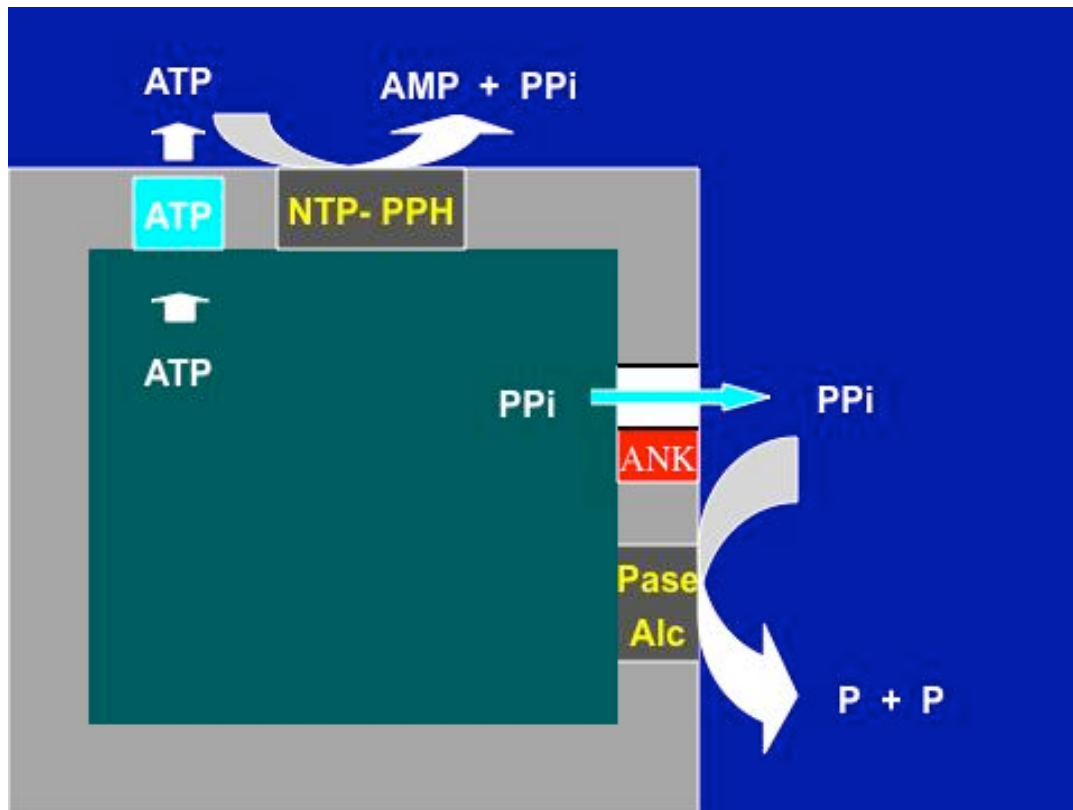


Figure 2 Metabolism of extracellular pyrophosphate (PPi).



Clinical features of CPPD are probably due to the interactions of various cells with CPP crystals. CPP crystal-induced acute inflammation follows patterns similar to monosodium urate crystal-induced inflammation, including activation of interleukin 1, which seems to play an important part in triggering inflammation (Martinon *et al*, 2006) and could become a target for treatment. CPP crystals may also interact with synovial fibroblasts, leading to the release of metalloproteinase and other mediators involved in joint destruction (Cheung *et al*, 1981).

2.6 Clinical presentation

CPPD is most frequently asymptomatic. CC is often recognised incidentally on radiographs of elderly healthy individuals. Therefore it should not be too easily considered as a certain cause of joint symptoms.

Acute CPP crystal arthritis has been called ‘pseudo-gout’ because it was mistaken for gout before the introduction of synovial fluid microscopy and discovery of monosodium urate and CPP crystals, which then made it possible to discriminate between these two conditions. It is a common cause of acute arthritis in the elderly, which has to be distinguished from other causes of severe acute monoarthritis such as septic or reactive arthritis. Similarly to a gout flare, acute CPP crystal arthritis has a brusque onset, and is self-limiting. It most often affects the knee, with other commonly affected joints being the wrist, ankle and shoulder. Triggering factors include trauma, intercurrent illness or surgery, bisphosphonate infusion (Wendling *et al*, 2008), parathyroidectomy (White *et al*, 1988) (which may dissolve crystal deposits by lowering calcium levels)

and joint lavage of the affected joint. Arthroscopic lavage of a joint with pre-existing CC has been estimated to provoke acute CPP crystal arthritis in 26% of cases, probably by promoting crystal shedding in the joint space (Pasquetti *et al*, 2004). Hyaluronate intra-articular injection has been repeatedly reported as a triggering factor (Dilsa *et al*, 1999), though this has been disputed (Punzi *et al*, 2000). Granulocyte colony stimulating factor has also been reported to favour acute CPP crystal arthritis in patients with neutropenia, a finding consistent with the important role of polymorphonuclear cells in the genesis of crystal-induced acute inflammation (Ames and Rainey, 2007). Severe inflammation of a large joint may be accompanied by fever and simulate a bacterial infection. Septic arthritis and CPP crystal arthritis can coexist and so bacteriological studies should be conducted even in SF exhibiting CPP crystals (Zhang *et al*, 2010). Oligoarticular or even polyarticular acute CPP crystal arthritis may occur and the inflammation can also be less intense or acute. In superficial joints, such as the wrist, erythema and swelling may be prominent. Attacks of arthritis are generally intermittent with long intercritical periods, but some patients have frequent attacks affecting the same, or a different, joint each time. As the pattern can vary it is sensible to look for CPPD in all cases of undiagnosed more or less inflammatory arthropathy, either intermittent or persistent, with or without associated OA.

Chronic CPP crystal inflammatory arthritis may mimic RA (McCarty 1976), with longstanding bilateral and symmetrical synovitis, frequently involving the wrists and finger joints and tendon sheaths, associated with increased acute phase reactants and increased cellularity of the SF. Radiographs differ from those for RA and typically exhibit CC and fine subchondral bone sclerosis underlining bone contours, epiphyseal geodes and frequent osteophytosis, with no marginal erosion. SF analysis allows appropriate diagnosis by demonstrating the presence of CPP crystals. Predominant involvement of proximal joints may also mimic polymyalgia rheumatica, a disease which also predominantly affects the elderly (Pego-Reigosa *et al*, 2005).

OA with CPPD usually differs little from OA without CPPD. Prospective studies have been unable to show any difference in the outcome of OA according to the presence of CPPD (Neogi *et al*, 2006; Viriyavejkul *et al*, 2007). CPP crystals are often identified in OA SF and may be only an epiphenomenon, secondary to cartilage damage in OA (Nalbant *et al*, 2003). However, some sites, such as the ankles, elbows, wrists and shoulders seem to be more frequently involved in CPPD than in 'primary' OA. Involvement of the trapezioscapoid joint has been strongly associated with CPPD, and may suggest this diagnosis, especially when the first carpometacarpal joint appears normal (Peter *et al*, 2001). Large or multiple small subchondral bone cysts can be found in OA with CPPD, particularly at the wrist, where radioulnar arthropathy, non-traumatic scapholunate dissociation and carpal collapse can also be seen (Resnick and Utsinger, 1974; Bourqui *et al*, 1983). Osteophytosis has also been reported to be associated with CC (Neame *et al*, 2003).

Destructive arthropathies have been described in elderly women with CPPD (Richards and Hamilton, 1974; Menkes *et al*, 1976). Several joints are often involved—in particular, the hip, knee, spine, wrist and shoulder. Joint space narrowing is associated with subchondral bone destruction, which may lead to a pseudo-Charcot

joint picture. Progression of destruction can be rapid: the so called rapidly destructive OA of the hip has been linked to CPPD (Menkes *et al*, 1985).

Haemarthrosis is a classic feature of CPPD. Bleeding in the joint can be recurrent and seems to follow bone erosion.

Spinal involvement of CPPD may be restricted to asymptomatic deposits in intervertebral discs. These CPP deposits can also be responsible for acute or subacute inflammatory episodes. Inflammation can be associated with destructive changes suggestive of infectious discitis. Imaging studies show the absence of abscess. A reassuring vacuum phenomenon is frequently exhibited by CT scan or plain radiographs (lateral extension views). Interapophyseal joint involvement can be responsible for joint erosion and instability, spondylolisthesis and sometimes large cysts of the pedicles. Cervical spine involvement can be associated with cervical myelopathy, sometimes related to dural CPPD. The craniocervical hinge can be involved and CPPD is together with basic calcium phosphate deposition disease a source of the crowned dens syndrome, characterised by calcium deposits around the dens and responsible for acute pain of the upper cervical spine and occiput (Feydy *et al*, 2006; Salaffi *et al*, 2008). CPP deposits in the transverse ligament can be associated with erosion of the adjacent dens and type II fracture (Kakitsuba *et al*, 2000).

Tendons and fascia can be affected by CPPD. Tendon deposits appear in radiographs as fine linear calcifications starting at a distance from the bone attachment. Their appearance is therefore very different from the rounded opacities of basic calcium phosphate deposition. Achilles, quadriceps and gastrocnemius tendons are often affected (Gerster *et al*, 1977; Tang *et al*, 1996). Plantar or finger flexor fascia can also be involved. An ultrasound scan is a useful tool for detecting CPP deposits in tendon or fascia (Falsetti *et al*, 2004). These deposits are most frequently asymptomatic, although local pain, nerve entrapment syndromes and finger extensor tendon rupture have been associated with tendon or fascia CPPD (Gerster *et al*, 1980; Patrick *et al*, 1988; Waguri-Nagaya *et al*, 2001).

Tumoural deposits of CPP crystals are rare but have been reported in various sites: fingers, knees, hips, temporomandibular joints, most frequently in patients lacking CC (Sissons *et al*, 1989; Ishida *et al*, 1995). In some instances deposits appear to follow a cartilaginous metaplasia of the synovium. Others, such as those in the finger pulp, arise far from the joints. Rare CPPD in the retina, dura or other extra-articular sites has also been reported.

2.7 Diagnosis

As emphasised by the EULAR recommendations for the diagnosis of CPPD (Zhang *et al*), identification of CPP crystals in synovial fluid or joint biopsy specimen allows a definite diagnosis. CPP crystals are poorly birefringent and are better seen by regular light than by polarising microscopy (Ivora *et al*, 1999). Under

compensated polarising light microscopy, crystals appear as positively birefringent. They can be observed, in particular, in the knee in the SF of asymptomatic joints (Martinez and Pascual, 2005). The demonstration of typical CC by radiographs (figure 3) is of good diagnostic value but may lack sensitivity (Utsinger *et al*, 1975). Radiographs of knees are the most frequently positive. Other joints such as the pubic symphysis, wrists, shoulders, or others less frequently, display CC on radiographs. Ultrasound scanning appears to be a promising tool to provide evidence of CPP deposits and may be more sensitive than radiography, in particular at the wrist (Frediani *et al*, 2005; Filippou *et al*, 2007) and at the knee (Barskova *et al*, 2013). Although metabolic predisposition is rare, patients with young age at onset (age under 55 years) or florid polyarticular chondrocalcinosis should be screened for primary hyperparathyroidism (serum calcium, parathyroid hormone), haemochromatosis (ferritin), hypomagnesaemia (serum magnesium) and hypophosphatasia (alkaline phosphatase) (Zhang *et al*, 2011).

Figure 3 Chondrocalcinosis.



2.8 Management

Very few studies have dealt with CPPD management (Zhang *et al*, 2011). No drug has been shown to influence CPP deposition and therefore CPPD management remains purely symptomatic. Magnesium supplementation led to reduction in CC in one hypomagnesaemic patient (Runeberg *et al*, 1975) and can be recommended in cases of hypomagnesaemia. Treatment of underlying hyperparathyroidism or haemochromatosis does not seem to affect the course of CPPD (Barskova *et al*, 2013). In vitro, probenecid reduces the activity of the ANKH transporter (Ho *et al*, 2000) but has not been tested in human CPPD.

Acute CPP crystal arthritis is best treated by rest, local ice packs, SF aspiration (which also allows SF examination and identification of CPP crystals) and intra-articular steroid injection (Zhang *et al*, 2011). Colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) can be used but may be poorly tolerated by the elderly. Moreover, support for their use is mainly indirect, extrapolated from studies in acute gout attacks. Adrenocorticotrophic hormone and parenteral or oral glucocorticoids (at an oral dose equivalent to 30–35 mg

on the first day, then tapered over a few days) can be used for joints which are difficult to inject in patients intolerant of, or refractory to, colchicine and NSAIDs (Ritter et al, 1994; Werlen et al, 1996; Roane et al, 1997). Low-dose colchicine (1 mg/day) may be used as a preventative treatment in patients with frequently relapsing flares (Alvarellos and Spilberg, 1986). Interleukin 1 inhibitors are active on crystal-induced inflammation and could become a therapeutic alternative in patients with contraindication to colchicine, NSAIDs and steroids (Announ et al, 2009; Moltó et al, 2012). Management of OA with CPPD does not differ from that of OA without CPPD. Chronic CPP crystal inflammatory arthritis can be improved by low-dose colchicine (Das et al, 2002), NSAIDs, steroids and hydroxychloroquine (Rothschild and Yakubov, 1997) or methotrexate (Chollet-Janin et al, 2007). Hydroxychloroquine was shown to be helpful in one placebo-controlled study (Rothschild and Yakubov, 1997). Methotrexate has been tested in a double-blind, placebo-controlled crossover study, but the results have been disappointing with no statistically significant reduction in the DAS44 score, pain level or secondary outcome (Finckh et al, 2014). Radiation synovectomy has been shown to improve chronic CPPD with OA (Doherty and Dieppe, 1981). The risk/benefit ratio of these drugs should be considered cautiously as CPPD most frequently affects the elderly. Asymptomatic CPPD does not require any treatment (Zhang et al, 2011).

SUMMARY POINTS

- **CPPD is mainly a disease of the elderly. It is usually a sporadic disease but its presence requires consideration and investigation for primary hyperparathyroidism, haemochromatosis and hypomagnesaemia.**
- **Definite diagnosis is obtained by identification of CPP crystals in SF. X-ray demonstration of CC is most frequently obtained by radiographs of the knees; it is highly suggestive of CPPD but may lack sensitivity. US scan appears to be a promising diagnostic tool.**
- **The most frequent CPPD presentation is asymptomatic CC, which requires no treatment.**
- **Demonstration of CPP crystals in an OA joint is most likely an incidental finding with no implication for prognosis.**
- **Treatment of acute CPP crystal arthritis mainly relies on joint aspiration and intra-articular steroid injection**

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3 Basic calcium phosphate crystal deposition disease

LEARNING OUTCOMES

- Describe the natural course and the clinical presentations of basic calcium phosphate crystal deposition disease
- To recognise localised periarticular disease using X-rays or sonography
- Use the principles of its management

3.1 Introduction

Basic calcium phosphates (BCP) crystals, in contrast to acidic calcium phosphates such as brushite, form at basic pH and include apatite, octacalcium phosphate and tricalcium phosphate (McCarty et al, 1983*).

Deposits were long recognised in tendons and bursae where they are common and easy to demonstrate by X-ray examination. The demonstration of intra-articular BCP crystals came later (Dieppe et al, 1976; Schumacher et al, 1977) and remains difficult as crystals are too small to be identified by light microscopy.

3.2 Periarticular BCP deposits

3.2.1 Epidemiology and predisposing factors

Calcific tendinitis or bursitis is common, especially in the shoulder. In 1941 a study of a large office worker population of North America estimated that the prevalence of deposits discernible by X-rays in the shoulder was 2.7%. Prevalence was highest in middle-aged women (19.5% between 31 and 40 years), and nearly half of the deposits were bilateral (Bosworth, 1941). Shoulders are affected in roughly 60% of patients, followed by the hip and elbow, wrist, hand (Gondos, 1957; Amor et al, 1977). Calcifications can be observed in almost any joint. They are frequently multiple (Welfling et al, 1965; McCarty and Gatter, 1966; Amor et al, 1977), leading to the hypothesis that systemic factors play a role in the pathophysiology. Familial occurrence has been reported (Cannon and Schmid, 1973; Hajiroussou and Webley, 1983). An association with diabetes mellitus has

been observed (Mavrikakis et al, 1989). Calcifications can arise in the presence of various connective tissue diseases, mainly scleroderma and dermatomyositis/polymyositis (Reginato and Schumacher, 1977). Rarely, deposits appear to be favoured by the elevation of serum [Ca \times P] product observed in vitamin D intoxication, primary hyperparathyroidism and terminal renal failure (Bardin et al, 1988; Moskowitz et al, 1969*). Local factors have been incriminated at the shoulder. Deposits mainly involve the supraspinatus tendon at approximately 1 cm from its insertion into the greater tuberosity of the humerus, which is considered a critical zone of relative avascularity (Rathbun and Macnab, 1970). BCP deposition could follow tendon injury and necrosis or cartilaginous metaplasia of the tendon, induced by ischaemia (Uthoff et al, 1976; Uthoff and Sarkar, 1989*). It can also follow tissue damage caused by local steroid injections (Dalinka et al, 1984*).

3.2.2 *Natural course*

It has long been noted that deposits can spontaneously disappear (Bosworth, 1941). The natural history seems to follow several phases (Hayes and Conway, 1990). In the first phase, deposits are entirely contained in the tendon and usually do not cause any symptoms (asymptomatic phase). The second phase is characterised by growth of the deposit, which becomes liquefied, and may lead to enlargement of the tendon and impingement-like symptoms (mechanical phase). In the third phase, crystals reach the periphery of the tendon and/or the calcification ruptures into an adjacent bursa. Crystals therefore come into contact with cells, leading to acute painful episodes (inflammatory phase). Rupture into the bursa favours resorption of the calcification, which may then disappear.

3.3 Clinical presentation

Most periarticular BCP deposits are asymptomatic.

3.3.1 *BCP crystals*

BCP crystals can cause acute microcrystalline tendinitis or bursitis (McCarty and Gatter, 1966; Cannon and Schmid, 1973; Amor et al, 1977). Pain is of abrupt onset and very intense. If the calcification is superficial—that is, in a finger or a toe, erythema and swelling can develop. Untreated, the episode lasts from a few days to a few weeks. Radiographs usually demonstrate the causative calcification, which may, however, have disappeared during the acute attack. A history of recurrent flares and demonstration of calcifications in other sites, such as the hips, usually allows the correct diagnosis to be made. Arthrocentesis may be required to rule out septic arthritis. Acute attacks may affect nearly every joint, including finger joints (Selby, 1984*) and the great toe. Gout is another differential diagnosis. Whereas gout attacks usually involve men, BCP-induced podagra is most commonly seen in young or middle-aged women (Fam and Rubenstein, 1989*).

3.3.2 Chronic pain

BCP tendon calcification can cause chronic pain, which can be polyarticular when calcifications are multiple; multiple tendon calcifications should be included in the multiple regional pain investigation, especially in young or middle-aged women. Chronic pain is particularly common at the shoulder. One small study disclosed rotator cuff calcification in 14 of 34 shoulders that were painful for more than a year (Caroit et al, 1978). Pain can be due to chronic tendonitis or enlargement of the tendon, leading to subacromial impingement. The latter mechanism is supported by the frequent finding of a painful arch in anterior arm elevation between 70 and 110° (Kessel and Watson, 1977).

3.3.3 Bone erosions

Bone erosions have been discussed by Fritz et al (1994)* and Kraemer and El-Khoury (2000). Para-osteal calcifications may be associated with adjacent cortical erosion, particularly at the diaphyses of the proximal femur and humerus. Clinical presentation is usually dramatic with intense pain, marked tenderness and frequent swelling of the affected area. The erythrocyte sedimentation rate and C-reactive protein are raised. A bone scan shows an increased uptake of the isotope, and T2-weighted MRI an increased signal intensity of the soft tissues and bone marrow in the same area. Radiographs and CT scan demonstrate para-diaphyseal calcification and an adjacent cortical erosion. Over a few weeks or months, the calcification, then the cortical erosion, disappear and the patient usually recovers completely.

3.3.4 Axial involvement

BCP deposits can involve the longus coli tendon, anterior to the C2 and C1 vertebral bodies. Acute attacks are responsible for severe pain of the upper cervical spine and pharynx, which may be associated with fever and dysphagia, leading to suspicion of a retropharyngeal abscess. Radiographs and CT scan demonstrate the longus coli calcification, associated with swelling of the prevertebral soft tissue (Hall et al, 1986).

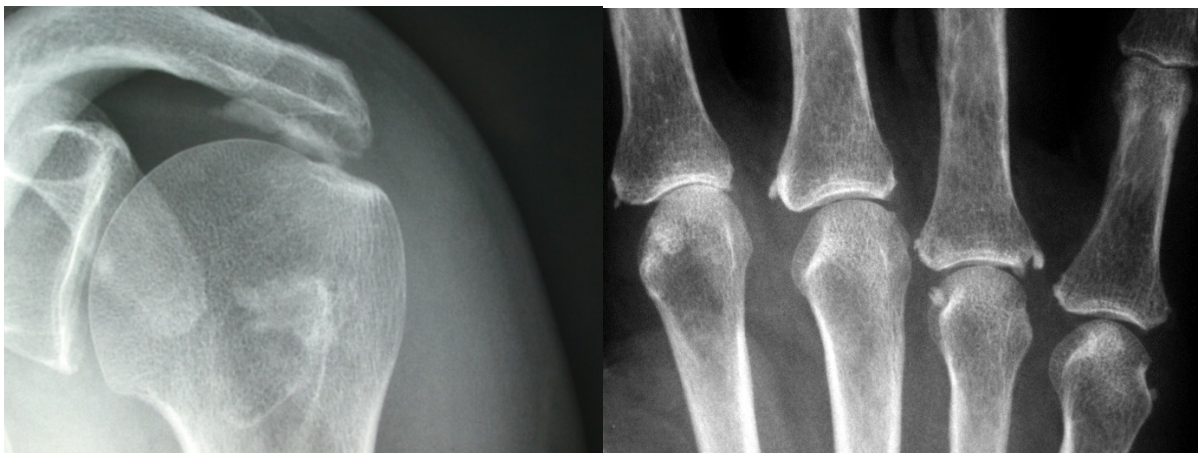
Disc deposits of BCP (Taylor and Little, 1963) are often localised inside the nucleus pulposus or adjacent to the anterior aspect of the disc and are most frequently asymptomatic, although they can trigger acute episodes of spinal pain (Amor et al, 1977). Disc calcification is a key feature of ochronosis and has been shown to be composed of BCP (Lagier and Sit'aj, 1974).

BCP deposits appear to be a cause of the crowned dens syndrome, which can also occur owing to calcium pyrophosphate deposition. Both types of crystals can give rise to acute inflammatory episodes of the craniocervical hinge (Bouvet et al, 1985*; Malca et al, 1995).

3.3.5 Diagnosis

Diagnosis of periarticular calcifications relies on imaging techniques using X-rays or ultrasound (figure 1). Plain radiographs show homogeneous ovoid opacities, without a cortex or trabeculation, in contrast to heterotopic ossification or accessory ossicles. Ultrasound is valuable, picking up even small deposits (Farin and Jaroma, 1995; Papatheodorou et al, 2006). By allowing precise localisation of calcification in the tendon and providing information on its consistency (liquid or solid), an ultrasound scan has also been found helpful for guiding needle aspiration of the deposit (Farin et al, 1996a).

Figure 1 Left: Subacromial calcification. Right: Calcifications by the metacarpophalangeal joints.



3.3.6 Management

Acute inflammatory episodes are best treated by local ice, rest, short immobilisation of the affected joint and local steroid injection. Non-steroidal anti-inflammatory drugs (NSAIDs) or systemic steroids at a starting dose of 30 mg equivalent prednisone/day are also effective. Colchicine can be used, in particular to prevent frequently relapsing flares, at a dosage of 1–2 mg/day. A recent pilot study favours the efficacy of anakinra, which can therefore be used in patients for whom NSAIDs and steroids are contraindicated (Zufferey and So, 2013*). There are no controlled data on these treatments, which are supported only by experience. A rare underlying hyperphosphataemic or hypercalcaemic disease should be treated.

Removal of the deposit can be considered in patients with chronic pain, particularly at the shoulder. X-ray or ultrasound-guided aspiration and lavage of the calcification, often followed by local steroid injection, is an effective procedure (Farin et al, 1996b; Aina et al, 2001; del Cura et al, 2007). Disruption of BCP crystal deposit during the procedure may trigger an acute inflammatory episode, which may help to remove the BCP deposit. Removal has also been performed by open surgery, which has now been replaced by arthroscopy. Extracorporeal shock wave therapy has been the topic of a large number of open studies and of several randomised controlled trials, which have proved its efficacy (Rompe et al, 1995; Ebenbichler et al, 1999; Loew et al, 1999; Speed et al, 2002; Gerdesmeyer et al, 2003).

3.3.7 Intra-articular BCP deposits

BCP crystals are difficult to identify in synovial fluid (SF) because they are too small to be detected by polarising light microscopy. They form non-birefringent rounded aggregates, which can be stained by a calcium stain, the alizarin red S stain (Paul et al, 1983*). This test is not specific for BCPs as other calcium crystals can also be stained. Transmission (or scanning) electron microscopy coupled with energy dispersive analysis is necessary for definite diagnosis. Such techniques are not available everywhere and are time consuming, making them inappropriate for routine use.

Intra-articular BCP crystals can induce acute arthritis (Schumacher et al, 1977), sometimes owing to the rupture of a periarticular calcification into the joint cavity (Gerster and Fournier, 1995). The term Milwaukee shoulder has been coined by McCarty et al, to denominate a destructive arthropathy of the shoulder associated with a large rotator cuff tear, periarticular calcification and a paucicellular and frequently haemorrhagic SF containing BCP crystals (McCarty et al, 1981). Collagenase and neutral protease were identified in the SF (Halverson et al, 1981), leading to the hypothesis that BCP crystals can induce joint destruction, since calcium crystals have been shown in vitro to induce release of these enzymes from synovial cells (Ea et al, 2011*). However, the clinical presentation of Milwaukee shoulder is very close to cuff tear arthropathy (Neer et al, 1983), and mechanical factors are likely to play an important role. Moreover, the finding of apatite in the SF of a destructive arthropathy can be considered as a non-specific finding, resulting from crystal shedding from the eroded subchondral bone. Finally, apatite crystals are often found in osteoarthritic (OA) SF (even more frequently than CPP crystals) and are almost constantly present in the remaining cartilage of OA joints examined at the stage of articular prosthesis (Ea et al, 2011*). The role these crystals might play in the OA process remains under investigation (Ea et al, 2011*).

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12

module

EULAR on-line course on Rheumatic Diseases

Crystal arthropathies

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A previous version was co-authored by Franco Schiavon, Eliseo Pascual, Thomas Bardin and Pascal Richette



IN-DEPTH DISCUSSION I

**Essentials of crystal detection and identification in
synovial fluid**

Identification of monosodium urate (MSU) crystals and calcium pyrophosphate (CPP) crystals provides an aetiological definitive diagnosis of gout and CPP crystal arthritis. The diagnosis of these two conditions is often approached clinically, and when the disease has a 'typical' presentation (such as repeated podagra in a hyperuricaemic patient or an acute knee arthritis in a patient with 'typical' chondrocalcinosis) the diagnosis is usually correct. But as the presentation diverges from the most characteristic one and in the absence of synovial fluid (SF) analysis for crystals the possibility of error increases, and requires a diagnostic investigation which is not always simple or conclusive. It is in such patients where the diagnosis is less evident that other doctors usually consult rheumatologists, and they expect—and know we can provide—an evidence-based diagnosis for crystal arthritis. Other crystals visible by the optic microscope are of limited interest. This subject is dealt with in greater depth in the EULAR online course.

The size of MSU and CPP crystals allows detection and reasonable provisional identification with an ordinary optical microscope (Pascual et al, 1989). Fitting the microscope with polarised filters—analyser and polariser—(simple polarised microscope) allows detection/identification by shape + birefringence; this microscope is commonly used in pathology departments. Finally, adding a first-order red compensator to the system (compensated polarised microscope) allows more definitive identification of both crystals; this last setting remains the standard for crystal identification in SF (Phelps et al, 1968). After training, crystal identification in SF is consistent (Lumbreras et al, 2005). Beginners fear they may have difficulty in differentiating MSU and CPP crystals but, in general, most analysts find the appearance of the crystals is different and recognise them at first glance. Training consists in becoming familiar with both crystals and then recognising them in new samples. An ordinary microscope fitted with the proper filters (some most popular brands provide sets of these) is the correct tool. A ×600 lens allows better vision and, for learning, a ×1000 lens allows a closer look (especially important in the polymorphic CPP crystal) and familiarisation with the crystals. Finally, a bright halogen light or similar is important for observation under polarised light—especially simple polarised light—since the strength of the brilliance of the crystal depends on it. Beginners should first become familiar with the use of the microscope—focusing, regulating the condenser and so on—and also with other elements in SF such as cells and other occasional common artefacts—for example, cotton fibres, starch from gloves or dust particles.

Both types of crystals are seen in SF taken from joints affected by an acute attack and in gout also in SF from previously inflamed joints if the patients have not received urate-lowering treatment. CPP crystals have also been regularly identified in SF samples from previously inflamed joints—a treatment which can eliminate the crystals from the joints is much needed. In gout, crystals are regularly recovered by needling a tophus.

1. With an *ordinary microscope* both MSU and CPP crystals are easily seen and with experience can be identified by their shape, and can be used when polarising microscopes are unavailable.

(i) All MSU crystals are needle shaped, their size varying from very small to about twice the diameter of a white blood cell both intracellularly and extracellularly (figures 1A, B). Often crystals are abundant and are easily seen already in the first $\times 400$ microscope field examined; when scarce, detection of the crystals with this method may be problematic.

(ii) CPP crystals are polymorphic. Their shape varies from a rhombus to thin needles; rods or thick needles and parallelepipeds are intermediate forms (figures 2A–D, 3A, C). Sizes vary from very small to about twice the diameter of the usual white blood cell. Extracellular crystals are seen but it is worth checking for crystals inside cells where they are very commonly found. Here using a magnification of $\times 1000$ has an advantage in enabling acquaintance with the crystals, facilitating later recognition. Examination with the ordinary light microscope allows a reasonable detection and identification of MSU and CPP crystals and it is worth doing if no polarised microscope is available.

Figure 1: Bright field microscopy. (A) $\times 400$; (B) $\times 1000$ monosodium urate (MSU) crystal. MSU crystals are well distinguished and all crystals are needle shaped. If abundant (and often they are) their presence is immediately obvious.

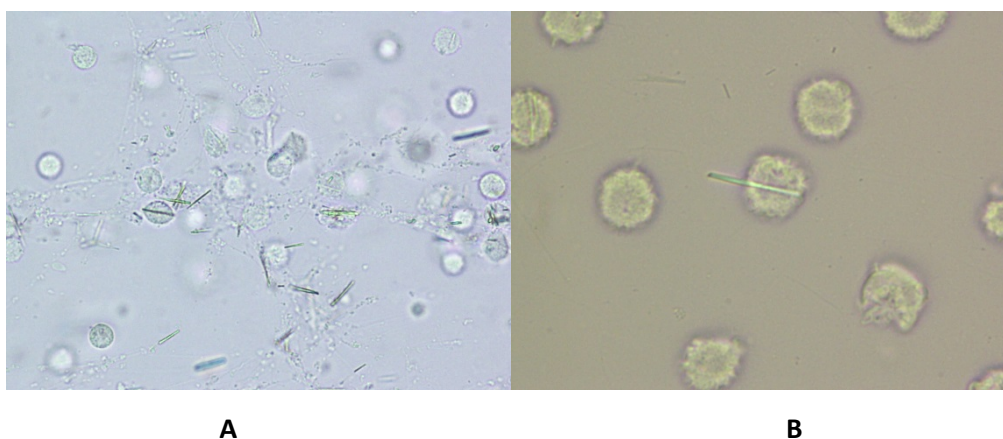


Figure 2: Bright field microscopy. (A, B) $\times 400$; (C, D) $\times 1000$. (A) Abundant calcium pyrophosphate (CPP) crystals; (B) single parallelepiped crystal. (C, D) To become familiar with the crystals $\times 1000$ magnification offers greater detail. Photomicroscopy offers only a very thin plane on focus. At the microscope the fine-focus knob allows all the structure to be brought into focus and seen more clearly.

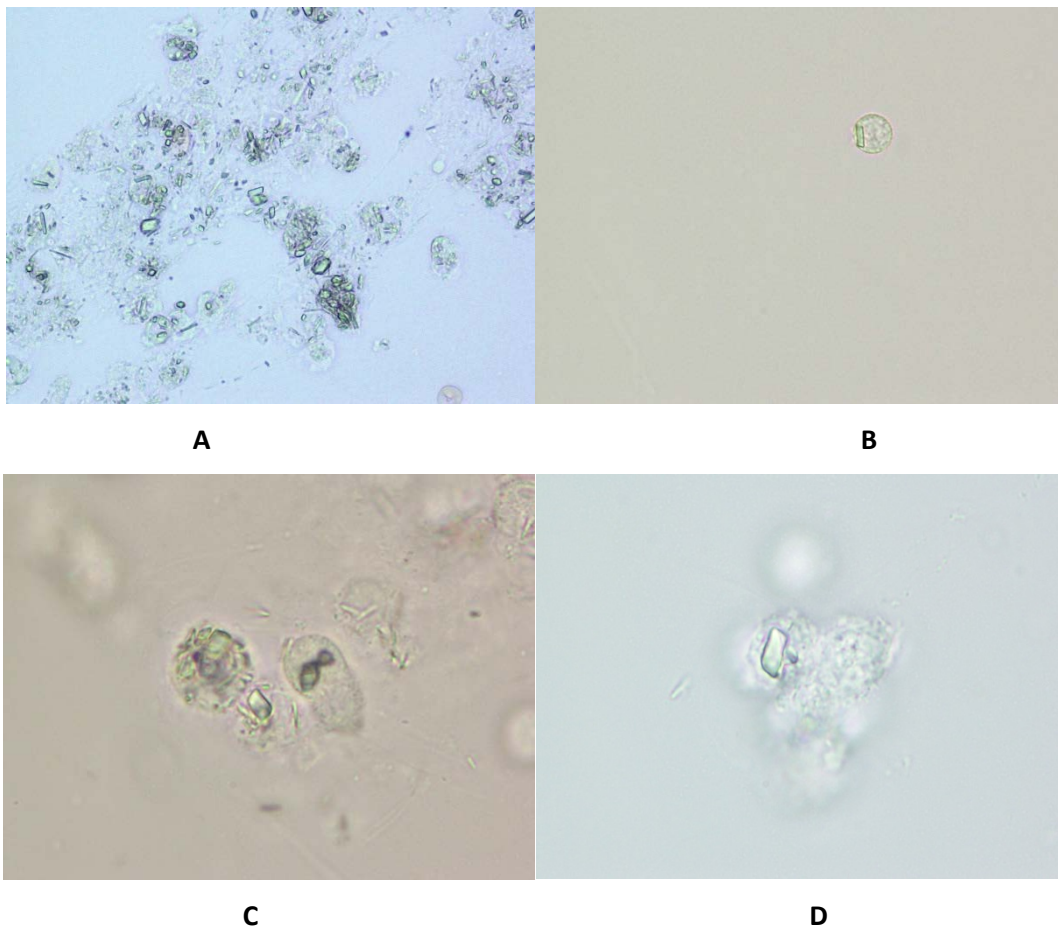
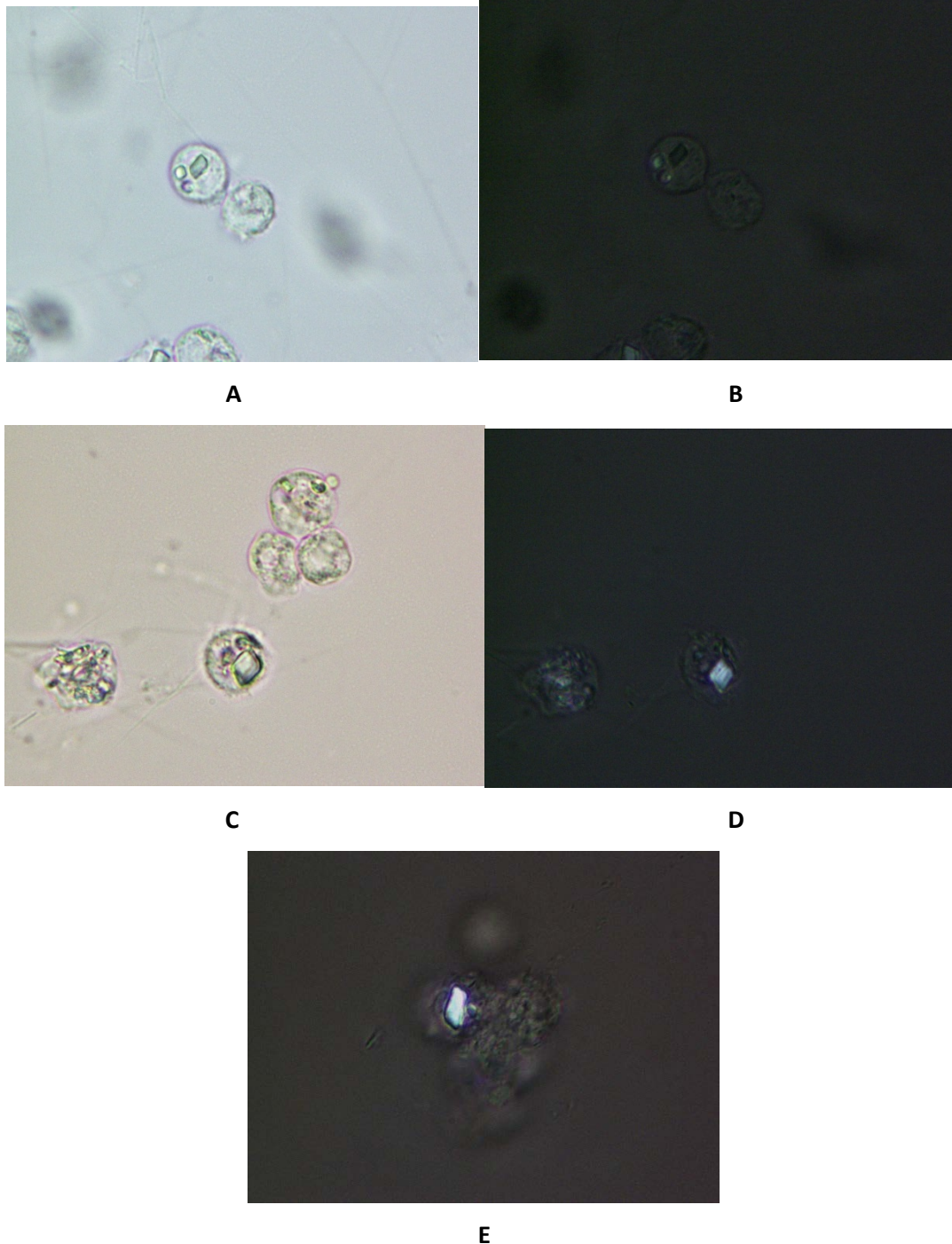


Figure 3: (A, C) Bright field microscopy $\times 600$. Calcium pyrophosphate (CPP) crystals are seen and distinguished by shape. (B, D) Same as A and C after crossing the polarised filters for simple polarised microscopy. (E) Simple polarised microscopy $\times 1000$. These figures show the range of birefringence of CPP crystals from none to quite brilliant—seldom reaching that of monosodium urate crystals. About 80% of CPP crystals do not show any birefringence. (For photography, polarised filters are not totally crossed to allow some background detail.)



2. The *simple polarised microscope* allows detection and identification by birefringence.

- (i) All *MSU crystals* are strongly birefringent and shine brightly against the dark background of the microscope field (which results from crossing the polarised filters) (figures 4A–C). This setting is the ideal for finding MSU crystals if they are few, since owing to their brightness they are easily seen in the dark microscope field. Small MSU crystals may not show birefringence. Additionally, birefringence cannot be seen when the long axis of a crystal is oriented parallel to the axis of either of the polarised filters (position of extinction).
- (ii) Only about one-fifth of *CPP crystals* show any birefringence (Ivorra *et al*, 1999) and, in general, it is much fainter than that of MSU crystals. Therefore, absence of birefringence should not be taken as an indicator of the absence of CPP crystals (figures 3A–E). The often very thin rods or even needle-shaped CPP crystals usually show no birefringence, allowing easy distinction from MSU crystals.

3. *Compensated polarised microscopy* is the standard tool for crystal analysis in SF. It determines the sign of birefringence, which depends on whether the wavelength traversing the long axis of the crystal has increased or reduced when polarised light traverses them.

- (i) *MSU crystals* show negative birefringence, or elongation, recognised because the long axis of the crystal is yellow when parallel to the compensator axis (or direction of slow vibration)—most often marked with an arrow and the Greek letter λ , and blue if perpendicular to it (figures 5A–E).
- (ii) *CPP crystals* are positively birefringent, showing a lighter yellow colour when the long axis is perpendicular to the compensator axis, and lighter blue than MSU crystals if parallel (figures 6A–C).
- (iii) All MSU crystals behave similarly in this system and being all similarly birefringent all clearly show their negative birefringent sign. Not all CPP crystals clearly show their birefringent sign; many do not show birefringence on simple polarised microscopy and may not show it with compensated polarised microscopy. Other CPP crystals because of their shape are difficult to orient in relation to the compensator axis, and occasional crystals may show negative birefringence.

Figure 4: Simple polarised microscopy. (A, C) $\times 400$; (B) $\times 600$. Monosodium urate crystals are easily seen because of 'shine' due to their strong birefringence. (A, B) Synovial fluid sample; (C) crystals obtained by needling a tophus; these crystals are usually larger than those seen in synovial fluid. (For photography, polarised filters are not totally crossed to allow some background detail.)

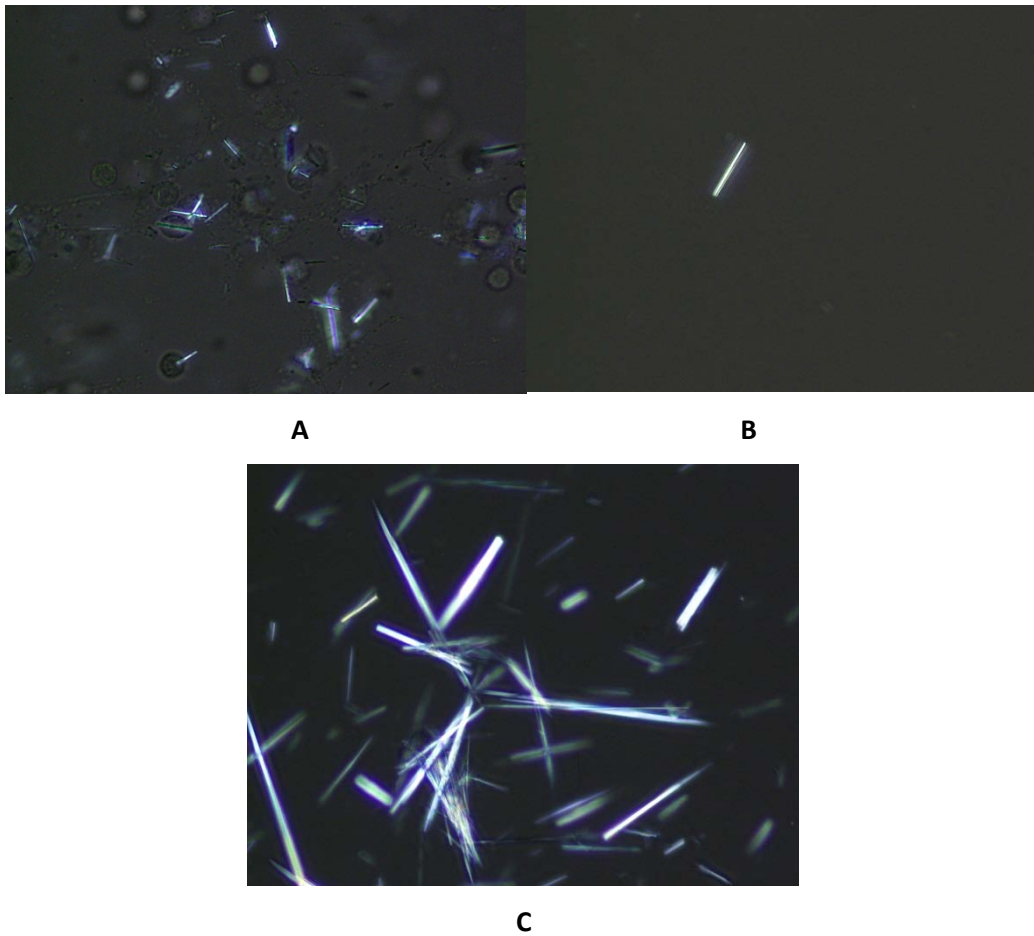


Figure 5: Compensated polarised microscopy. The arrow (λ) indicates the direction of the axis of the compensator. (A, B) $\times 400$ Synovial fluid: single monosodium urate (MSU) crystal oriented perpendicular and parallel to the axis of the compensator. (C) $\times 400$ Synovial fluid: multiple MSU crystals (and cells) showing yellow or blue colour, depending on their orientation. (D, E) $\times 400$ MSU crystals from needling two different tophi. Size can be much larger than crystals found in synovial fluid. These figures show the appearance of MSU crystals as seen by compensated polarised microscopy.

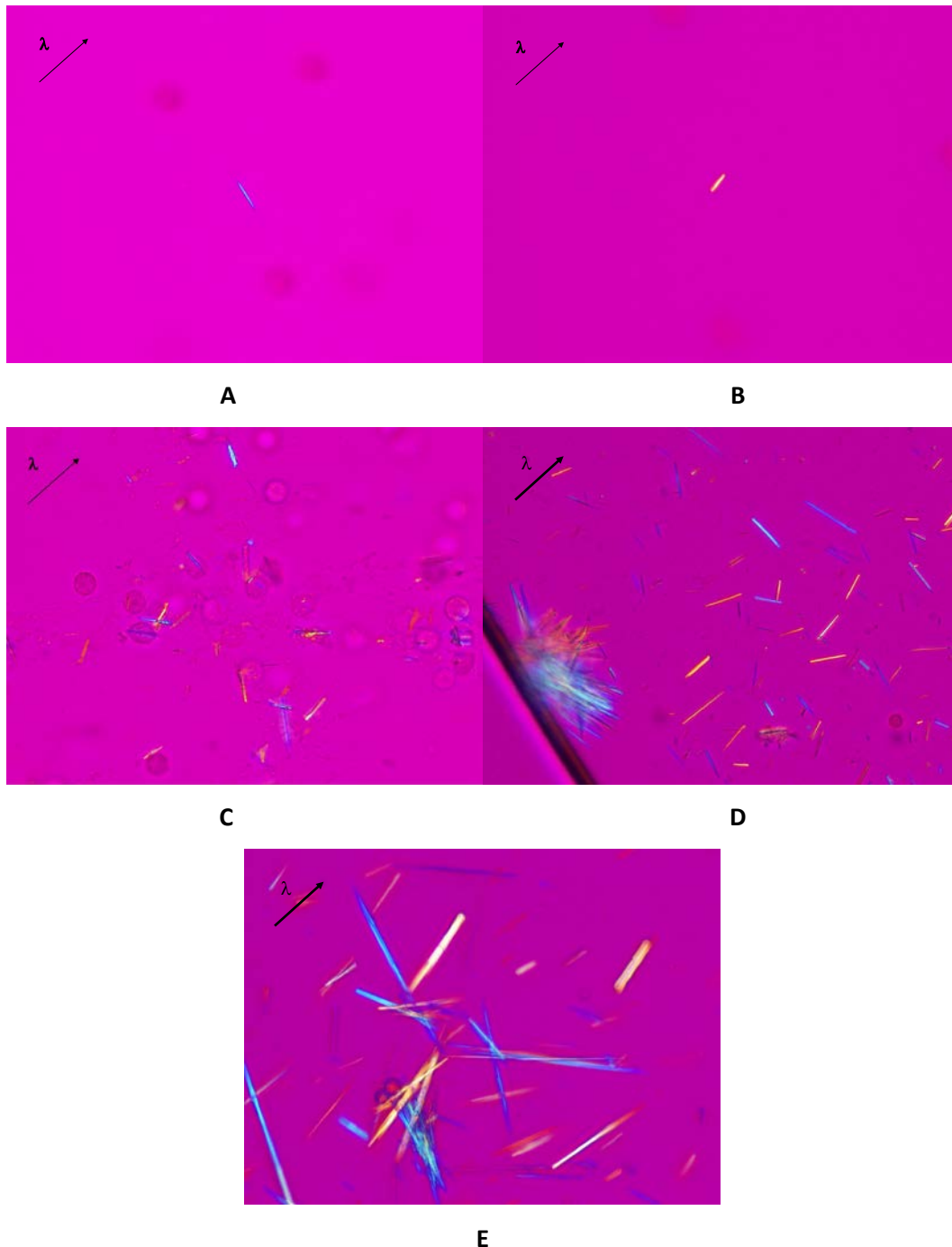
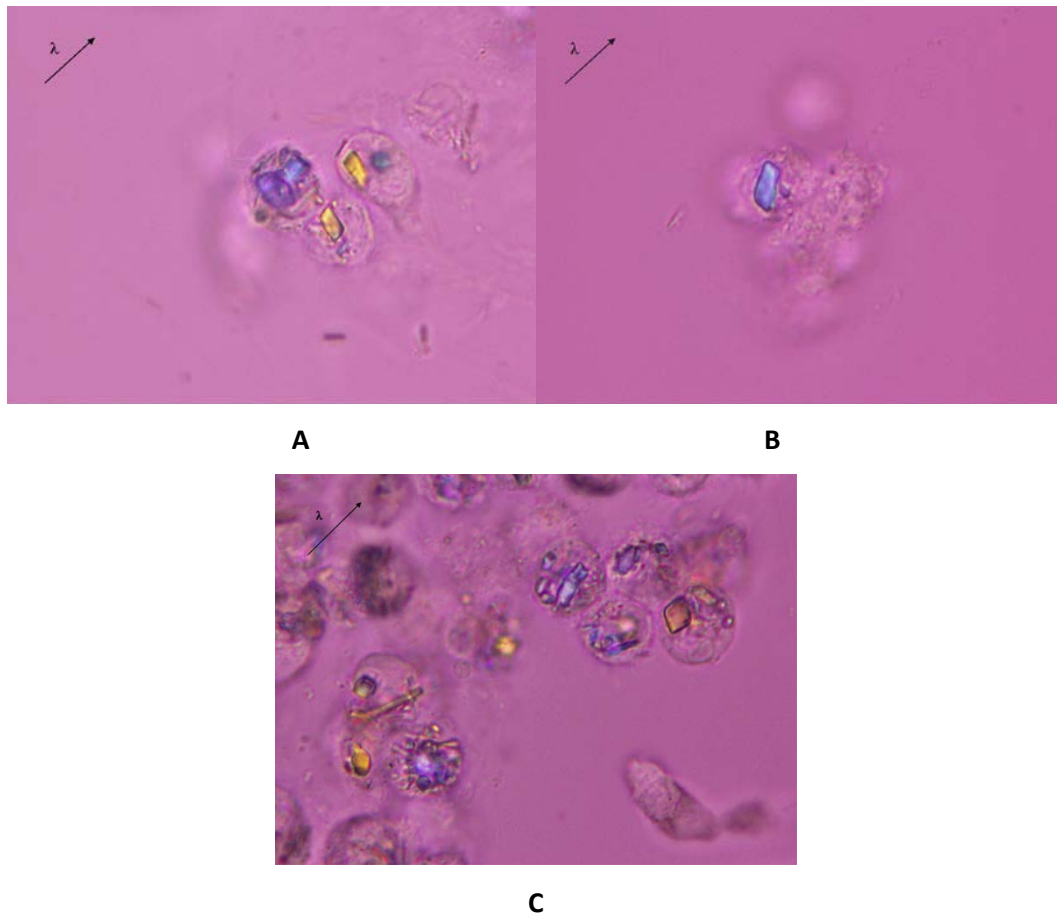


Figure 6: Compensated polarised microscopy $\times 1000$. (A, B) Characteristic parallelepipedic calcium pyrophosphate (CPP) crystals showing positive elongation (birefringence): blue if parallel and yellow if perpendicular to the axis of the compensator (arrow (λ)). (C) Compensated polarised microscopy $\times 1000$. These abundant CPP crystals show the frequent difficulty of determining the sign of elongation of crystals whose identity is clear from their shape. Crystals are here shown at $\times 1000$ for educational purposes. Usually observation is at $\times 400$ —or better at $\times 600$ —which allows good distinction of the crystals.



The sample to be examined should be fresh, or at least examined during the day it is obtained, and if possible kept at 4°C in a refrigerator to avoid decay of the cells, which is important, especially for the frequently intracellular CPP crystals. For examination a small drop of SF fluid (a large drop makes the preparation too thick) should be placed on a glass slide and a cover slip paced over it. No fixation or staining is required. The time spent looking for crystals before deciding that a preparation is negative has not been critically ascertained; however,

in most preparations crystals are abundant and often seen in the first field examined. Occasionally, fluids require a prolonged examination.

If training with a compensated polarised microscope is started without first acquiring experience with an ordinary microscope and then a simple polarised microscope this may cause problems, as a compensated polarised microscope can be a difficult instrument to use.

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12

module

EULAR on-line course on Rheumatic Diseases

Crystals arthropathies

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IN-DEPTH DISCUSSION II

Diagnosis of monoarthritis

The presentation of a patient with non-traumatic acute monoarticular arthritis is a common clinical scenario for which there is a wide differential diagnosis. Crystals induced arthritis, reactive arthritis, rheumatoid arthritis, Lyme disease, pigmented villonodular synovitis, haemarthrosis, cellulitis, transient synovitis of unknown aetiology and a variety of systemic or local diseases can result in a painful swollen peripheral joint. Arriving at a correct diagnosis is crucial for appropriate treatment particularly for non-gonococcal bacterial arthritis; promptly distinguishing between joint infection and other cause of monoarthritis is vital because septic arthritis can be devastating. Indeed, a delay in diagnosis and treatment of septic arthritis can lead to severe cartilage and joint destruction associated with high morbidity and mortality despite the use of adequate antibiotic therapy. Furthermore prognosis worsens with an increasing time interval between onset of infection and treatment (Margaretten et al 2007, Tarkowsky, 2006). The initial approach to diagnosing the underlying cause of an acute monoarthritis involves taking a careful history and examination. The history should include a review of symptoms, previous joint disease or family history of such, concurrent illnesses, past sexual contacts, travel, gastrointestinal and genitourinary infections, psoriasis, medication use or other risk factor for crystals arthritis (diuretic therapy, hypertension, obesity, renal insufficiency), chondrocalcinosis (recent medical or surgical illness, old age, history of hyperparathyroidism, haemochromatosis or inborn errors of metabolism) or septic arthritis, (age older than 80 years, diabetes mellitus, rheumatoid arthritis, HIV infections or immunosuppressed status, recent joint surgery, evidence of infection outside the joint). The physical examination should include looking for other involved joints and for systemic manifestation of predisposing diseases. On their own, however, the patient's history and physical examination are usually not sufficient to make a diagnosis.

The most common underlying cause of an acute monoarthritis includes crystal arthritis, septic arthritis and reactive arthritis. Reactive arthritis (ReA) develops about 1-6 weeks following an enteric (*Salmonella*, *Shigella*, *Campylobacter* and *Yersinia*) or urogenital (*Chlamydia trachomatis*) infection and a typical presentation includes asymmetric monoarthritis of lower limb joints. In the early stages of ReA synovial cell count can be quite high and polymorphonucleate leucocytes can dominate the picture. A history of gastroenteric illness preceding the arthritis, young age, lower limb involvement and unsafe sexual intercourse would favour the diagnosis of ReA. Extra-articular additional symptoms can be found (ocular and skin symptoms). Nevertheless infection can be asymptomatic, particularly in women (Chlamydia) (Kumar et al, 2014) and most patients do not have the classic triad of symptoms involving the urethra, conjunctiva and synovium (Mathews and Ravindran, 2014).

Gout, pseudogout and septic arthritis appear quite similar on physical examination. Established risk factors for septic arthritis include age older than 80 years, diabetes mellitus, rheumatoid arthritis, recent joint surgery, joint prosthesis skin infections and HIV infections (Margaretten et al, 2007). Risk factors for gout include hypertension, obesity, metabolic syndrome, renal insufficiency, type 2 diabetes mellitus, alcohol abuse and diuretic therapy. Direct joint trauma, intercurrent medical illness (i.e. infection) or surgery may trigger acute pseudogout in elderly patients.

Fever may or may not be present in these conditions and does not help to differentiate between them. Fever, sweats and rigours are more common in septic arthritis but have a low sensitivity for the diagnosis (57%, 27% and 19% respectively) (Margaretten et al, 2007, Nolla et al 2015). Peripheral blood measurement of white blood cells, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) have poor diagnostic utility because they can be elevated in various pathological conditions including not only crystal arthritis but also inflammatory joint disease. Moreover, their absence does not exclude the diagnosis of septic arthritis. Serum urate is usually elevated in patients with gout. However, during the acute attack serum urate can be within the normal range due to increased renal excretion of uric acid (release of ACTH from adrenal stimulation during a painful attack) and increased inflammatory activity (pro-inflammatory cytokines IL6 and IL1 β are directly correlated with lower uric acid levels) (Bădulescu M et al. 2013). Furthermore, an elevated urate level in serum per se is not a confirmatory test for gout. Therefore, clinical and serum findings alone are not reliable for the diagnosis.

The key to establish the diagnosis is prompt microscopic analysis and culture of synovial fluid aspirated from the affected knee. Aspiration of synovial fluid should be made always before antibiotic treatment is started. Once aspirated joint samples are obtained, it is imperative that they are quickly transported to clinical microbiology and not be allowed to stand for a long time without processing or culturing. The injection of synovial fluid into blood cultures bottles can increase the detection of pathogens. If synovial fluid cannot be obtained with closed needle aspiration, for joints not easily accessible as hip, shoulder and sacroiliac joint, arthrocentesis must be done by imaging guidance. If septic arthritis is suspected blood should always be cultured before starting antibiotic treatment to increase the chances of obtaining causative organisms. Indeed, in 9% of patients blood cultures are the only source of a positive microbiological diagnosis. The synovial fluid must be analysed for gram stain, white blood cells count (WBC) and differential and cultured for bacteria. A negative Gram stain does not by itself rule out septic arthritis since the sensitivity of the synovial fluid Gram staining is limited and it is positive in 71% of Gram positive septic arthritis, 40-50% of cases of Gram negative septic arthritis and in < 25% of cases of gonococcal septic arthritis (Garcia-De la Torre and Nava-Zavala, 2009). Culture is positive in 50% of patients. In cases where there is a high index of suspicion of septic arthritis though with a negative culture, a synovial membrane biopsy and tissue culture may be required to identify the pathogen. If an abnormal and/or slow growing organism is suspected like *Brucella* or *Neisseria gonorrhoeae*, the laboratory should be warned since these organisms often require a special culture medium and extended culture time for its growth. Acute microcrystalline arthritis and septic arthritis may have similar values for WBCs. The concentration of synovial white blood cells (WBCs) in septic arthritis is usually increased; a count of $> 50 \times 10^9/L$ with $> 90\%$ of polymorphonuclear cell increase the likelihood ratio of septic arthritis. The higher the synovial fluid leukocytes count the greater the likelihood of septic arthritis: more than 100,000/ mm³ WBCs has a likelihood of 7.7 for the diagnosis (Smith et al, 2006, Mathews et al, 2008). Nevertheless, lower cell counts (below 50,000 cells/mm³) are not rare.

The diagnosis of gout is made by identifying monosodium urate crystals in the synovial fluid. Rarely gout and septic arthritis coexists making it essential to analyse the synovial fluid for both crystals and the presence of microorganisms (Lim et al, 2015). There are several possible mechanisms by which gout may increase the risk of septic arthritis: a) joint damage resulted from release of IL-1, inducible nitrox oxide synthetase, MMP and osteoblast activation after urate deposition can contribute to an increase risk of development of septic arthritis similar to joint damage associated with rheumatoid arthritis (Mathews, et al 2010), b) subcutaneous tophi predisposes patients' to skin breakdown and ulceration and direct inoculation of bacteria and, c) gout patients are more likely to have arthrocentesis or intraarticular steroid injection which may also contribute to the risk of septic arthritis. (Lim et al, 2015) It is recommended that synovial Gram stain and culture are sent even when urate crystals are identified in synovial fluid (Yu et al, 2003). In pseudogout synovial crystals of pyrophosphate dihydrate are poorly visualized by plain light microscopy but compensated polarized light microscopy may permit recognition of their weak positive birefringence. They are though less readily identified and often less numerous than urate crystals and may be missed. Chondrocalcinosis and calcification may be visible on standard radiography but their presence is not a prerequisite for a diagnosis of pseudogout.

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Clinical epidemiology – critical appraisal of evidence

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LEARNING OUTCOMES

- Identify major bias in randomised controlled trials
- Interpret estimation of treatment effect and its precision
- Explain the concept of p value and confidence interval
- Apply therapeutic evaluation results in clinical practice
- Explain the caveats of translating evidence into practice
- Identify major bias in studies evaluating diagnostic tests
- Interpret diagnostic test characteristics (sensitivity, specificity, predictive values, receiver operating characteristic curve, and likelihood ratio)
- Apply diagnostic accuracy results in clinical practice
- Identify major bias in meta-analysis of randomised controlled trials
- Assess heterogeneity and interpret meta-analysis results
- Apply meta-analysis results in clinical practice

1- INTRODUCTION

*“Read not to contradict or confute;
nor to believe and take for granted;
...but to weigh and consider.”*

Francis Bacon, *Of Studies* (1597)

Critically appraising a paper is important in order to be able to interpret the data appropriately and to be able to apply this evidence to practice. This chapter concentrates on the critical appraisal of randomised controlled trials (RCTs), of meta-analyses of RCTs, and of studies of diagnostic test accuracy. There are sources of guidance on aspects of critical appraisal for other types of studies (e.g. qualitative research (Giacomini et al., 2000a; Giacomini et al., 2000b), economic evaluations (Drummond et al., 2015), prognosis studies (Hayden et al, 2013), non-randomised studies of the comparative effectiveness of interventions (Sterne et al, 2016)) but these will not be covered in this module.

Irrespective of the type of study, a practical approach to critically appraising medical literature uses a common set of key questions (Guyatt and Rennie, 1993*; Guyatt et al, 1994*; Jaeschke et al, 1994a*; Jaeschke et al, 1994b*; Oxman et al, 1994*; Murad et al., 2014*; Guyatt et al, 2015*). By answering these questions the reader can obtain a solid picture about the value of the particular piece of evidence at hand.

‘What is the aim of the study?’

Usually you find the answer to this question at the end of the introduction. A clearly focused objective for studies evaluating the effects of treatment will typically mention the Population, the Intervention, the Comparator, and the Outcome (PICO). The population entails the relevant patients, the intervention delineates the management strategies of interest (i.e., drugs, medical devices, but also educational, rehabilitative, behaviour change, service re-organisation, and so on), the comparator is the alternative course of action against which the intervention is to be compared, and the outcome identifies the measure of the efficacy of the intervention (**Box 1**).

Box 1. Examples of PICO objectives for studies evaluating the effects of treatment

- The effect of monthly intravenous injections of sifalimumab versus placebo on attainment of SLE responder criteria at 52 weeks among patients with moderate-severe active SLE
- The efficacy of standardised monitoring using the DAS28 versus usual care on DMARD prescription and disease activity in rheumatoid arthritis
- The effectiveness of a multifaceted podiatry intervention in reducing falls among people aged over 65 years

Note that the PICO format may need to be adapted for other types of study. For example, a clearly focussed objective for a study evaluating the diagnostic accuracy of a new test for a disease of interest will mention the population, the test, the reference standard, and the disease of interest (see **Box 2**).

Box 2. Example of a focussed objective for a diagnostic accuracy study

- To compare the sensitivity and specificity of the CONTEST and PEST screening questionnaires against rheumatologist diagnosis in patients presenting to primary care with suspected psoriatic arthritis

‘Are the results of the study valid?’

When judging the believability or credibility of the results, you should ask ***‘are the study methods appropriate to generate valid results?’*** Furthermore, studies may be well-designed but not go according to plan. Bias may be introduced by problems with recruitment, loss to follow-up, missing data, or selective reporting. So, consider also ***‘was the design well-executed?’*** and ***‘are the results reported in a full and transparent way?’*** The source of funding may be important when looking for (hidden) threats to the study’s validity such as selective reporting of outcomes in clinical trials. Industry-sponsored trials tend to report more favourable results and conclusions than non-industry-sponsored trials and the source of this bias may be difficult to discern from the report alone (Lundh et al., 2012). If, when reading a research article, you have serious concerns about the potential for bias, or the study is simply too small to generate an estimate with an appropriate level of precision (‘under-powered’), then you may choose not to read on.

What are the results?’

Studies do not produce a simple ‘yes/no’ result. In general, they produce an estimate that has a *direction* (‘positive’, ‘negative’), a *magnitude* (‘large’, ‘small’), and an accompanying level of *precision* (typically summarised by the 95% confidence interval). Depending on the design and objective of the study, that estimate may be a relative risk, an odds ratio, a difference in means, a hazard ratio, a likelihood ratio or some other parameter. But it is important to note that when we ask the question ‘are the results of the study valid?’ what we are really focussed on is whether the estimate from the study is unbiased.

‘How can I apply these results to patient care?’

This question has two parts. First, ***‘can you generalise (apply) the results to your patient?’*** For example, one should hesitate to apply a treatment if the patient is too dissimilar from those who participated in the clinical trial. Second, ***‘if the results are generalisable to the patient, what is the net impact of implementing the drug/medical device/diagnostic technology etc?’*** For treatments, have the investigators measured all outcomes of importance to patients? The impact depends on both the benefits and risks (side effects and toxic effects) of intervention and the consequences of withholding the intervention. For other types of study (e.g.

diagnostic test accuracy) there may be no good evidence available on the impact of introducing the new diagnostic test into routine practice.

This common set of key questions provides a general approach to clinical evidence presented in the literature. In the following, we will look at specifics of three different study types, which are often used in clinical practice: intervention studies, diagnostic studies, and meta-analyses.

2- RANDOMISED CONTROLLED TRIALS

To evaluate the efficacy of a treatment the best choice is to compare two (or more) groups: one group undergoing the treatment of interest, and one (or more) not (control group).

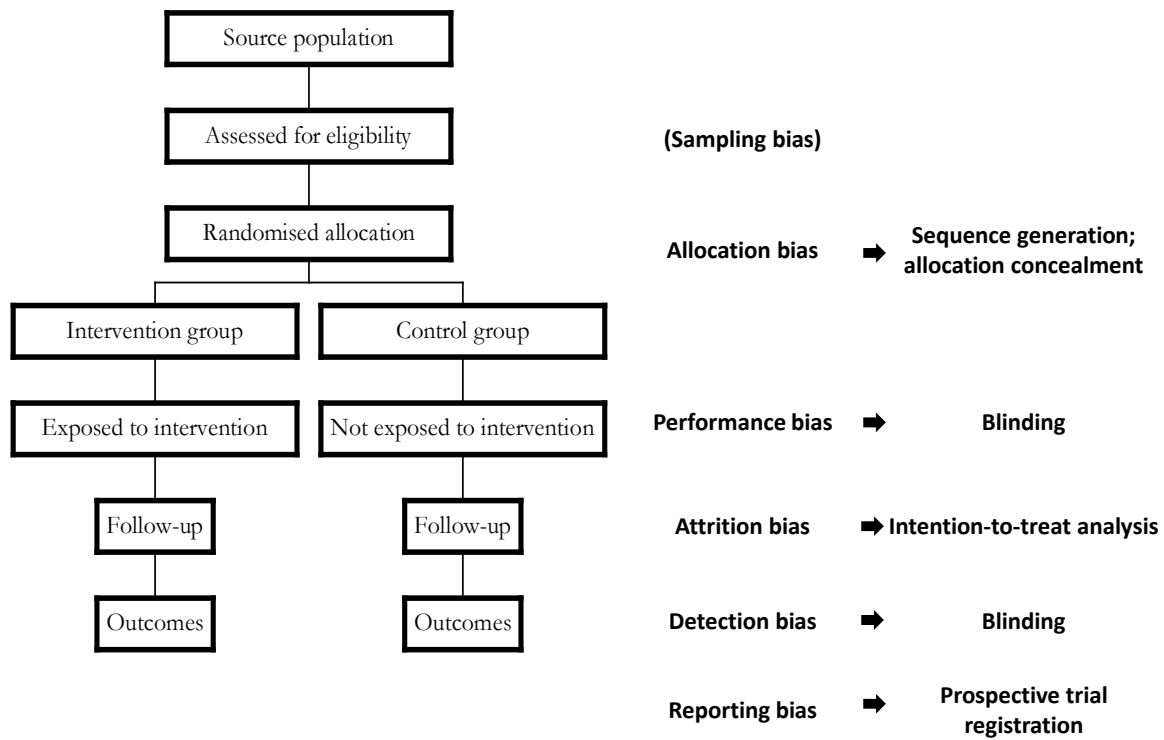
However, many factors other than the treatment under evaluation could influence patient recovery or improvement. These include the natural history of a disease, patient characteristics, special (study-related) attention paid to the patient (Hawthorne effect), regression to the mean, placebo effect, concomitant treatments, or measurement error.

The potential of these factors to bias the estimate of treatment effect is minimised if:

- Patients in each group are similar at the beginning of the study (at baseline); they have the same natural history of the disease under investigation, and show the same demographic and clinical characteristics
- This similarity between patient groups is maintained throughout the study: the same attention is paid to patients in each group, and there are no differences in access to or use of concomitant treatments
- Outcomes are measured using the same methods in each group

Systematic bias is defined as anything that erroneously influences the conclusions about groups and distorts comparisons. Readers will encounter descriptions of many forms of bias in the medical literature, sometimes using inconsistent terminology. Some of the main sources of bias in RCTs and methods to overcome them are summarised in **figure 1**. Definitions and examples are provided in **Box 3**. These issues are discussed in more detail in the following sections.

Figure 1 Sources of bias in randomised controlled trials and methods to overcome them. (Adapted from Greenhalgh, BMJ 1997;315:305–8.)



Box 3. Definitions and examples of different sources of bias in RCTs

Sampling bias	<p>Systematic differences in characteristics between patients enrolled in the trial and those in the source population</p> <p>Patients who were enrolled into a RCT of diclofenac vs paracetamol for knee OA were younger (median age: 60 years, range 44-79) than the age distribution for all patients who attended the investigator sites and met the eligibility criteria (median age: 68 years, range 42-97).</p>
Allocation bias	<p>Systematic differences in baseline characteristics between Intervention and Control groups</p> <p>At the end of recruitment to a RCT of CBT versus simple advice and information for low back pain, 77 patients had been allocated to CBT but only 67 had been allocated to control. The groups differed in terms of baseline pain and depression scores. Investigators had allocated patients to groups on the basis of the last digit of their date of birth.</p>
Performance bias	<p>Systematic differences in care/attention received (other than intervention) between Intervention and Control groups</p> <p>In a placebo-controlled trial of the effect of long-term menopausal hormone therapy on cardiovascular outcomes, both arms had an equal (and low) proportion of participants using statins at baseline. However, in the following years the rate of initiating statins was significantly higher in the placebo arm (Manson et al., 2016).</p>
Attrition bias	<p>Systematic differences in study withdrawals and loss to follow-up between Intervention and Control groups</p> <p>In a trial of hip protectors for prevention of fall-related hip fracture, 26% of participants randomised to intervention or control did not complete questionnaires at 12-months. This attrition was higher in the control arm than in the intervention arm (28% vs 22%). Although baseline characteristics had been well-balanced by the original randomisation, when the comparison was then limited to those who were successfully followed up at 12 months, patients in the control arm were less likely than those in the intervention arm to have had a previous fracture at baseline (Birks et al., 2004; Dumville et al., 2006).</p>
Detection bias	<p>Systematic differences in outcome assessment between Intervention and Control groups</p> <p>In an open-label RCT of honey-impregnated wound dressings versus usual care for venous ulcers, investigators found a small, statistically significant benefit on ulcer healing at 12 weeks when evaluated by a nurse who was not blinded to treatment allocation. However, no benefit was seen when the outcome measure was ulcer healing judged from before-after photographs by an independent expert blinded to treatment allocation.</p>
Reporting bias	<p>Selective reporting of outcomes</p> <p>In an RCT investigators recorded a few more serious adverse events among participants randomised to the active treatment arm. But they couldn't be easily explained clinically, only a small number of participants were affected, and the trial was underpowered to detect any statistically significant between-arm differences in harms. In the interests of brevity and simplicity, the investigators decided to omit them from the paper.</p>

2-1 Are the Results of the Study Valid?

2-1-1 Randomisation

Randomisation, the random allocation of patients to intervention or control groups, is the best way of minimising systematic differences between groups at baseline in characteristics, known and unknown, that may affect the outcome. Proper randomisation rests on two equally important elements to ensure that participants are assigned to groups on the basis of a chance (random) process characterised by unpredictability: (1) sequence generation, and (2) allocation concealment.

Adequate generation of the sequence usually involves a random-number table or a computerised random-number generator. Deterministic allocation methods (sometimes called 'quasi-random' methods), such as alternation, date of birth or first letter of name, are inadequate for two reasons: first, their predictability, which allows for the scheduling of participants, and second, the possible correlation between the item used (month of birth, first letter of name, etc) and the outcome.

When implementing the sequence of randomisation, if the allocation is not concealed before the patient is assigned to a group, all benefits of randomisation are lost. Investigators or clinicians can schedule patients so that those with particular characteristics receive a certain allocation, thereby biasing the allocation. A review assessing the quality of reports of RCTs in rheumatology published between 1997 and 1998 found the method of allocation concealment described in only 19% of reports (Hill et al, 2002). More recently Nüesch et al (2009) found 46 of 158 (29%) osteoarthritis trials had adequate allocation concealment. While allocation bias can work in the either direction (Paludan-Müller et al, 2016), inadequate/unclear sequence generation and allocation concealment tend to result in exaggerated estimates of treatment effects, particularly when the outcome measure is subjective (Page et al, 2016).

Allocation concealment is generally assured when treatment and placebo are indistinguishable (same appearance, same schedule of administration, same taste, etc) the care provider and the patient are blind. In other cases, the following are some approaches that assure adequate concealment schemes:

- Pre-numbered or coded identical sealed, opaque envelopes administered serially to participants
- Centralised (e.g., after patient consent is obtained, the investigator calls a 24-hour free phone service to obtain the patient allocation group) or pharmacy-controlled randomisation
- On-site computer system combined with group assignments in a locked unreadable computer file that can be assessed only after entering characteristics of an enrolled participant.

Sealed opaque envelopes have been used for randomisation for a long time. However, this process is open to deliberate tampering because the investigator can open several envelopes beforehand and then allocate

patients to the desired treatment. Indeed, sometimes treatment allocation can be seen if the envelope is held against a very bright light (Torgerson and Roberts, 1999).

It can readily be appreciated that randomisation prevents “confounding by indication” which presents nearly insurmountable problems for observational studies seeking to compare the intended effects of treatments based on patterns of use in routine practice. In routine practice, treatment allocation is guided by prognosis and not at random: patients receiving one treatment can seldom be assumed to have the same baseline risk of outcome as those not receiving that treatment.

Important demographic and clinical characteristics for each study group should be described so that readers can assess how comparable the groups were at baseline for the known prognosis factors. It is generally not useful to test these differences statistically, as by the virtue of randomisation, all observed differences must be ‘by chance’. It should rather be the magnitude and direction of the differences that may detect potential subversion of the randomisation. If several differences were large and all favoured one group our index of suspicion about the trial would be heightened.

2-1-2 Blinding

Similarity between the treatment and the control groups, except for the specific treatment condition, must be maintained during the study. Blinding is the best way to maintain this similarity and thus avoids performance bias and detection bias. Blinding refers to keeping people who are involved in the trial, such as participants, healthcare providers (i.e., those administering the treatment), and those assessing the trial outcomes, unaware of the treatment being administered.

Although the term ‘double blind’ implies that neither the care provider nor the patient knows which treatment was received, it is ambiguous with regard to blinding of other people, including those assessing patient outcomes (Montori et al, 2002). Authors should state, and readers should carefully assess, who was blinded (participants, care providers, outcome assessors, monitors, or data analysts).

Blinding of participants and healthcare providers prevents performance bias. This bias may occur if additional therapeutic interventions (i.e., co-interventions) are provided preferentially in one of the comparison groups. It guarantees the same follow-up, the same attention to the patient, and the same ‘placebo effect’ in the two groups.

Blinding of outcome assessors minimises the risk of detection bias. This type of bias occurs if treatment group influences the process of outcome assessment—for example, non-blinded neurologists assessing the outcome of a trial demonstrated an apparent treatment benefit, whereas blinded neurologists did not (Noseworthy et al, 1994). Blinding of outcome assessors is particularly important for subjective outcomes (e.g., pain scores or stiffness), which present great opportunities for bias in measurement. In general, blinding becomes less

important in reducing detection bias as the outcome becomes less subjective. Objective (hard) outcomes leave little opportunity for detection bias. Knowledge of the intervention would not greatly affect measurement of a hard outcome such as death (Schulz and Grimes, 2002), although it might influence subjective assessment such as cause of death. Note that although clinicians and patients cannot be blinded in some trials (e.g., surgery), assessors can usually be blinded.

Blinding of data analysts can also prevent bias because knowledge of the intervention received may influence the choice of analytical strategies and methods. When the two treatments under study are indistinguishable (same characteristics, same schedule of administration, same dosage, etc), blinding of patients, care providers and outcome assessors is easy to achieve (Boutron et al, 2006*). If treatments differ, a 'double-dummy' procedure may be useful but not always feasible. In a double-dummy procedure, the patients of group A receive the drug A and a placebo of drug B, and patients of group B receive the drug B and a placebo of drug A. A typical example would be the comparison of an intravenous drug to an oral drug.

When blinding of patients and care providers is not feasible (e.g., surgery, regimen, rehabilitation or psychotherapy), performance bias may occur. Sometimes blinding seems feasible but cannot be effective: because of the specificity of adverse effects, such as bradycardia with β -blockers, patients and/or care providers will quickly become un-blinded to the treatment. In these situations, methods to blind outcome assessors are particularly useful to avoid detection bias (Boutron et al, 2006*). These methods rely mainly on a centralised assessment of the main outcome. Although centralised assessment is easy to implement for investigations (e.g., laboratory tests or radiography) or clinical events (blinded adjudication committee), it requires more inventive solutions for physician-driven data (such as videotaping, audiotaping or photography of clinical examination) (Boutron et al, 2006*). For patient-reported outcomes, centralised assessment is of course much more problematic.

2-1-3 Analysis approach

Even if a rigorous trial has been undertaken and has avoided all the biases, an incorrect analytical approach can introduce bias. In a randomised superiority trial the most robust analytical method that prevents attrition bias is the intention-to-treat (ITT) analysis (Hollis and Campbell, 1999).

The advantages of an ITT analysis are balance in prognostic factors arising from the original random treatment allocation, an unbiased estimate of treatment effect, and the admission of non-compliance and protocol deviations, which thus reflects a real clinical situation (Heritier et al, 2003). Even if a patient crosses over from one treatment to another he has to be analysed in the group to which he was initially randomised. An ITT analysis answers the question 'Which choice of treatment is better for the patient?', not 'Which treatment received is better for the patient?'. The former is the only question that can be answered without bias and it is the most pragmatic one to choose a treatment.

Box 4. Analysis approaches in RCTs

intention-to-treat (ITT) analysis	all patients are analysed in the group to which they were initially randomised, even if they 'cross over' into the other intervention arm, stop their intervention, or are lost to follow-up
per-protocol (on-treatment) analysis	analysis is restricted to participants who fulfil the protocol in terms of eligibility, interventions (treatment received), and outcome assessment
treatment-received analysis	patients are analysed according to the treatment they actually received, regardless of the treatment they were originally allocated to receive

Many authors claim they perform an ITT analysis when in fact they do not. Circumstances where a true ITT analysis is not performed include:

- patients who are excluded from the analysis if they do not receive treatment
- ineligible patients who are randomised
- exclusion of patients lost to follow-up or for whom the outcome was not assessed.

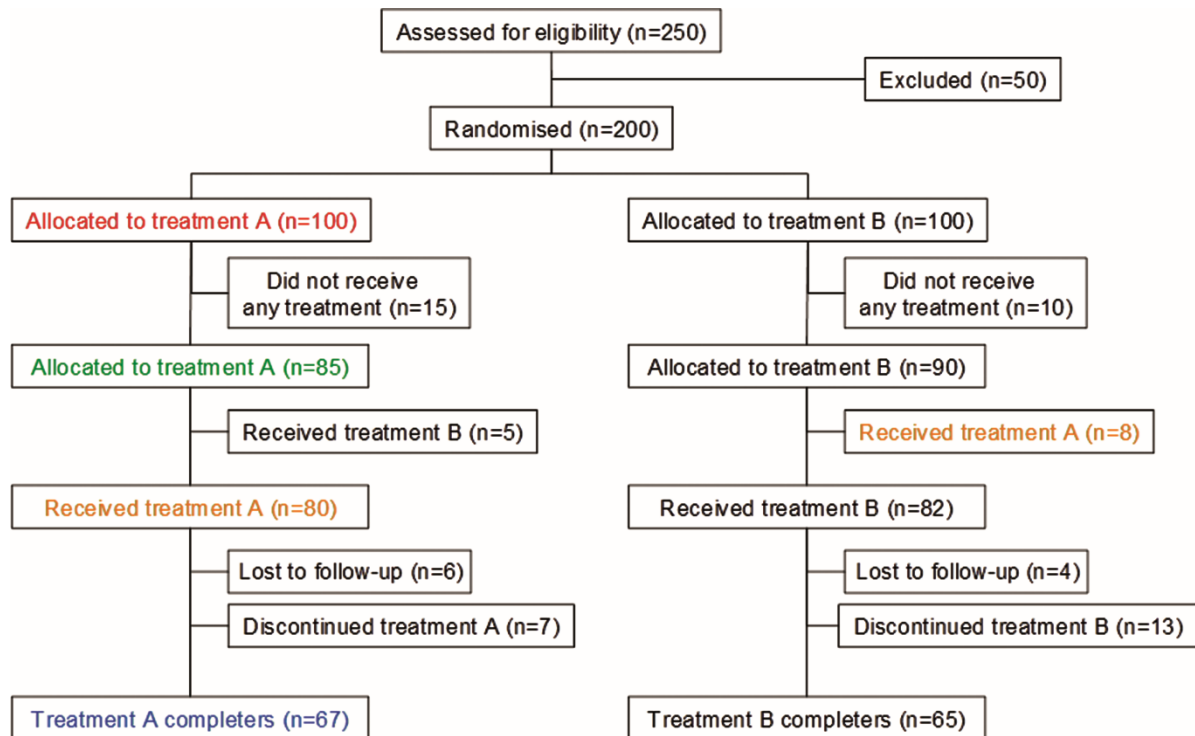
Check the ITT assumption by looking at the flow chart of the progress of patients through the phases of the trial and comparing the number of patients randomised to the number analysed (**figure 2**). Analysis excluding patients who never received any treatment is usually called “modified-” or “quasi-ITT” analysis.

The only acceptable exclusions from an analysis are patients in a strictly double-blinded study who did not receive any treatment. As patients do not know the treatment they will receive, their exclusions are unlikely to be caused by a disillusion in the allocation. If the attrition rate is low and is equally distributed between the study arms, the analysis is unlikely to be too biased. The rule of thumb for attrition is as follows: if it is less than 5%, it is unlikely to have introduced bias; if it is greater than 20% (particularly if it is unequal between groups), then there is a real risk of bias; if it is between 5% and 20%, we need to be cautious and look for sensitivity analyses of the data.

Non-compliance with assigned therapy means that the ITT analysis may underestimate the real benefit of the treatment; it is a conservative analysis. Additional analyses such as per protocol or treatment-received analysis may therefore be considered, but only to generate more research hypotheses not used to inform the treatment decision (see box 4). In particular, because ITT analysis may underestimate effects, it is not appropriate for examining adverse effects or equivalency trials. An alternative analytical approach, which in theory does not affect the randomisation, is to use a complier average causal effect (CACE) analysis. This

approach, if certain assumptions are fulfilled, produces an estimated effect of treatment taking into account non-compliance (Hewitt et al, 2006).

Figure 2 Flow chart of participants through each stage of a randomised controlled trial. (Adapted from Moher et al, JAMA 2001;285:1987–91.)



Patients included in each type of analysis of treatment A effect :

Intention-to-treat analysis
 Modified Intention-to-treat analysis
 Per-protocol analysis
 Treatment received analysis

If a large proportion of patients cross over to opposite treatment arms or are lost to follow-up, the interpretation of study results will be difficult, and neither an ITT nor a per-protocol analysis provides reliable information. An extreme example is the Spine Patient Outcomes Research Trial (SPORT), which compared standard open discectomy versus non-operative treatment for patients with lumbar intervertebral disk herniation. Only 60% of patients assigned to surgery received surgery, as compared with 45% of those assigned to non-operative treatment (Weinstein et al, 2006). Whatever the analysis performed, none will be informative.

The reality of conducting clinical trials means that the ITT principle is not usually fully met, especially when outcome data are missing. Therefore, performing an ITT analysis usually implies choosing a method to handle missing data. Because missing data may occur for various reasons, including adverse events related to the treatment, the method used for data imputation must be conservative—that is, not favour the treatment group.

One widely used method for data imputation is replacement by the last observation available for the patient (last observation carried forward (LOCF)), but the assumptions needed for this to produce a valid estimate are seldom met. LOCF should be viewed with suspicion in favour of preferred methods, including multiple imputation and mixed effects models (Bell et al, 2014) and sensitivity analyses (i.e., analysis evaluating the influence of different methods of handling missing data). An example of a simple sensitivity analysis is provided in **Box 5**.

Box 5. Example of simple sensitivity analysis

Kontiokari et al (2001) undertook an RCT of cranberry juice to prevent recurrent urinary tract infections (UTIs) among women. They found a significant benefit of the treatment; however, 8% of the cranberry group and 10% of the control group were lost to follow-up. The authors checked their data by assuming all of those who dropped out of the cranberry group got an infection and all of those in the control did not. The new results still showed a significant advantage for cranberry juice

2-1-4 Outcome measurement

A crucial issue in assessing trials is the actual measure of whether something works or not. The outcome chosen to conclude the effectiveness of the treatment could be either a clinical event (e.g. death, fracture), a therapeutic decision (e.g. length of stay, transfusion, surgery), a patient-reported outcome (e.g. pain, fatigue), or a biological, physiological, or morphological measurement (e.g. synovitis from MRI).

Most outcomes can be measured as a dichotomous variable (e.g. event/no event), as a continuous variable (e.g., blood pressure, glycaemia, WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scale) or as time to the onset of an event (survival time data).

Whatever its nature, a good outcome must:

- be clinically relevant
- be unique
- be recognised in other studies
- have good reliability and reproducibility
- be available for all patients to avoid attrition bias.

Clinical relevance and surrogate outcomes

To decide whether to apply the study results, one needs evidence that treatment improves outcomes that are important to patients. Having an elevated blood pressure is of little interest to the patient, whereas having a stroke is of major importance.

A good outcome must be clinically relevant for the patient; examples include death, length of hospital stay, myocardial infarction, fractures, and quality of life. The length of follow-up has to be consistent with disease evolution. For example, a follow-up of only 1 month is unlikely to be appropriate for chronic disease outcomes. Kyriakidi and Ioannidis (2002) showed that only 11% of RCTs of systemic sclerosis had a follow-up of more than 1 year.

However, usually these outcomes are substituted by 'surrogate' outcomes, generally biological or imaging markers, which are easier to measure and believed to be indirect measures of the clinically relevant outcome. For example, change in bone mineral density is often used as a surrogate to measure the effectiveness of treatments for the prevention of osteoporotic fractures. As well as being of questionable clinical relevance, surrogate outcomes are often misleading (Fleming and DeMets, 1996). For example, Riggs et al (1990) found that sodium fluoride substantially increased bone mineral density but did not prevent fractures.

Surrogate outcomes are widely used because observing a difference in a surrogate measure requires a much smaller sample size and shorter follow-up as compared with a clinical outcome. Trials designed to observe changes in bone mineral density require only a few hundred participants, whereas those designed to observe a fracture endpoint require many thousands of participants. Surrogate outcomes, however, are useful in helping to guide research at its earliest stages.

Many diseases have a plethora of possible outcomes that can be measured by different scales or instruments. This may make interpretation and comparison of different studies very complex. For example, before concerted efforts to standardise outcome measurement in rheumatology RCTs, Gotzsche et al (1989) found more than 70 outcomes used in 196 RCTs of NSAIDs for rheumatoid arthritis. Where available and appropriate, consensus guidelines for core outcome sets – see, for example, OMERACT (<http://www.omeract.org/>) and COMET (<http://www.comet-initiative.org/>) – and previously developed and validated scales should be used, as this will enhance quality of measurement and assist in comparison with similar studies. Examples can be found at. Authors should indicate the origin and properties of scales. Readers should be sceptical of studies involving unconventional outcomes.

The primary outcome

A single primary outcome must be defined a priori. The study must be designed and the sample size calculated to demonstrate whether the treatment has an effect or not on this primary outcome. When outcomes are assessed at several time points after randomisation, the pre-specified time point of primary interest must also be defined a priori. These decisions may help avoid a multiplicity of statistical tests, some of which by chance alone, will be statistically significant.

The α level is the chance taken by researchers to make a type I error: incorrectly declaring a difference, effect or relationship to be true because of only chance producing the observed state of events. Customarily, the α level is set at 0.05—that is, in no more than one in 20 statistical tests the test will show some effect when in fact there is no effect. If more than one statistical test is used, the chance increases of finding at least one test result in the whole experiment that is statistically significant only due to chance and to incorrectly declare a difference or relationship to be true. In five tests this chance equals 0.22, or 1 in 5; in 10 tests, this chance increases to 0.40, or about 1 in 2. There remains a debate on whether and how far to extend the principle of correction for multiple testing, e.g. in multi-arm trials (Wason et al., 2014).

Other outcomes of interest are secondary outcomes. There may be several secondary outcomes, and these should also be pre-specified and fully reported (not just those showing a statistically significant difference). Important outcomes must be considered, but a single study must not have too many outcomes. Adverse events and reactions are important but often poorly handled secondary outcomes.

Many trials recruit participants over a long period. If an intervention is working particularly well or badly, the study may need to be ended early for ethical reasons. Interim analysis could be performed. However, as explained above, performing repeated multiple statistical examinations without appropriate correction can lead to erroneous results and interpretations. The overall study results are not biased if interim analysis is planned in advance, statistical methods adapted, and results of analysis are interpreted by an independent committee which may decide to stop, or not stop, the study.

Composite outcomes

With no obvious choice of primary outcome in a trial, trialists can adopt the composite of several outcomes. An example of a composite outcome to evaluate the efficacy of a new stent could be the occurrence of one of the following events: death, reinfarction, stroke, or repeat target vessel revascularisation.

The advantages of this option could be to avoid the need for arbitrary choices in deciding which outcome to elect as the primary one and to increase the power of a study for the same number of patients included (as more events are supposed to occur, and the composite more robustly and accurately represents the outcome of interest). This solution helps deal with the issue of multiplicity of tests. However, a major disadvantage lies in the interpretation of results. Composite outcomes sometime combine events of very different severity, and the treatment effect can be driven by the least important outcome, which is often the most frequent. When interpreting results it is important to bear in mind that the effect described relates to the entire composite outcome and not to each component of the outcome.

Freemantle et al (2003) proposed five recommendations on the appropriate use of composite outcomes:

- Trialists should follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Moher et al, 2010*) and identify precisely the pre-specified primary and secondary outcome measures, reporting the results clearly in publications that describe the trial.
- When trials report composite variables as primary outcomes, these should be interpreted together rather than as demonstrating efficacy of individual components of the composite.
- Components of composite outcomes should always be defined as secondary outcomes and reported alongside the results of the primary analysis, preferably in a table.
- Authors and journal editors should ensure that the reporting of composite outcomes is clear and avoids the suggestion that individual components of the composite have been demonstrated to be effective.
- Systematic overviews and quantitative meta-analyses should be used to identify the effects of treatments on rare but important endpoints that may be included as part of composite outcomes in individual trials.

Reliability and reproducibility

Some outcomes are easier to measure than others. Death (from any cause) is usually easy to assess, whereas joint-space narrowing or quality of life are more difficult to measure. Some strategies can be used to improve the quality of measurements. For example, assessment of joint-space narrowing is more reliable if performed by two independent trained observers and if technical acquisition of radiography is standardised. A measure of reproducibility, corrected for agreement by chance, such as the kappa (κ) coefficient, helps in assessing the quality of the measure.

Independence

Standard methods of analysis assume that the data are 'independent'. For RCTs, this usually means that each comparison test involves only one observation per participant. Treating multiple observations from one participant as independent data is a serious error; such data arise when outcomes can be measured at successive times or from different parts of the body. For example, in a trial of osteoporosis, treating two vertebral fractures in the same patient as two independent observations is incorrect. The correct approach is to count the number of patients with at least one vertebral fracture. Data analysis should be based on counting each participant once (Altman and Bland, 1997; Bolton, 1998) or should involve specific statistical procedures taking into account the clustered or multi-level nature of the data (i.e. fractures within patients). An analysis of 196 trials in rheumatoid arthritis (Gotzsche, 1989) found that 63% of trials used multiple observations.

2-1-5 Subgroup analysis

Multiple analyses of the same data incur considerable risk for false-positive findings. As previously discussed, this risk should lead to a limitation on the number of outcomes and the number of occasions on which they are assessed. The same risk imposes that multiple analyses of the same outcome in different subgroups of patients must be avoided.

Because of the high risk for spurious findings, subgroup analyses do not have great credibility. When considering results of a subgroup analysis, remember the following (Rothwell, 2005b; Sun et al., 2014*):

- Subgroup analysis should be defined before starting the trial and should be limited to a small number of clinically important questions.
- If important subgroup-treatment effect interactions are anticipated, trials should ideally be powered to detect them reliably.
- Significance of the effect of treatment in individual subgroups should not be reported; rates of false-negative and false-positive results are extremely high. The only reliable statistical approach is to test for a subgroup-treatment effect interaction, but few trials are powered to detect this.
- All subgroup analyses that were done should be reported.
- Until their findings are reproduced in other trials, subgroup analyses must be regarded as hypothesis-generating, and not as hypothesis testing.

2-3 What are the Results?

If the results are valid and the study likely yields an unbiased assessment of treatment effect, then the results are worth examining further.

First, for each outcome, study results should report a summary of the outcome in each group (e.g. the proportion of participants with the event, or the mean and standard deviation (SD) of measurements) (Guyatt et al, 1994*).

Then, to appreciate the treatment effect, two additional data must be reported:

- the contrast between the two groups, known as the measure of treatment effect, and
- an estimation of the precision of this measure, the statistical significance of the treatment effect (confidence interval (CI) and/or p value).

2-3-1 Measures of effect size

Readers of randomised clinical trials can expect to encounter several different summary measures of treatment effect. The more common ones are shown in **Box 6**.

Box 6. Some common summary measures of treatment effect used in RCTs

<i>Level of measurement</i>	<i>Example</i>	<i>Summary measure of treatment effect</i>
Dichotomous	Proportion of patients dead at follow-up	Risk difference (RD) (also known as absolute risk reduction (ARR)) Risk ratio (also known as relative risk) (RR) Relative risk reduction (RRR)
Time-to-event	Time to first hip fracture	Hazard ratio (HR) Difference in mean/median survival time
Continuous	Percentage change in femoral neck bone mineral density	Difference in means

Dichotomous outcomes

Consider the simple trial finding in **Box 7**.

Box 7. An example of a RCT with a dichotomous outcome

	Treatment group	Control group
Proportion of participants dead at 12 month follow-up	15%	20%

How might these results be expressed?

One way would be as the absolute difference (known as the risk difference (RD) or absolute risk reduction (ARR)) between the proportion dying in the control group (x) and the proportion dying in the treatment group (y):

$$ARR = x - y = 0.20 - 0.15 = 0.05 = 5\%.$$

Another way would be as a relative risk (RR): the risk of events among patients having the new treatment relative to the risk among patients in the control group:

$$RR = y/x = 0.15 / 0.20 = 0.75 = 75\%$$

The most commonly reported measure of dichotomous treatment effects is the complement of the relative risk, the relative risk reduction (RRR), which is expressed as a percentage:

$$RRR = (1 - RR) \times 100 = (1 - 0.75) \times 100 = 25\%$$

or

$$RRR = ARR/x = (0.20 - 0.15)/0.20 = 25\%$$

A RRR of 25% means that the new treatment reduced the risk of death in the treatment group by 25% as compared with the control group; the greater the RRR, the more effective the treatment. Investigators may compute the RR over a period of time, as in a survival analysis, and call it a hazard ratio. When authors do not specify whether they are talking about RRR or ARR—for example, ‘Drug X was 30% effective in reducing the risk of death,’ or ‘The efficacy of the vaccine was 92%’—they are almost invariably talking about RRR.

For some treatments and conditions, the benefit of a specific treatment, as measured by the RR or RRR, remains approximately constant over patient populations at various baseline risks (Cook and Sackett, 1995). Since a single estimate of treatment effect can be provided for a broad class of patients, RR and RRR appear attractive. However, it is often clinically important to consider the baseline (control) risk of an event before recommending treatment, because for a given RRR, the expected absolute benefit of treatment could vary considerably as the baseline risk changes. For example, an estimated RRR of 50% might be important for patients at moderate to high risk for a particular adverse event. However, for patients with a low probability of an event, the risk reduction might not be sufficient to warrant the toxic effects and cost of treatment (Cook and Sackett, 1995).

Because RRR or RR fails to discriminate between enormous and very small effects in absolute number, the ARR is considered a better measure of treatment effect. However, the ARR is usually expressed as a decimal fraction (e.g., 0.06, 0.14, etc) which is difficult to interpret in clinical practice. The reciprocal of ARR, the number needed to treat (NNT), is therefore recommended (Osiri et al, 2003):

$$\text{NNT} = 1/\text{ARR}$$

The NNT is the number of patients who would need to be treated with the new treatment rather than the control for one additional patient to benefit (Laupacis et al, 1988). It can be obtained for any trial that has reported a dichotomous outcome.

In the example above, the ARR between the proportions in the control and treatment groups who died is 0.05, so the NNT would be $1/0.05 = 20$ —that is, 20 patients would need to be treated in order to prevent one additional death.

A large treatment effect, in the absolute scale, leads to a small NNT. A treatment that leads to one saved life for every 10 patients treated is clearly better than a competing treatment that saves one life for every 50 treated.

The ideal NNT is 1, whereby everyone has improved with treatment and no one has improved with the control. The higher the NNT, the less effective the treatment. However, the value of an NNT is not just numeric. For example, NNTs of 2–5 are indicative of effective therapies such as analgesics for acute pain, NNTs of

approximately 1 might be achieved by treating sensitive bacterial infections with antibiotics, whereas an NNT of 40 or more might be useful in the use of aspirin after a heart attack.

A correctly specified NNT must always give the comparator, the therapeutic outcome, the duration of treatment necessary to achieve that outcome, the 95% CI and the baseline risk of event without treatment.

While NNT estimates the benefit of a treatment, the number needed to harm (NNH) may estimate the potential risk of the treatment. Its calculation is similar to the NNT:

$$NNH = 1/(\text{proportion of adverse events in the treatment group} - \text{proportion of adverse events in the control group})$$

Comparison of NNT and NNH, by weighing benefits and risks, helps to evaluate the benefit/risk ratio of a treatment.

The NNT reflects the fact that the effect of a treatment for a patient is related not only to its RRR but also to its baseline risk. For a given treatment, RRR is the same for all patients, but NNT varies with the individual patient baseline risk. The higher the probability that a patient will experience an adverse outcome with no treatment, the more likely the patient will benefit from treatment and the fewer patients need to be treated to prevent one adverse outcome. Box 8 provides an illustrative example.

Box 8. Example of weighing benefits and harms in patients with different baseline risks of each

Results of clinical trials suggest that hormone replacement therapy reduces the relative risk of spine fracture over a lifetime by approximately 30%, but such therapy also increases the risk of stroke by 50%. Consider two menopausal women with different baseline expected rates of spine fracture and stroke: patient A has low bone mineral density but no cardiovascular risk factors; patient B has normal bone mineral density but many cardiovascular risk factors. The table below summarises the NNT and NNH values for these two women to help in clinical decision making by balancing the risks and benefits in each case.

		Risk without HRT	Risk with HRT	Relative risk variation (reduction or increase)	Absolute risk variation (reduction or increase)	NNT or NNH
Patient A	Spine fracture	0.20	0.14	0.30	0.06	17
	Stroke	0.01	0.015	0.50	0.005	200
Patient B	Spine fracture	0.10	0.07	0.30	0.03	33
	Stroke	0.03	0.045	0.50	0.015	67

Treating approximately 200 women like patient A will prevent 12 spine fractures ($200 \times 1/17$) but induce one stroke. Given the small increased risk of stroke and the number of spine fractures prevented, many clinicians might suggest hormone replacement therapy for such patients.

However, treating approximately 200 women like patient B will prevent only six spine fractures ($200 \times 1/33$), but will induce three strokes ($200 \times 1/67$). Obviously, hormone replacement therapy is less indicated in these patients.

HRT Hormone replacement therapy; NNT Number needed to treat ; NNH Number needed to harm

Continuous outcomes

For continuous outcomes, the measure of treatment effect is the difference in means between the treatment and control group. The standard deviation (SD) reflects the dispersion of values around the mean.

Results of continuous outcomes are usually difficult for clinicians to use in clinical practice because of problems in assessing their clinical importance or in comparing benefits with risks across various therapeutic options.

Comparing the effect of treatment among studies involves the effect size (d): the difference between two means (treatment minus control group) divided by the pooled SD of the two groups – equivalent to the number of SDs between the two means:

$$d = (\text{Mean}_t - \text{Mean}_c) / \text{SD}_{\text{pooled}}$$

$$\text{with } \text{SD}_{\text{pooled}} = \sqrt{\frac{(n_t - 1)SD_t^2 + (n_c - 1)SD_c^2}{n_t + n_c}}$$

and where: *t* refers to treatment group, *c* refers to the control group, and *n* is the number of subjects. Box 9 provides an illustrative example.

Box 9. Estimating effect size from continuous outcomes: a worked example

	Treatment group (n=98)	Control group (n=96)
Mean (SD) HAQ score at 3 months	6.0 (2.5)	5.3 (2.1)

$$\text{SD}_{\text{pooled}} = \sqrt{\frac{(98 - 1)2.5^2 + (96 - 1)2.1^2}{98 + 96}} = 2.3$$

The effect size (d) = $(\text{Mean}_t - \text{Mean}_c) / \text{SD}_{\text{pooled}} = (6 - 5.3) / 2.3 = 0.3$

The division by the SD allows for comparison of effect sizes across studies.

Opinions vary on how to interpret effect size, but the most accepted advice is by Cohen (1992), for whom 0.2 is indicative of a small effect, 0.5 a medium effect, and 0.8 a large effect size.

HAQ Health Assessment Questionnaire

Translating a continuous measure (e.g., HAQ) to a dichotomous measure such as ‘therapeutic success (yes/no)’ usually leads to more clinically meaningful results. This dichotomisation may help in interpreting and assessing the clinical significance of trial results. It allows for an NNT calculation that is usually more meaningful than the difference in means. It is more meaningful to say ‘one needs to treat five patients for halving the EVA score in one patient’ than ‘difference in EVA score between treatment and placebo is 9.7 mm (SD = 3.7)’.

However, dichotomising a continuous variable can result in loss of information and statistical power.

A relevant cut-off value is specific to each outcome. For a patient-reported outcome such as the minimal clinically important improvement, which is the smallest change in measurement that signifies an important difference or improvement in symptoms, or the patient acceptable symptom state, the score below which patients consider themselves well, may help to determine a clinically relevant cut-off value for the dichotomisation (Tubach et al, 2005a; Tubach et al, 2005b).

2-3-2 Measures of precision of the treatment effect

Confidence interval

Realistically, the true measure of the treatment effect can never be known. The best we have is the estimate provided by rigorous controlled trials, and the best estimate of the true treatment effect is that observed in the trial. This estimate is called a point estimate, a single value calculated from observations of the sample that is used to estimate a population value or parameter. The point estimate reminds us that, although the true value lies somewhere in its neighbourhood, it is unlikely to be precisely correct. We usually (though arbitrarily) use the 95% CI to estimate the neighbourhood within which the true effect likely lies. One can consider the 95% CI as defining the range that includes the true value of the effect 95% of the time.

If the CI of a ratio contains 1 (or zero for a difference), the result is compatible with no effect, and the difference is not statistically significant. Consider the examples in Box 10.

Box 10. Confidence intervals and sample size in RCTs

If a trial randomised 100 patients each to treatment and control groups, and there were 20 deaths in the control group and 15 deaths in the treatment group, the authors would calculate a point estimate for the RRR of 25%. You might guess, however, that the true RRR might be much smaller or much greater than this 25%, with a difference of only five deaths. In fact, you might surmise that the treatment might provide no benefit (an RRR of 0%) or might even do harm (a negative RRR), and you would be right. This is because the 95% CI of the RRR is –38% (i.e., patients given the new treatment might be 38% more likely to die than control patients) to 59% (i.e., patients subsequently receiving the new treatment might have a risk of dying almost 60% less than that of non-treated patients). The trial really has not helped us decide whether to offer the new treatment.

If the trial enrolled 1000 patients per group, and the same event rates were observed as before, for 200 deaths in the control group ($x = 200/1000 = 0.20$) and 150 deaths in the treatment group ($y = 150/1000 =$

0.15), again, the point estimate of the RRR is 25% ($1 - y/x = 1 - [0.15/0.20] \times 100 = 25\%$). In this larger trial, you might think that the true reduction in risk is much closer to 25% and, again, you would be right. This is because the 95% CI for the RRR for this set of results is on the positive side of zero and is 9% to 41%.

What these examples show is that the larger the sample size of a trial, the greater our confidence that the true RRR (or any other measure of efficacy) is close to what we have observed. In the second example above, the lowest plausible value for the RRR was 9% and the highest 41%. The point estimate—in this case, 25%—does not change and is the value most likely to represent the true RRR. Values beyond the upper or lower boundaries of the 95% CI are extremely unlikely to happen if a study of the same size is repeated.

95% CIs are important for continuous outcomes as well, as illustrated in **Box 11**.

Box 11. Confidence interval for a continuous outcome

In a study of respiratory muscle training for patients with chronic airflow limitation, one primary outcome measured how far patients could walk in 6 min in an enclosed corridor. In the experimental group receiving respiratory muscle training, this 6 min walk improved, from a mean of 406 metres to 416 metres (up 10 m), and in the control group, from a mean of 409 m to 429 m (up 20 m). The point estimate for improvement in the 6-min walk due to respiratory muscle training therefore was negative, –10 m (or a 10 m difference in favour of the control group). The lower boundary of the 95% CI was –26 m (i.e., the results are consistent with a difference of 26 m in favour of the control treatment) and the upper boundary was +5 m.

Even in the best of circumstances, adding 5 m to the 400 m recorded at the start of the trial would not be important to the patient, and this result effectively excludes an important benefit of respiratory muscle training as applied in this study.

2-3-3 The p value

Many journals require or strongly encourage the use of CIs. Although p values may be provided in addition to CIs, results should not be reported solely as p values (Moher et al, 2001*). Yet CIs are not always reported, so one must look at the p value of the primary outcome.

Depending on the test used, there are many ways to calculate a p value, but its meaning is always the same. The p value tells how often the results would have occurred by chance of no difference between the two groups. In other words, the p value describes the risk of a false-positive conclusion that there is a difference when, in truth, there is no difference.

The p value reflects the statistical significance of a difference but not its size. A small difference observed with a large sample is more significant statistically than the same difference observed with a small sample. Thus, a difference could be statistically significant but clinically insignificant. The p value tells us only if the observed difference is likely to be true ($p < 0.05$) or only the result of chance ($p > 0.05$)—that is, statistically not

significant. A value of $p < 0.05$ means that this result would have arisen by chance on less than one occasion in 20.

If the p value is exactly 0.05, then the lower boundary of the 95% CI for the RRR must lie exactly at zero (RR of 1), and one cannot exclude the possibility that the treatment has no effect. As the p value decreases below 0.05, the lower boundary of the 95% CI for the RRR rises above zero.

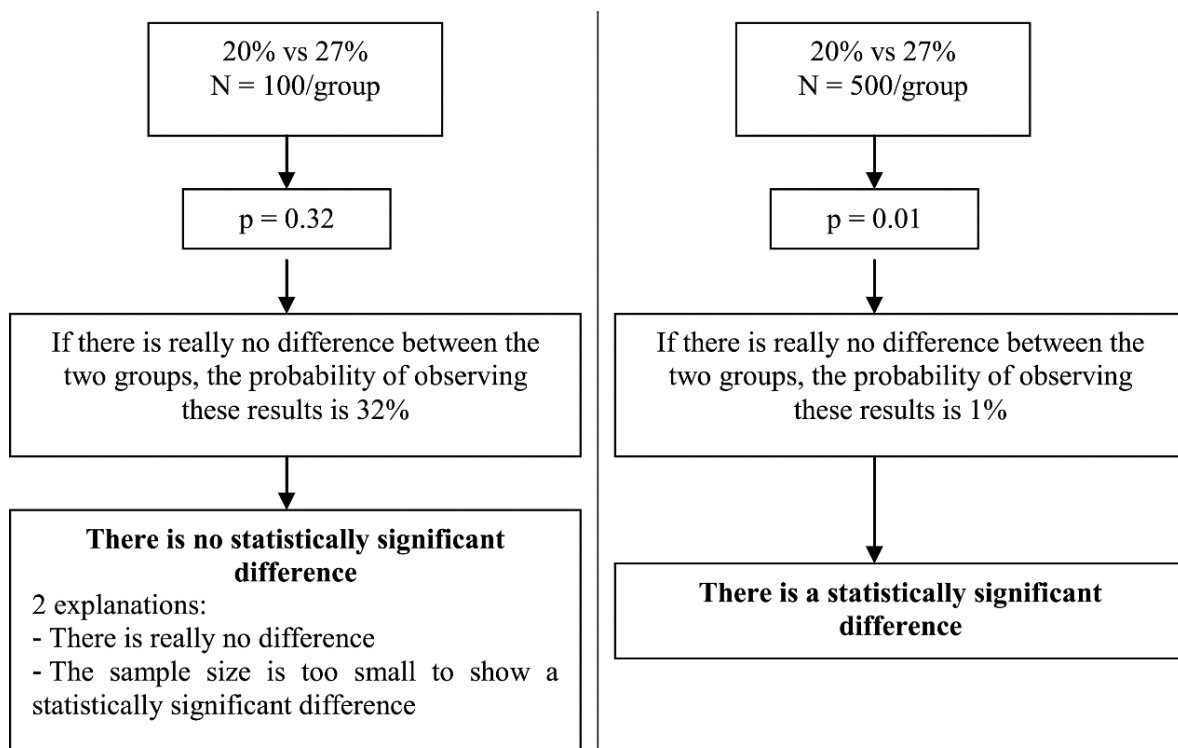
2-3-4 Clinical relevance versus statistical significance

When looking at the results of a study, one must consider two important concepts: clinical significance, and statistical significance. The former addresses the size of the treatment effect, and the latter its credibility.

The literature is full of statistically significant but clinically irrelevant results. A clinically significant finding would be one clinically useful for a patient. For example, a study may find that a certain medication causes a statistically significant ($p < 0.05$) decrease in blood pressure of 2 mm Hg, but this would not be a clinically significant decrease in blood pressure. In contrast, a study finding a statistically significant decrease in blood pressure of 20 mm Hg would be more clinically significant.

Statistical significance depends on the size of the difference between the groups, and on the number of patients. The p value alone gives no information on the magnitude of the effect. Clinically trivial differences can be statistically significant if the sample size is sufficiently large. Conversely, clinically important differences can be statistically not significant if the sample size is too small—that is, if the study lacks power (Figure 3).

Figure 3 Clinical significance and interpretation of the p value.



If the study has a positive result (the treatment group did significantly better), look at the low end of the 95% CI and determine whether this minimum treatment effect is still important or clinically significant. If so, the study results can be considered definitive. However, if one cannot consider this minimum treatment effect clinically significant, then the study cannot be considered definitive, even if its results are statistically significant (i.e., they exclude a risk reduction of 0). Remember, any difference towards the end of the CI has a low chance of being the 'true' difference, which must be taken into account.

If the study has a negative result (the treatment and control groups did about the same), there are two possible explanations: first, there is really no difference between the treatment and control groups; and second, the study did not have enough power (not enough subjects) to find a difference if there really was one. This is called a β -error, or a type II error, and the study is referred to as being underpowered. To interpret these results, look at the high end of the 95% CI and determine whether this effect would be clinically important. If so, the study failed to eliminate a potentially important treatment effect (i.e., the sample size was too small). We can conclude that, although the investigators have failed to show that the experimental treatment was better than the placebo, they also failed to show that it was not better; they have not excluded a large, positive treatment effect.

If the study report does not give a CI, another approach is to look closely at the hypothesis assumed for the sample size calculation. With a too-small sample size, even a clinically meaningful difference will never be statistically significant.

Sample size calculation for dichotomous outcomes requires four components: type I error (α), power, event rate in the control group, and a minimal treatment effect of interest (or, analogously, an event rate in the treatment group). Calculation of continuous outcomes requires, instead of event rate in the control and treatment group, difference between means and assumptions on the SD.

The sample size is probably too small if in the calculation:

- the clinically relevant minimal treatment effect assumed is too large (a smaller but still clinically relevant difference should have been chosen)
- the event rate in the control group is overestimated
- the SD is underestimated for continuous outcomes.

As an example, Keen et al (2005) found that in 50% of rheumatology reports of RCTs with negative or indeterminate results published in 2001–2002, the studies were underpowered.

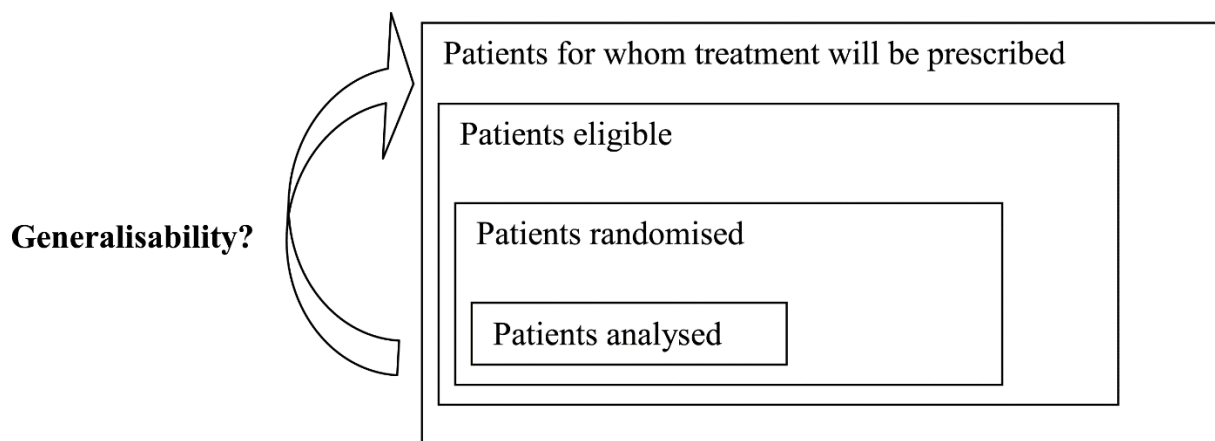
Having determined the magnitude and precision of the treatment effect, we can turn to the final question of how to apply the article's results to patients in clinical practice.

2-4 How Can I Apply These Results to Patient Care?

2-4-1 Generalisability of study results

When answering the question ‘Are the results of the study valid?’ we in fact only explored the internal validity—that is, any bias that can explain the observed effect in the subjects studied. Now we ask about the study’s external validity—that is, the generalisability of the study results (figure 4) (Guyatt et al, 1994*). Of course, if the internal validity of the study is poor, there is no point in proceeding further. If the study result is not valid even for the subjects studied, its application to other groups of subjects is irrelevant. However, if we conclude that it is a reasonably valid result, and that a causal association is a reasonably likely explanation, we need to explore the external validity of the results.

Figure 4 Differences between patients analysed and patients for whom treatment will be prescribed, raising the issue of generalisability of study results.



There is no external validity per se. The results of a study will never be relevant to all patients and all settings, but studies should be designed and reported so that clinicians can judge to whom the results can reasonably be applied.

The following criteria must be considered before applying results to patients (Rothwell, 2005a):

- **Setting of the trial:** country; healthcare system; recruitment from primary, secondary or tertiary care; selection of participating centres and clinicians.
- **Selection of patients:** eligibility and exclusion criteria, ‘run-in’ or ‘washout’ period, ‘enrichment’ strategies, ratio of randomised patients to eligible non-randomised patients.
- **Characteristics of randomised patients:** severity or stage in the natural history of disease, comorbidities, racial group, other baseline clinical characteristics.

- **Difference between trial protocol and routine practice:** relevance of control intervention, co-interventions, prohibition of certain non-trial treatments, therapeutic or diagnostic advances since the trial was performed.
- **Outcome measure and follow-up:** clinical relevance of outcomes (surrogate, complex scale, composite outcome, etc), frequency of follow-up, adequacy of the length of follow-up.
- **Adverse effect of treatment:** completeness of reporting of adverse effects, rate of discontinuation of treatment, selection of trial centres and/or clinicians on the basis of skill or experience, exclusion of patients at risk for complications, exclusion of patients who experienced adverse effects during a run-in period, intensity of trial safety procedure.

The clinical setting is never exactly the same as the trial setting and your patient often has attributes or characteristics different from those enrolled in the trial. These differences may lead to less benefit, as was shown between a phase III clinical trial and a phase IV cohort study on the use of etanercept for rheumatoid arthritis (Farahani *et al*, 2005). So one must ask whether these differences may really diminish the treatment response or increase greatly the risk of adverse events—that is, ‘Is my patient so different from the study patients that I cannot apply the results to my patient?’

2-4-2 Consideration of adverse effects

Before applying results of a study to a patient, one must consider the possible harm that any intervention might do. Regardless of this crucial information, reporting of harms in RCTs has received less attention than reporting of efficacy and is often inadequate. In 2004 an extension of the CONSORT statement focused on better reporting of harms-related data from RCTs (Ioannidis *et al*, 2004).

Looking at the rate of adverse effects (or the NNH) reported in each group helps in appraising the risks of a treatment. However, studies are never powered to detect a statistically significant difference in rates between groups. Sample sizes are usually too small for a reasonable chance of detecting an unexpected adverse effect. Therefore, some authors suggest the creation of a composite outcomes basket to be used as the primary safety outcome in clinical effectiveness trials (Tugwell *et al*, 2005).

3 DIAGNOSTIC EVIDENCE

The objective of a diagnostic test is to accurately classify patients with or without a target condition. This target condition could be a specific disorder (such as Sjögren syndrome, Behçet disease or sarcoidosis), or a specific state (such as remission, response). A diagnostic test may be a clinical symptom, a laboratory test, a morphologic exam (radiography, magnetic resonance imaging (MRI), etc) or a more invasive act such as biopsy or surgery. The result of a diagnostic test may be dichotomous, categorical or continuous (although to

facilitate decision-making a cut-off value is often selected). Although the following section deals with the simplest situation of a single diagnostic test giving a dichotomous result (positive/negative) it will be readily recognized that in clinical practice, diagnostic tests are seldom used and interpreted in isolation. Instead, any test or piece of information that may indicate the presence or absence of the target disorder suspected in a patient will be used and interpreted in the context of overall diagnostic profile of the patient.

Several different types of research study may be used to evaluate a new diagnostic test at different stages in its development:

- **Step 1: Technical performance**—is the test feasible and does it have good reproducibility?
- **Step 2: Diagnostic performance**—do the test results allow for an accurate diagnosis to be made?
- **Step 3: Diagnostic impact**—does the test change diagnostic confidence and displace other investigations?
- **Step 4: Therapeutic impact**—do the results of the test contribute to planning and delivering a therapy?
- **Step 5: Impact on health**—does the use of the test contribute to the improved health of the patient?

Randomised controlled trial designs may be best-suited to studies seeking to evaluate the impact on clinician behaviour and patient outcomes of introducing a new diagnostic test (Steps 3-5). These studies are still relatively uncommon. Instead, nearly all publications focus on the first two steps: technical and diagnostic performance (Dixon, 1997). We will focus on critical appraisal of articles reporting diagnostic performance. Further detail on critical appraisal of the validity of studies evaluating a diagnostic test is available from Jaeschke *et al*, 1994a*, Jaeschke *et al*, 1994b* or the QUADAS/QUADAS-2 checklists (Whiting *et al*, 2003; Whiting *et al*, 2011).

For establishing diagnostic performance—cross-sectional study designs are most appropriate. Investigators will typically sample patients whom they suspect may have the target condition, for example by including consecutive patients presenting with a particular set of symptoms or signs. Alternatively, a case-control design may be used in which patients with the target disorder are included along with a sample of healthy controls who do not. While this may be an attractive option, this approach can represent an ‘ideal contrast of extremes’ which tends to result in systematically better performance of diagnostic tests.

Irrespective of the sampling approach used to recruit patients, participants undergo both the new diagnostic test (‘index test’) and a reference standard (sometimes referred to as a ‘gold’ standard but since it is also typically subject to some (small) degree of error or misclassification the term ‘reference standard’ is preferred)—. The reference standard is accepted as the best means of establishing the ‘true’ presence or

absence of the target condition. Investigators then compare findings from the index test in those patients classed as having/not having the target disorder as determined by the reference standard.

3-1 Are the Results of the Study Valid?

3-1-1 Adequacy of the reference standard

The reference standard is the method used to determine the presence or absence of the target condition. To assess the diagnostic accuracy of the index test, its results are compared with those of the reference standard; subsequently, indicators of diagnostic accuracy can be calculated. Estimates of test performance are based on the assumption that the index test is being compared to a reference standard, which is 100% sensitive and specific. If there are any disagreements between the gold standard and the index test results, it is assumed that the index test is incorrect. Thus, from a theoretical point of view, the choice of an appropriate reference standard is very important.

Making a judgement as to the degree of error and misclassification in the reference standard may not be straightforward. Clinical subject-matter knowledge is often needed to judge whether a given test, combination of tests, or consensus panel of experts is an appropriate reference standard.

3-1-2 Delay between administering index test and reference standard

Ideally, the results of the index test and the reference standard are collected from the same patients at the same time. If this is not possible and a delay occurs, misclassification due to spontaneous recovery or to progression to a more advanced stage of disease may occur. This situation is known as disease progression bias. The length of the time that may cause such bias can vary between target conditions. For example, a delay of a few days is unlikely to be a problem for chronic conditions, but for many infectious diseases, a delay of only a few days may be important.

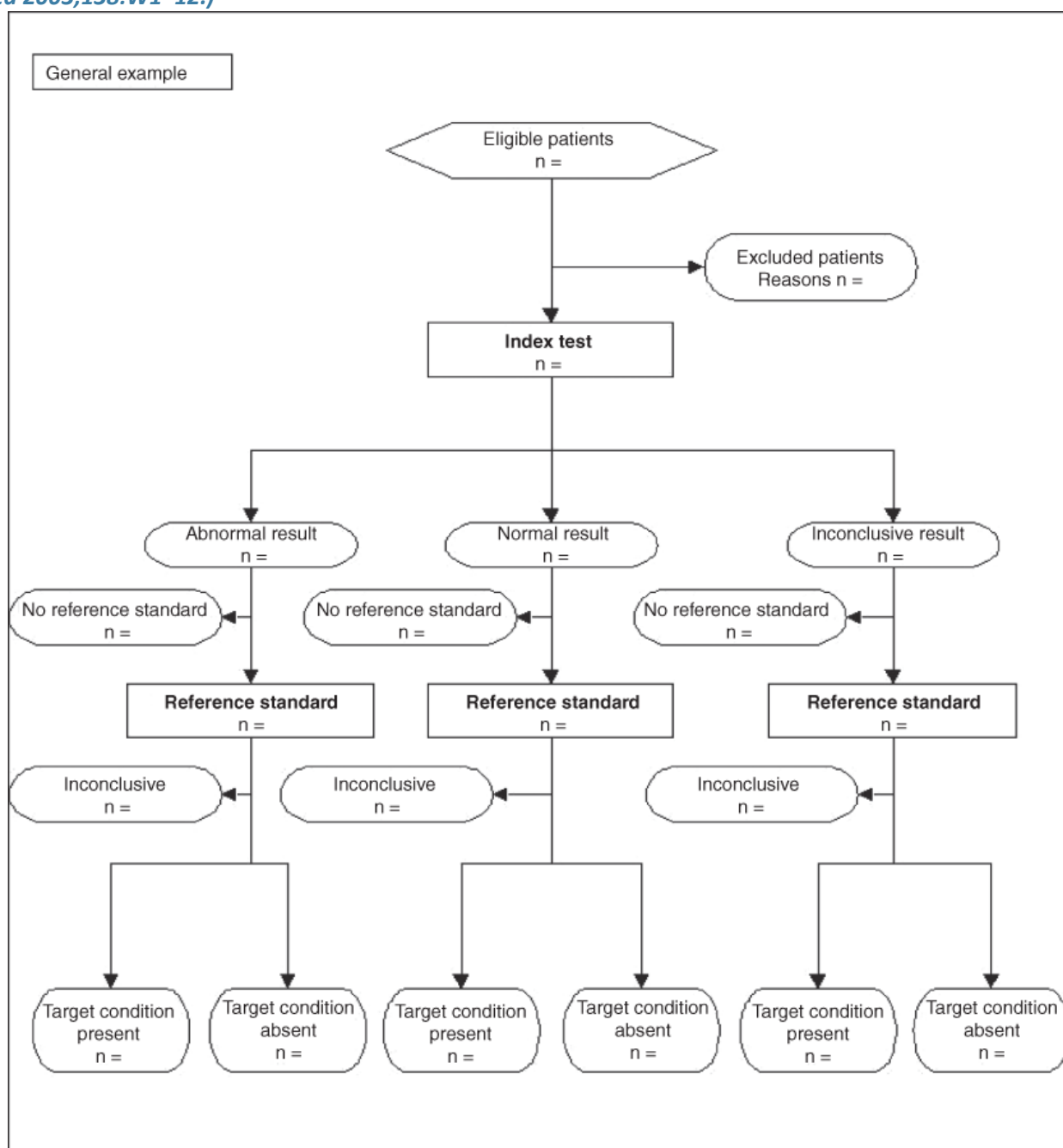
3-1-3 Partial verification

Partial verification bias (also known as work-up bias) occurs when not all of the study group undergo the reference standard. If the results of the index test influence the decision to perform the reference standard, then biased estimates of test performance may arise (Whiting *et al*, 2004). If patients are randomly selected to receive the reference standard, the overall diagnostic performance of the test is, in theory, unbiased. In most cases, however, this selection is not random, possibly leading to biased estimates of the overall diagnostic accuracy. The easiest way to check for bias is by checking the flow chart of the progress of patients through the study (Figure 5).

3-1-4 Differential verification

Differential verification bias occurs when some of the index test results are verified by a different reference standard. This is especially a problem if these reference standards differ in their definition of the target condition—for example, histopathology of the appendix and natural history for the detection of appendicitis. This situation usually occurs when patients testing positive on the index test receive a more accurate, often invasive, reference standard than those with a negative test result. The link (correlation) between a particular (negative) test result and it being verified by a less accurate reference standard will affect measures of test accuracy in a similar way as for partial verification, but less seriously.

Figure 5 Example of a flow chart of a diagnostic accuracy study. (Adapted from Bossuyt et al, *Ann Intern Med* 2003;138:W1–12.)



3-1-5 Lack of independence of index test from reference standard

When the result of the index test is used in establishing the final diagnosis, incorporation bias may occur. This means that the index test to be evaluated is part of or incorporated in the reference standard test. This incorporation leads to circularity—that is, it will probably increase the amount of agreement between index and reference standard test results and hence overestimate the various measures of diagnostic accuracy. Knowledge of the results of the index test alone does not automatically mean that these results are incorporated in the reference standard. For example, a study investigating MRI for the diagnosis of multiple sclerosis could have a reference standard composed of clinical follow-up, cerebrospinal fluid analysis and MRI. In this case, the index test forms part of the reference standard. If the same study used a reference standard of clinical follow-up, and the results of the MRI were known when the clinical diagnosis was made but were not specifically included as part of the reference, then the index test does not form part of the reference standard.

Interdependency all relates to the interpretation of the results of the index and the reference standard test. This situation is similar to 'blinding' in intervention studies. Interpretation of the results of the index test may be influenced by knowledge of the results of the reference standard, and vice versa. This bias is known as review bias and may lead to inflated measures of diagnostic accuracy. The extent to which this bias may affect test results relates to the degree of subjectivity in the interpretation of the test result. The more subjective the interpretation, the more likely the interpreter can be influenced by the results of the reference standard in interpreting the index test, and vice versa. One must consider the topic area and determine whether the interpretation of the index test or reference standard results could be influenced by knowledge of the results of the other test.

3-1-6 Completeness of reporting

A diagnostic test can produce an uninterpretable/indeterminate/intermediate result with varying frequency, depending on the test. These problems are often not reported in diagnostic accuracy studies with the uninterpretable results simply removed from the analysis. This situation may lead to the biased assessment of the test characteristics. Whether bias occurs depends on the possible correlation between uninterpretable test results and the true disease status. If uninterpretable results occur randomly and are not related to the true disease status of the individual then, in theory, these results should not have any effect on test performance. Whatever the cause of uninterpretable results, they must be reported so that their impact on test performance can be determined.

3-1-7 Sample size considerations

Performing and reporting sample size calculation is as important in diagnostic test studies as in RCTs evaluating therapy (Knottnerus and Muris, 2003). One practical approach is to consider for calculations the expected sensitivity: the minimal acceptable lower confidence limit for sensitivity and the prevalence of the disease (Flahault et al, 2005).

3-2 What are the Results?

The results of a simple diagnostic accuracy study with a single diagnostic test ('index test') yielding a dichotomous (positive/negative) result can be displayed in a 2x2 table (see Box 12). From this all basic calculations can be derived.

Box 12. 2x2 table for diagnostic accuracy studies

		Target condition (according to reference standard)	
		Present	Absent
Diagnostic test result	Positive	True Positives (TP)	False Positives (FP)
	Negative	False Negatives (FN)	True Negatives (TN)

3-2-1 Sensitivity and specificity

Sensitivity and specificity are the most widely used statistics in describing a diagnostic test.

- **Sensitivity (Sn)** = proportion of patients with the target condition who have a positive test result (TP/(TP+FN))
- **Specificity (Sp)** = proportion of patients without the target condition who have a negative test result (TN/(TN+FP))

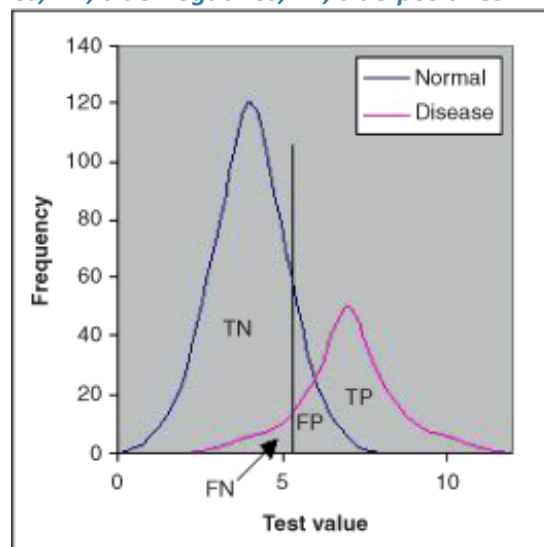
The sensitivity and specificity of a diagnostic test depend on the cut-off selected to define a 'positive' test result. Figure 6 shows the number of patients with and without a disease according to the value of a diagnostic test. This distribution overlaps: the test (like most) does not distinguish normal from disease with 100% accuracy. The area of overlap indicates where the test cannot distinguish normal from disease. In practice, we choose a cut-off value (indicated by the vertical black line) above which we consider the test result to be abnormal and below which we consider the result to be normal. The position of the cut-off value determines the number of true-positive, true-negative, false-positive, and false-negative results. We could use a different

cut-off value for different clinical situations depending on whether the goal is to minimize false-positive findings or false-negative findings.

High sensitivity is favoured when a false-negative result ('missed diagnosis') is more detrimental than a false-positive one ('false alarm'). This might be the case when there is an acceptable, affordable, safe, effective treatment or in early disease where delayed diagnosis is associated with substantially worse prognosis).

High specificity is favoured when a false-positive result is more detrimental than a false-negative one. This might be in circumstances where treatment carries significant risk of harm.

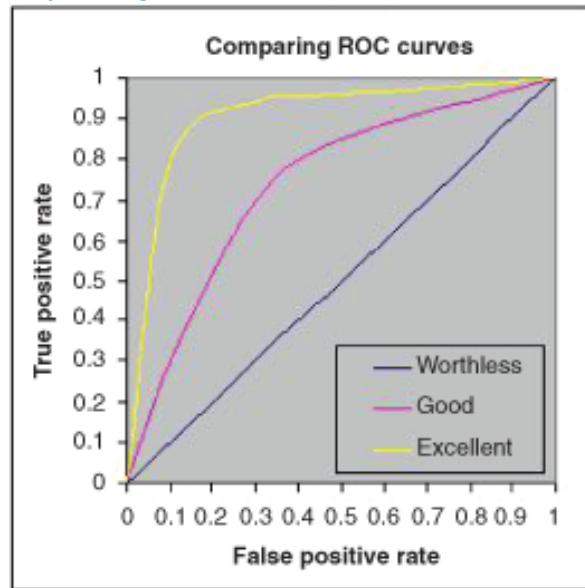
Figure 6 The number of patients with and without a disease according to the value of a diagnostic test. FN, false-negatives; FP, false-positives; TN, true-negatives; TP, true-positives.



3-2-2 Receiver operating characteristic curve

For each diagnostic test, the choice of a cut-off value between normality and abnormality is a compromise between sensitivity and specificity. A receiver operating characteristic (ROC) curve plots for various cut-off values of the same diagnostic test the sensitivity against 1 minus the specificity—that is, the true-positive results against the false-positive results.

The cut-off value minimising both the number of false-positive and false-negative results is the point of the curve nearest the top of the left-hand corner. The closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the test. Thus, the area under the curve is a measure of test accuracy. An area of 1 represents a perfect test; an area of 0.5 represents a worthless test. Figure 7 shows three ROC curves representing excellent, good, and worthless tests plotted on the same graph.

Figure 7 Comparison of receiver operating characteristic (ROC) curves.

3-2-3 Positive and negative predictive values

In clinical practice, however, the test result is all that is known. We need to know how good the test is at predicting the presence or absence of the target. Predictive values help answer this question.

- Positive predictive value (PPV) = proportion of patients with a positive test result who truly have the targeted condition ($TP/(TP+FP)$)
- Negative predictive value (NPV) = proportion of patients with a negative test result who truly do not have the target condition ($TN/(TN+FN)$)

PPVs and NPVs seem attractive but are of limited utility only because they depend critically on the prevalence of the disease in the patients being tested. The rarer the disease, the more a negative test result indicates no disease and the less a positive test result really indicates a disease. Predictive values observed in one study do not therefore apply to other populations with different background risk (e.g., prevalence) of the disease.

The prevalence can be interpreted as the probability before the test is carried out that the subject has the disease, known as the prior probability of disease. The positive and negative predictive values are the revised estimates of the same probability for subjects with positive and negative test results and are known as posterior probabilities. The shift between the prior and posterior probabilities is another way of assessing the usefulness of the test: it is the likelihood ratio.

3-2-4 Likelihood ratio

When we decide to order a diagnostic test, we want to know which test will best help us rule in or rule out disease in our patient. In the language of clinical epidemiology, we take our initial assessment of the likelihood

of disease ('pre-test probability'), do a test to help us shift our suspicion one way or the other, and then determine a final assessment of the likelihood of disease ('post-test probability').

Likelihood ratios (LRs) tell us how much we should shift our suspicion for a particular test result. Because test results can be positive or negative, there are at least two LRs for each test. The positive LR (LR+) tells us how much to increase the probability of disease if the test is positive, whereas the negative LR (LR-) tells us how much to decrease the probability if the test result is negative.

- Positive likelihood ratio (LR+) = $[TP/(TP+FN)] / [FP/(TN+FP)] = \text{Sensitivity} / (1-\text{Specificity})$
- Negative likelihood ratio (LR-) = $[FN/(TP+FN)] / [TN/(TN+FP)] = (1-\text{Sensitivity}) / \text{Specificity}$

A worked example of the all the above calculations is provided in Box 13.

Box 13. An example of diagnostic accuracy calculations

Investigators evaluated the diagnostic accuracy of simple point-of-care reagent strips for diagnosing presence/absence of inflammatory synovial fluid (SF) in 208 consecutive patients undergoing arthrocentesis. The reference standard was a microscopic white blood cell count of ≥ 2000 cells/mm³ obtained from laboratory analysis of the SF samples.

		Inflammatory SF (reference standard)		
		Present	Absent	
Reagent strip (<i>'index test'</i>)	Positive	60	17	77
	Negative	18	113	131
		78	130	208

Sensitivity (Sn) = $60/78 = 0.77 = 77\%$
 Specificity (Sp) = $113/130 = 0.87 = 87\%$
 Positive predictive value (PPV) = $60/77 = 0.78 = 78\%$
 Negative predictive value (NPV) = $113/131 = 0.86 = 86\%$
 Likelihood ratio (LR+) = $Sn / (1-Sp) = 0.77 / 0.13 = 5.9$
 Likelihood ratio (LR-) = $(1-Sn) / Sp = 0.23 / 0.87 = 0.26$

The LR is used to assess how good a diagnostic test is and to help in selecting an appropriate diagnostic test(s) or sequence of tests. It has advantages over sensitivity and specificity because it can be calculated for several levels of the symptom/sign or test, used to combine the results of multiple diagnostic tests, and used to calculate post-test probability for a target disorder (**Box 14**).

Box 14. Using likelihood ratios to update diagnostic probability

A 50-year-old woman consults for recent wrist arthritis with morning stiffness and without other symptoms. Based on her clinical presentation and his experience of similar cases in the past, the clinician judges that her probability of inflammatory arthritis is about 60%, a pre-test odds ratio (OR) of 6:4. If the clinician was to obtain a positive reagent test strip result ($LR+ = 5.9$) one can calculate the post-test probability of the patient having inflammatory arthritis given the positive test result:

Post-test odds = pre-test odds \times LR = $6/4 \times 5.9 = 8.85$

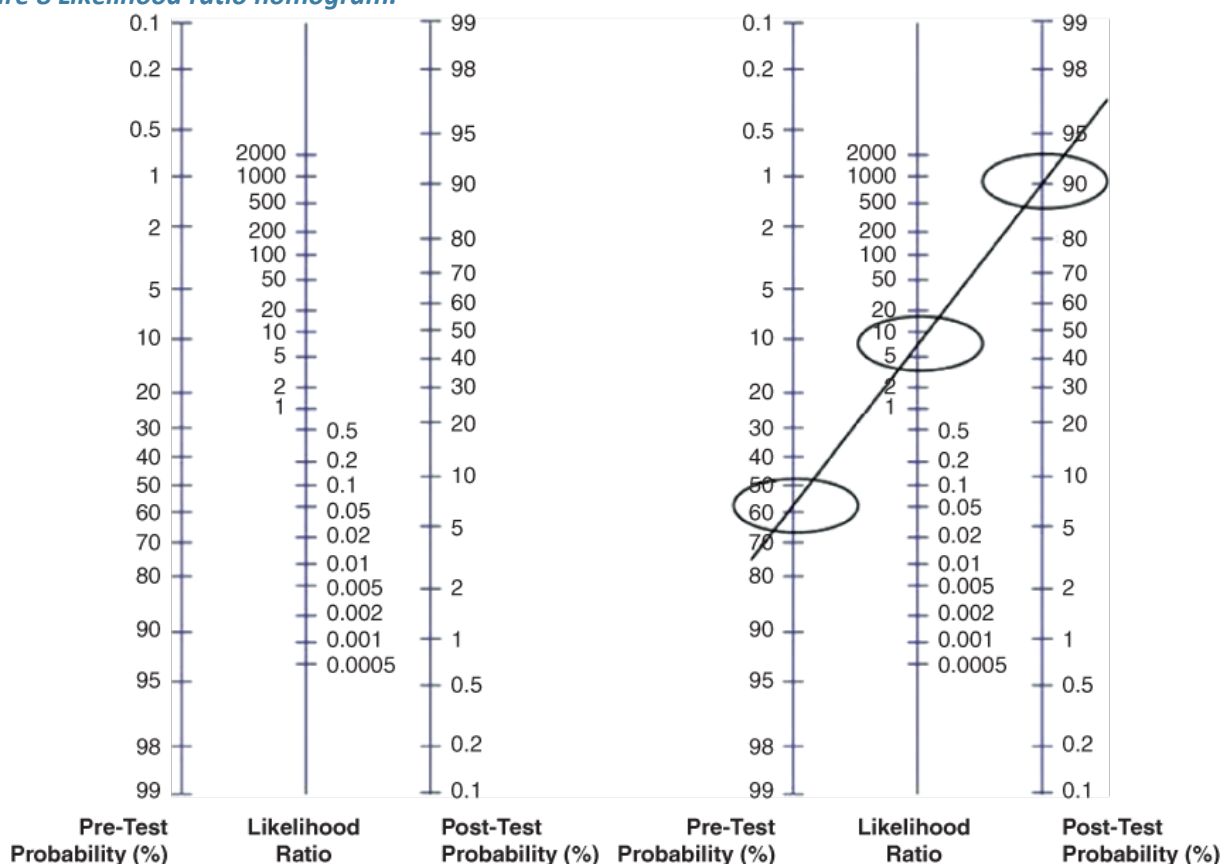
Post-test probability = post-test odds / (post-test odds + 1) = $8.85/(8.85 + 1) = 0.90 = 90\%$.

A positive reagent test result would change the probability of inflammatory arthritis from 60% to 90%

Switching back and forth between probability and LR's can also be done simply by using a nomogram (**Figure 8**).

An $LR > 1$ produces a post-test probability higher than the pre-test probability. An $LR < 1$ produces a post-test probability lower than that of the pre-test probability. When the pre-test probability lies between 30% and 70%, test results with a very high LR (say, >10) rule in disease. Correspondingly, a very low LR (say, <0.1) virtually rules out the chance that the patient has the disease.

Figure 8 Likelihood ratio nomogram.



3-2-5 Multiple diagnostic tests

Because no diagnostic test is perfect, with sensitivity and specificity of 100%, patients often undergo a series of diagnostic tests during evaluation. Computing the probability of disease depending on the results of five diagnostic tests can be tedious but is easier with LR_s (Box 14).

First, multiply all the LR_s for the various test results together to obtain a global LR. Then apply this global LR as usual to the pre-test probability to obtain the post-test global probability.

Box 15. Combining likelihood ratios from multiple tests to update diagnostic probability

A patient with no history of tick bite has a history of a skin lesion that was not seen by a physician and recurrent attacks of swelling in one knee. This patient has an estimated 40% pre-test probability of Lyme disease. The LR is 19.5 for a positive ELISA test result and 11.14 for a positive western blot test result (Tugwell et al, 1997).

Combine LR_s by multiplying together = $19.5 \times 11.14 = 217.23$

Post-test odds = pre-test odds \times LR = $4/6 \times 217.23 = 144.82$

Post-test probability = post-test odds / (post-test odds + 1) = $144.82 / (144.82 + 1) = 0.993 = 99.3\%$.

The combined effect of both positive tests would change the probability of Lyme disease from 40% to 99.3%

3-2-6 Confidence interval

As for estimation of treatment effect, measures of diagnostic accuracy are only an estimation of the true accuracy of the test calculated from observations of a sample. For all measures of diagnostic accuracy such as sensitivity, specificity, predictive values or LR, a 95% CI is needed to define the range of credible true values.

3-3 How Can I Apply the Results to Patient Care?

3-3-1 Representativeness of study patients

Differences in demographic and clinical features between populations may produce measures of diagnostic accuracy that vary considerably, known as spectrum bias, which may limit clinical applicability (generalisability) of a result (Mulherin and Miller, 2002).

We have already seen that PPVs and NPVs are widely affected by the prevalence of disease, but this is also true, to a minor extent, for sensitivity and specificity and LR (Box 16; Goehring et al, 2004).

Box 16. Sensitivity and specificity are not fixed but may differ across the spectrum of disease severity

In a study evaluating the accuracy of a rapid dipstick test for the diagnosis of UTI (Lachs et al., 1992), investigators found that the rate of false-negatives was higher in patients with diagnosed UTI but presenting fewer characteristic symptoms.

“In the 107 patients with a high (>50%) prior probability of UTI, who had many characteristic UTI symptoms, the sensitivity of the test was excellent (0.92; 95% CI: 0.82 to 0.98). In the 259 patients with a low (\leq 50%) prior probability of UTI, the sensitivity of the test was poor (0.56; 0.03 to 0.79).”

A study of very sick patients (with more marked findings) can make a test look better than it is. For example, a stress thallium test is more likely to produce abnormal results in patients with severe coronary artery disease than in patients with mild disease.

As noted earlier, applying the test only to patients with disease and healthy controls can also make the test look better than it is, because healthy controls are very unlikely to have an abnormal test result.

The spectrum of patients refers not only to the severity of the underlying target condition but also to demographic features and to the presence of a differential diagnosis and/or comorbidities.

It is therefore important that diagnostic test evaluations include patients with and without disease, selected because they have symptoms that would ordinarily cause the physician to order the test and with a spectrum of disease severity from mild to advanced (Knottnerus and Muris, 2003).

Patients may also withdraw from the study before results of the index and/or reference standard tests are known. If patients lost to follow-up differ systematically from those who remain, for whatever reason, then estimates of test performance may be biased.

3-3-2 Reproducibility of the test setting

A sufficient description of the execution of the index and reference standard tests is important for two reasons. First, variation in measures of diagnostic accuracy can sometimes be traced back to differences in the execution of the tests. Second, a clear and detailed description (or citations) is needed to implement a certain test in another setting. Tests executed in different ways would be expected to affect test performance. As an example, the timing and condition of blood samples taken will affect glycaemia results. The extent to which this situation affects results depends on the type of test being investigated.

The value of any test depends on its ability to yield the same result when reapplied to stable patients. Poor reproducibility can result from problems with the test itself (e.g., variations in reagents in radioimmunoassay

kits for determining hormone levels) or from its interpretation (e.g., the extent of ST-segment elevation on an electrocardiogram). This situation is especially important when expertise is required in performing or interpreting the test. Ideally, a report describing a diagnostic test will address the reproducibility of the test results with an appropriate measure.

For a dichotomous outcome, look for a κ coefficient that gives an estimate of the measure of reproducibility, corrected for agreement by chance (Fleiss, 1975). A value of 1 implies perfect agreement. Other values may be interpreted as follows:

- Poor agreement = <0.20
- Fair agreement = 0.20 to 0.40
- Moderate agreement = 0.40 to 0.60
- Good agreement = 0.60 to 0.80
- Very good agreement = 0.80 to 1.00

For a continuous outcome, the two best approaches are the Bland and Altman (1986) graphical method, which plots the difference between two measures against the mean of the two measures, and the intraclass correlation coefficient, which evaluates the level of agreement between raters in measurements (1 is perfect agreement and 0 is no agreement) (Shrout and Fleiss, 1979). A simple correlation coefficient is misleading because it measures correlation and not concordance (Fleiss, 1981).

3-3-3 Consistency of interpretation with clinical practice

Unless the interpretation of the index test results is fully automated and involves no interpretation, the availability of clinical data during the interpretation of test results may affect estimates of test performance. In this context, clinical data are defined broadly to include any information relating to the patient obtained by direct observation, such as age, sex and symptoms. The knowledge of such factors can influence the diagnostic test result if the test involves an interpretative component. If clinical data will be available when the test is interpreted in practice, then these data should also be available when the test is evaluated. If, however, the index test is intended to replace other clinical tests, then clinical data should not be available or should be available for all index tests. Determining what information will be available when test results are interpreted in practice is important before assessing studies for this item.

4 SYSTEMATIC REVIEW OF EVIDENCE: META-ANALYSIS

Meta-analysis is a method of combining the results from a number of studies of similar design to produce an overall estimate of effect that incorporates the information provided by all the studies (Egger et al, 2000).

One area of confusion is the distinction between review articles, systematic reviews, and meta-analyses. Many review articles are unsystematic, because the author does not look at all of the evidence. A systematic review has a formal approach to gathering, evaluating, and presenting the evidence; some systematic reviews are meta-analyses. A meta-analysis goes the final step by using formal statistical methods to calculate a pooled estimate when it is appropriate both clinically and statistically to pool identified studies. Sometimes a group of disparate studies are identified and it makes little clinical sense to pool them all together in a meta-analysis, but a subset of the identified studies may have similar patient populations, with no good clinical reason for the effects of treatment to differ. In this case, a meta-analysis allows for a more precise estimate of effect. Statistical heterogeneity can occur when seemingly homogenous studies are pooled but a large statistical variation in outcome exists, which may reveal undetected differences in patient populations or different intervention characteristics.

The Cochrane Collaboration is an international not-for-profit and independent organisation dedicated to making available up-to-date, accurate information about the effects of health care worldwide. It produces and disseminates systematic reviews and methodological guidelines to improve their quality (Higgins and Green, 2006). Thus, it is a valuable source of methodologically rigorous meta-analyses (Jadad et al, 1998*).

Various amounts and forms of data might be available for a meta-analysis: individual data for each patient or summary statistics from published papers (Whitehead, 2002). A meta-analysis involving individual patient data allows for a more extensive exploration of the data, particularly when individual patient data on prognostic or demographic variables are available. Therefore, many meta-analyses use summary statistics collected from each trial. We focus here on the critical appraisal of meta-analyses based on summary statistics from published reports reporting the results of RCTs.

The process of a meta-analysis consists of defining the question, defining the criteria for studies to be included, identifying and retrieving these studies, abstracting the essential information, performing an appropriate analysis, and reporting the results.

When reading an article reporting a meta-analysis, one should look at these different steps to critically appraise and decide whether or not the results are relevant to the respective patient population (Oxman et al, 1994*; Murad et al., 2014*).

4-1 Are the Results Valid?

4-1-1 Precision of the clinical question

The clinical question addressed by a meta-analysis must be narrow and focused enough to be relevant. A single meta-analysis cannot address all issues raised by a disease or an intervention. A well-focused clinical question should include PICO.

Thus, criteria used to select articles must be appropriate to this question. Inclusion and exclusion criteria must be defined precisely: patient population, intervention, outcomes considered, and study design.

Selecting studies for a meta-analysis is analogous to inclusion criteria for selecting patients for a study—both are filters that may reveal selection bias.

4-1-2 Validity of included studies

Inclusion of low-quality primary studies in a meta-analysis is likely to alter the summary measure of the intervention effect (Moher et al, 1998). For example, if the meta-analysis deals with RCTs, whether the randomisation process was concealed from patients or investigators; whether patients, caregivers, or persons assessing outcome were blinded to the treatment allocation; and the extent to which follow-up was complete is important (Hunt and McKibbin, 1997).

Each trial should be evaluated in terms of its internal and external validity. Quality assessment may then be used in the synthesis stage of the review to inform interpretation, e.g. to do an additional analysis obtaining a pooled estimate of treatment effect from only high-quality studies. It is not standard practice to exclude lower quality studies entirely from systematic reviews.

4-1-3 Reproducibility of study assessments

In the selection of studies included, even if clear inclusion criteria have been defined, the assessment of validity and extraction of data are often subjective and may lead to discrepancies in interpretation. We can be more confident of results if two people made these steps separately, compared results giving a measure of agreement such as the κ coefficient, and then resolved differences by consensus.

4-1-4 Completeness

A thorough search is needed to retrieve all studies of interest, whether the results are positive or negative. One major issue is publication bias, which derives from the selective publishing of studies with statistically significant or directionally positive results. This situation can lead to inflated estimates of efficacy in meta-analysis.

An appropriate search should include the use of bibliographic databases such as Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL: containing more than 990 000 records), and databases of current research. Reference lists of the articles retrieved must be checked, and recently published abstracts presented at scientific meetings can be examined, as can less frequently used databases. Personal contact with experts in the area helps decrease publication bias.

Sources, number of studies included in the meta-analysis, and reasons for exclusion may be summarised in a flow diagram.

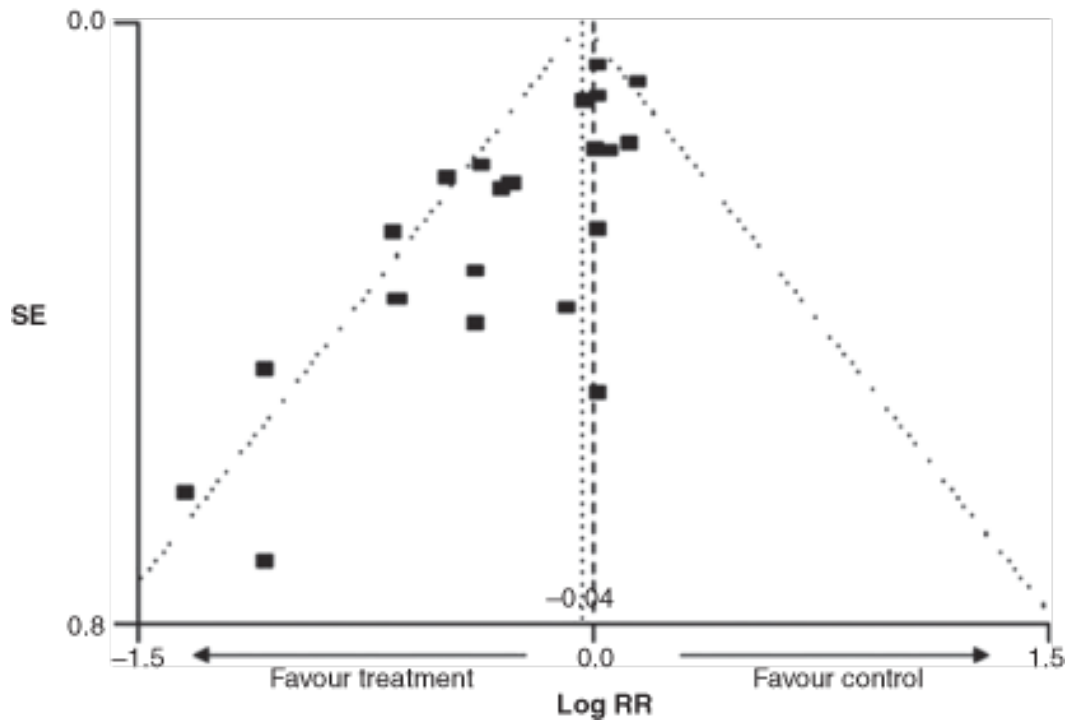
Since September 2005, the International Committee of Medical Journal Editors has required the registration of all clinical trials as a prerequisite for consideration for publication (De Angelis et al, 2004). The minimal registration dataset originally included the intervention, key inclusion and exclusion criteria, primary and key secondary outcomes, target sample size. Recent US and forthcoming European Union legislation has expanded the requirement to include the reporting of trial findings. Such mandatory registration and reporting of all trials should reduce non-publication of trials (publication bias) and selective reporting of trial findings.

One of the methods to assess publication bias is by looking at the 'funnel plot', if available (figure 9). This graph plots, for each study, the precision of the estimate of the treatment effect against the estimate of the treatment effect. We would expect results of less precise studies (with fewer participants and events) to be more affected by the play of chance and thus more widely scattered about the pooled estimate. Larger studies with more events should show results closer to the pooled estimate.

One must also pay attention to whether major studies in the field of interest have been published since the search and meta-analysis were performed.

It is important not to omit relevant studies in a meta-analysis and also not to include the same study twice. The latter may occur because of duplicate publication of the same data without cross-references to the original report. Patient data analysed more than once in a meta-analysis leads to biased estimates of treatment efficacy and exaggerated accuracy (Tramer et al, 1997).

Figure 9 Funnel plot to assess publication bias. For each study, the precision of the estimate of the treatment (eg, SE) is plotted against the size of the estimate (eg, log RR). With no publication bias, the estimates should be distributed symmetrically around the pooled result log RR = -0.04 according to the sample size or sampling variation (i.e., SE). In the above case, however, the distribution is asymmetric, suggesting that studies with large log RR (i.e., favour control), especially those with small sample size (or large SE), are less likely to be published.



4-2 What are the Results?

4-2-1 The issue of heterogeneity

Estimating a combined effect of a group of studies makes sense only if the effects found in the individual studies are similar enough.

Of course we expect some variation among studies because the individual estimates of treatment effect will vary by chance. What we need to know is whether there is more variation than we would expect by chance alone. This excessive variation is called statistical heterogeneity, or just heterogeneity. One can determine statistical heterogeneity visually or with a statistical test.

Visual method

The size of the treatment effect (and its CI) from each trial can be graphed on a 'forest plot'. If the magnitude or direction of the effect sizes differ greatly among studies, and if the CIs do not substantially overlap, one should suspect heterogeneity.

Statistical method

One must look at the result of a statistical test—a χ^2 ('chi-squared') test or Cochrane Q test. The information typically provided next to the forest plot in a published meta-analysis includes:

- a χ^2 statistic
- a number called the degrees of freedom (usually one less than the number of studies but can be less if some of the studies have no events)
- a p value obtained by referring the first two numbers to statistical tables.

A significant test result ($p < 0.05$ or 0.10) is often used to indicate evidence of heterogeneity; the difference in results among the individual studies is not likely to have been caused by chance. One must be careful when interpreting the p value because it depends highly on the number of studies included. With few studies, the test is not very good at detecting heterogeneity (it has 'low power'). Conversely, with many studies in a meta-analysis, the test can be too good at detecting heterogeneity.

A more useful way is to compare the χ^2 statistic with its degrees of freedom. A statistic larger than its degrees of freedom shows heterogeneity. Another value, I^2 , may be computed to quantify this heterogeneity. An I^2 of more than 50% indicates strong heterogeneity:

$$I^2 = (\chi^2 \text{ statistic} - \text{degrees of freedom}) / \chi^2 \text{ statistic}.$$

Authors should take heterogeneity into account both in the analysis and in the interpretation of results in a meta-analysis.

A meta-analysis involves two main methods of analysis: fixed-effects or random-effects analysis. Methods of fixed-effects meta-analyses (such as the Mantel-Haenszel or Peto method) are based on the mathematical assumption that a single common (or fixed) effect underlies every study in the meta-analysis. Under this assumption, if every study were infinitely large, every study would yield an identical result, which is the same as assuming no (statistical) heterogeneity among the studies. A random-effects analysis (such as the DerSimonian and Laird method) assumes that individual studies estimate different treatment effects (Lau et al, 1997). With statistical heterogeneity, there is debate about whether a fixed- or random-effects analysis is best. The best option is probably to perform both and then choose the most conservative result.

In the interpretation, authors should try to explain between-study variability in findings. Possible explanations include differences between patients (e.g., thrombolytic therapy in acute myocardial infarction may be more effective for patients who present shortly after the onset of chest pain than for those who present much later), between interventions (e.g., tissue plasminogen activator (tPA) may have a larger treatment effect than streptokinase), between outcome measurement (e.g., the effect may differ if the outcome is measured 30

days rather than 1 year after myocardial infarction), or methodology (e.g., the effect may be smaller in blinded trials or in those with more complete follow-up). Subgroup analysis and meta-regression are methods to help in detecting heterogeneity.

Subgroup analyses may be useful for addressing particular questions when data for different subgroups of patients are available from each study. As for primary studies, with subgroup analysis, results should be interpreted with caution, lest they turn into ‘fishing expeditions’. Such analysis should be planned at the protocol stage, based on good scientific reasoning, and kept to a minimum. The more subgroup analyses the reviewer undertakes, the greater the risk of a spurious conclusion. Meta-regression can formally test for evidence of different effects in different subgroups of trials. For example, meta-regression can be used to test whether treatment effects are larger in low-quality studies than in high-quality studies.

4-2-2 Interpretation of the overall results

One should view the overall results of a meta-analysis the same way as viewing the results of primary studies. In a meta-analysis of a therapeutic question, one should look for the pooled RR, RRR or OR if the outcome is dichotomous, and for the pooled effect size if the outcome is continuous. In meta-analysis regarding diagnosis, one should look for summary estimates of the LRs. As for primary studies, in meta-analyses, the CI will tell the precision of the estimation—that is, the range of values with a 95% probability of including the true effect.

Figure 10 shows the results of meta-analyses typically presented in graphic form, which shows, for each study, the point estimate (dots) and the CIs (horizontal bars). The diamond below all the horizontal lines represents the pooled point estimate with its CI. The vertical line in the middle is the ‘line of no effect’—that is, an RR or OR of 1 or an effect size of 0. A CI of a result crossing the line of no effect indicates no significant difference between the two groups (because of really no effect or because the sample size is too small to show a statistically significant effect). The weight of each study in the final pooled estimation is usually proportional to its sample size, as illustrated by the width of its dot.

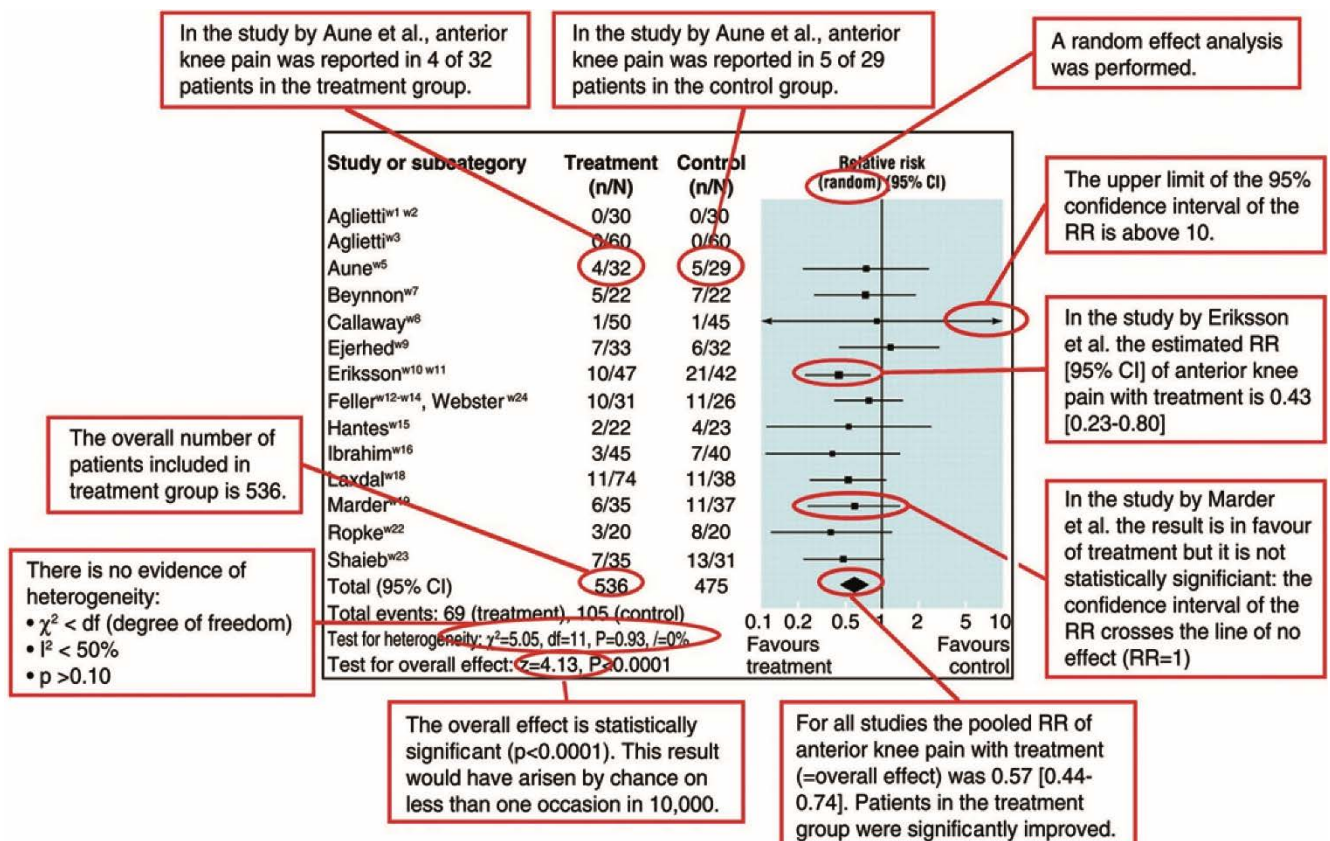
On a single figure, this presentation conveys an impression of the results of the individual studies, conveys the extent of heterogeneity, and reports the pooled estimate.

Various methodological choices must be made when planning and analysing a meta-analysis. Results obtained may depend highly on these choices. Sensitivity analyses may provide confidence in the result by addressing the question ‘Are the findings robust to the method used to obtain them?’. Sensitivity analyses involve comparing the results of two or more meta-analyses calculated using different assumptions.

The following are some examples of situations of sensitivity analyses:

- If a study is of doubtful eligibility for the meta-analysis, then compare the results including and excluding that study.
- Results may be calculated using all studies and then excluding poor-quality studies.
- Both fixed- and random-effects analyses might be undertaken to assess the robustness of the results to the method used.
- If a study appears to be an outlier (has results very different from the rest of the studies), then its influence on a meta-analysis might be assessed by excluding it.
- If missing information is 'imputed' (brought in from another source, perhaps by estimating it), then the effect of imputed numbers should be assessed through sensitivity analyses.

Figure 10 A standard meta-analysis plot of the relative risk (RR) for anterior knee pain after reconstruction of the anterior cruciate ligament. Treatment refers to hamstring autografts; control refers to bone-patellar tendon-bone autografts. (Reproduced with permission from Biau et al, *BMJ* 2006;332:995–1001.)



4-3 How Can I Apply the Results to Patient Care?

Because a meta-analysis involves pooling various studies, undertaken in different settings, the external validity is usually better than that for a single study. However, one must consider the patients in the individual studies and ascertain whether your patient is similar in terms of age, comorbidities, or other risk factors (such as smoking and family history). Does your patient have a comparable baseline risk for the outcome of interest, or is the risk higher or lower in a clinically meaningful way?

All important outcomes, good and bad, relevant to patients must be considered, even if meta-analyses frequently do not report the adverse effects of therapy. One reason for this omission is that the individual studies often measure these adverse effects either in different ways or not at all, so pooling or even effective summarisation of the results is difficult. However, in clinical practice, one should always determine whether the benefits of the intervention in question outweigh the harm to the patient.

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SUMMARY POINTS

➤ Intervention studies

- Random allocation of treatment will generate a comparable baseline in all study groups to avoid allocation bias.
- Blinding is the best way to avoid performance and detection bias. Studies should clearly state who (care providers, patients, outcome assessors and/or data analysts) was blinded.
- Intention-to-treat analysis is the most robust analytical method. All patients are analysed in the group to which they were initially randomised, even if they cross over to the other intervention arm, stop their intervention, or are lost to follow-up.
- The primary outcome must be unique, clinically relevant and used for sample size calculations.
- Study results should report both a measure of treatment effect and an estimation of the precision of this measure. Readers need to critically appraise statistical and clinical significance of a result.
- Subgroup analysis is not encouraged unless it is planned prior to the trial and the subgroup-treatment interaction should be used to identify predictors of treatment response.

➤ Diagnostic evidence

- The reference standard test must correctly classify the patient's condition, be independent from the index test, and be performed for all patients.
- Patients included in the study must be selected because they have symptoms that would ordinarily cause the physician to consider ordering the test.

➤ Systematic review of evidence: meta-analysis

- The quality of a meta-analysis relies on the quality of primary studies included.
- Estimating a combined effect of a group of studies only makes sense if the effects found in the individual studies are similar enough.

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EULAR on-line course on Rheumatic Diseases

Clinical epidemiology – critical appraisal of evidence

George Peat, Ian Scott, Weiya Zhang

A previous version was co-authored by Michelle Hui, Daniel Aletaha, Weiya Zhang, Philippe Ravaud, David Torgerson, Candice Estellat

IN-DEPTH DISCUSSION I

Methodological Issues of Non-inferiority and Equivalence Trials

A non-inferiority or equivalence trial aims to demonstrate that the experimental treatment is not clinically worse than a reference treatment (an active control treatment) by more than a pre-specified small amount (Δ), known as the non-inferiority or equivalence margin (Committee for Medicinal Products for Human Use 2005). The term *non-inferiority* is used when referring to a difference in effects lower than Δ , and *equivalence* when referring to a difference in effects between $-\Delta$ and $+\Delta$ (ICH Steering Committee 1998).

A non-inferiority or equivalence trial is useful when the efficacy of the reference treatment is clearly established and a placebo control group would be deemed unethical. The new treatment is expected to have non-inferior or equivalent efficacy as compared with the standard treatment, while usually claiming other advantages, such as reduced cost, better tolerability, or easier administration (e.g. once daily instead of 3 times a day; or oral instead of parenteral application; or not requiring additional – e.g. invasive – exams before or during therapy). The new treatment may also present an alternative or second-line therapy (Jones et al 1996).

There are number of challenges related to the design, conduct, analysis, and reporting of non-inferiority/equivalence trials, which have been discussed in the literature (D'Agostino et al 2003, Durrleman et al 1990, Ebbutt et al 1998, Garrett 2003, Piaggio and Pinol 2001, Rohmel 1998, Piaggio 2006, Le Henanff et al 2006).

Design

A non-inferiority or equivalence trial requires the efficacy of the reference treatment to be established or in widespread use, and therefore a placebo or untreated control group is deemed unethical (Piaggio 2006).

Sample size and *a priori* margin

Sample size calculation in non-inferiority or equivalence trials is as important as in superiority trials. It depends on the risk of type I error, the risk of type II error and the pre-stated non-inferiority margin, Δ (Blackwelder 1982, Blackwelder and Chang 1984). The margin is often chosen as "the smallest value that would represent a clinically meaningful difference" (Wiens 2002). If relevant, Δ should be smaller than the clinically relevant effect that is chosen to investigate superiority of reference treatment against placebo. The determination of this margin is crucial and must be done *a priori*, based on both statistical reasoning and clinical judgment (ICH Steering Committee 2000). Some reported margins are so large that they are clearly unconvincing. Depending on the choice of the primary outcome of the study, the margin of non-inferiority will be specified as a difference in means or proportions or the logarithm of an odds ratio, relative risk or hazard ratio (Piaggio 2006).

Choice of the reference treatment

The control treatment must be the drug demonstrated to be superior to placebo (and ideally be the gold standard in the particular clinical situation the study is investigating). It is generally not accepted to use a drug for comparison, which demonstrated to be equivalent to another drug with known superiority to placebo (to avoid transitive fallacy).

Analysis

For analysis of non-inferiority or equivalence trials both intention-to-treat (ITT) and per-protocol analyses should be performed (ICH Steering Committee 1998, Garrett 2003, Brittain and Lin 2005). Because of protocol violators and withdrawals, ITT analysis often leads to smaller observed treatment effects than if all patients had adhered to treatment. In superiority trials, ITT is a conservative approach and is recommended. For non-inferiority or equivalence trials, ITT analysis may often increase the risk of falsely claiming non-inferiority (type I error) and lead to biased conclusions.

However, dropouts and non-adherent participants from the 2 groups are potentially different, which may also bias a per-protocol analysis. Thus, both analyses, ITT and per-protocol, are required and considered to have equal importance in drawing a conclusion (Garrett 2003, Brittain and Lin 2005) and should therefore be interpreted next to each other to make a convincing claim.

Interpretation of results: Confidence Intervals

In superiority trials, we use statistical significance tests to determine whether the null hypothesis of “no difference” may be rejected, together with confidence intervals (CIs) to indicate the range of possible true values of the difference compatible with the observed data.

In a non-inferiority or equivalence trial, the conventional statistical test, including the p-value, has little relevance (Jones et al 1996): failure to detect a difference does not imply equivalence (Altman and Bland 1995). Vice versa, a difference that is detected may not have clinical relevance and may correspond to practical equivalence. Conclusions must be drawn by comparing the CI with the pre-specified non-inferiority margin, Δ (Jones et al 1996).

Interpretation of results of a non-inferiority trial is based either on the upper limit of a one-sided 97.5% CI, or the upper limit of a two-sided 95% CI. For an equivalence trial, the interpretation is based on the upper and lower limits of a two-sided 95% CI.

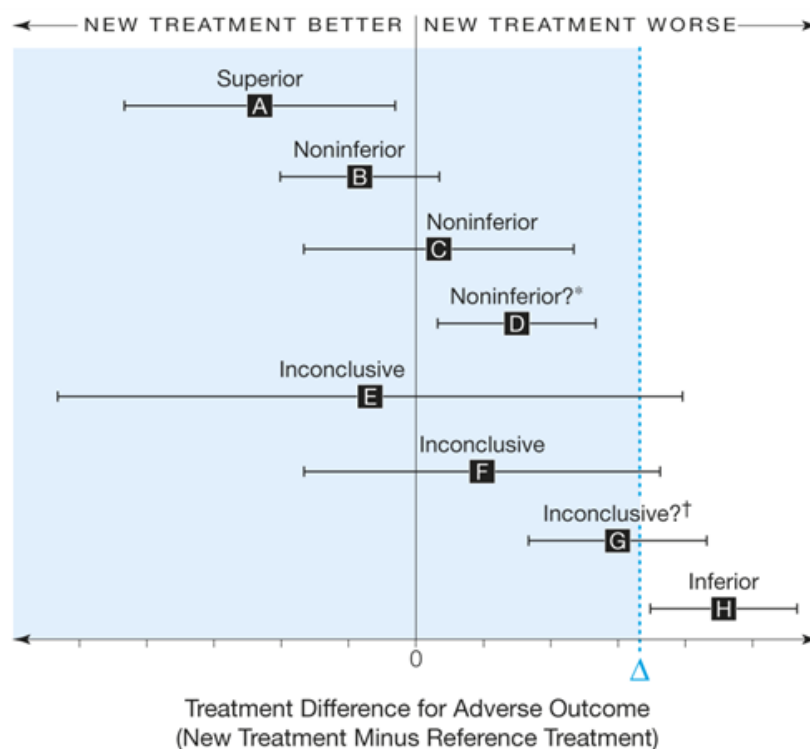
Figure 1 interprets several possible scenarios for non-inferiority trials. With an equivalence trial, the interpretation is analogous, but both margins need consideration, as claiming equivalence requires the complete CI to lie between $-\Delta$ and $+\Delta$ (Piaggio 2006).

Switching to or from superiority trials

Once non-inferiority is evident, it is acceptable to then assess whether the new treatment appears superior to the reference treatment, using an appropriate test or CI (i.e., not just the point estimate), preferably defined a priori and with an ITT analysis (Committee for Proprietary Medicinal Products 2001, Lewis 2002, Fleiss 1992).

It is inappropriate to claim non-inferiority post hoc from a superiority trial unless clearly related to a predefined margin of equivalence (Piaggio 2006). That is, both superiority and non-inferiority hypotheses need explicit specification in the trial protocol. It is, however, always reasonable to interpret a CI as excluding an effect of a particular size defined a priori (Piaggio 2006).

Figure 1: Possible scenarios of observed treatment differences for adverse outcomes (harms) in non-inferiority trials (adapted from the CONSORT statements for non-inferiority trials JAMA 2006;295:1152-60 (Piaggio 2006), permission being obtained)



Error bars indicate 2-sided 95% confidence intervals (CIs). Tinted area indicates zone of inferiority. A, If the CI lies wholly to the left of zero, the new treatment is superior. B and C, If the CI lies to the left of Δ and includes zero, the new treatment is non-inferior but not shown to be superior. D, If the CI lies wholly to the left of Δ and wholly to the right of zero, the new treatment is non-inferior in the sense already defined, but it is also inferior in the sense that a null treatment difference is excluded. This puzzling case is rare, since it requires a very large sample size. It can also result from having too wide a non-inferiority margin. E and F, If the CI includes Δ and zero, the difference is non-significant but the result regarding non-inferiority is inconclusive. G, If the CI includes Δ and is wholly to the right of zero, the difference is statistically significant but the result is inconclusive.

regarding possible inferiority of magnitude Δ or worse. H, If the CI is wholly above Δ , the new treatment is inferior.

**This CI indicates non-inferiority in the sense that it does not include Δ , but the new treatment is significantly worse than the standard. Such a result is unlikely because it would require a very large sample size.*

†This CI is inconclusive in that it is still plausible that the true treatment difference is less than Δ , but the new treatment is significantly worse than the standard.

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IN-DEPTH DISCUSSION II

**Specific Methodological Issues with Non-pharmacological
Interventions**

Non-pharmacological intervention (including surgery, technical operations, rehabilitation, physiotherapy, education or the use of external technical devices) represent a wide range of treatments for rheumatic disease. Assessing non-pharmacologic treatments involves specific methodological issues linked to difficulties associated with blinding, standardisation of the intervention, and lack of placebo control. Assessment and reporting of harm associated with these treatments is also often neglected. Specific methods may be required to assess the quality of reporting of randomised clinical trials (RCTs) of non-pharmacological treatment.

Blinding

Blinding is a cornerstone of therapeutic evaluation. Lack of reporting on blinding is associated with an increased risk of bias in estimating the “true” effectiveness of a treatment (Juni et al 2001, Noseworthy et al 1994, Pildal et al 2005, Schulz et al 1995) and could lead to performance bias (i.e., unequal administration of care, such as co-interventions or follow-up schedules) or detection bias (i.e., biased assessment of outcome). Lack of blinding of investigators also increases the risk of poor allocation concealment. Hence, when investigators are not blinded, it is particularly important to have a centralised randomisation of patients to avoid allocation bias (Ravaud and Boutron 2006).

Blinding is less frequently reported in RCTs assessing non-pharmacological treatments (Boutron et al 2003), possibly because of the difficulty in achieving and maintaining it (Boutron et al 2004). Fabrication of placebo is more difficult for surgery, rehabilitation or physiotherapy than for pharmacological treatment. However several other ingenious methods to obtain blinding of health-care providers, patients, and/or outcome assessors have been described and inventoried (Boutron et al 2007).

Blinding of health care providers and or patients may involve sham interventions or use of sham devices. For example, Moseley and colleagues used a sham surgical procedure in a trial assessing arthroscopic surgery for osteoarthritis of the knee. The placebo group received skin incisions and underwent a simulated debridement without insertion of the arthroscope (Moseley et al 2002).

These methods do, however, raise important issues. First, it can be considered ethically unacceptable to use sham interventions, because these treatments are not devoid of risk. Second, placebo treatments in clinical trials should not have any specific activity, but the inactivity of sham non-pharmacological interventions is debatable. For example, the use of sham acupuncture (involving needles placed at trigger points) as a placebo to acupuncture has been widely discussed. Third, for most non-pharmacological treatments, the relationship between patients and health-care providers affects the therapeutic effect of the non-pharmacological treatment. Consequently, the use of sham interventions underestimates the treatment effect in placebo-controlled trials by ignoring the effect of this relationship (Paterson and Dieppe 2005).

If blinding of patients cannot be achieved, effort must be taken to prevent detection bias by blinding outcome assessors. Issues of blinding outcome assessors depend highly on the nature of the outcome (Boutron et al 2007):

- For an objective (hard) outcome such as death, there is little opportunity for detection bias (Schulz et al 2002), and blinding is not a problem.
- With an outcome measured from a complementary test (radiography, biology, etc.), blinding of outcome assessors is quite easy to achieve with a centralised assessment.
- For physician-driven data that assumes contact between patients and outcome assessors, such as clinical exam or echography, more ingenious solutions are needed to blind outcome assessors: videotaped standardised clinical exam, photographs, outcome assessor distinct from care provider and patient instructed not to tell the treatment they received.
- Finally, for patient-reported outcomes, blinding outcome assessors necessitates blinding patients.

Standardisation and care provider experience

Studies of non-pharmacological treatments can involve complex interventions of various interconnecting parts, with the collaboration of several health-care providers and, in some cases, individualization of interventions (Campbell et al 2000, Devereaux et al 2005, Herbert and Bo 2005). There is evidence, particularly for surgery, that health-care providers' skills could be a determinant of outcome and harm, and, therefore, health-care providers should be considered part of the treatment. For example, the success of hip arthroplasty or knee arthroplasty depends on preoperative care, anaesthetic management, surgical procedure, surgical device, postoperative rehabilitation, surgeons' expertise and volume of activity at the centre. Consequently, planning and analysing trials of non-pharmacological treatments requires standardization of the intervention and measurement of the health-care provider's adherence to this pre-defined intervention. Care provider learning curve, setting and volume of activity of the centre must also be considered.

Safety

Assessment of harm associated with non-pharmacological treatments is largely neglected and relies mainly on case reports (Cherkin et al 2003, Ethgen et al 2005). In fact, in contrast to pharmacological treatments, non-pharmacological treatments do not need to undergo strict pre-clinical and clinical development and post-marketing evaluation, and reporting of adverse events to regulatory agencies is not required. Further, several non-pharmacological treatments for rheumatic diseases, such as rehabilitation, behavioural interventions and use of complementary alternative medicine, are generally perceived as low risk, even though these therapies might be associated with risk of adverse events, which can be serious (Ernst 2001). For instance, vertebral

artery dissection or cauda equina syndrome have been described after spinal manipulation and pneumothorax after acupuncture (Norheim and Fonnebo 1995, Lee et al 1995). Lack of systematically collected data on harm raises some concerns about the evaluation of the risk–benefit balance of these treatments. For example, would we be confident of the cardiovascular safety of some intensive exercise therapy programs proposed for osteoarthritis and rheumatoid arthritis, without the evaluation and recording of the adverse events observed during trials? Moreover, non-pharmacological trials, as many pharmacological ones, are not sufficiently powered to detect a difference in rate of adverse events.

Quality assessment

Assessing the quality of trial reports is particularly important for clinicians' critical appraisal of the health-care literature and for meta-analysis (Moher et al 1999). A checklist of items seems the most appropriate tool because it would allow for examination of key dimensions individually (Juni et al 2001). These checklists have, however, been developed and validated in the context of pharmacological treatments and do not take into account specific methodological issues in assessing non-pharmacological treatment such as the influence of care providers (Khuri et al 1999, Soljak 2002), standardization, feasibility of blinding and the risk of bias in unblinded trials. Therefore, a checklist specific for assessing the quality of reports of non-pharmacological trials, the tool A Check List to Evaluate A Report of a Non-Pharmacological Trial (CLEAR NPT), has been developed by a panel of 55 experts (Boutron et al 2005). This checklist should allow readers and reviewers to assess the quality of articles and protocols in this field.

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Psychosocial aspects of the rheumatic diseases

Dennis C. Turk, Kati Thieme

A previous version was coauthored by Kati Thieme, Rinie Geenen, Arnstein Finset (2014) - Rinie Geenen, Arnstein Finset (2012) - Rinie Geenen, Kathleen Mulligan, Mike Shipley, Stanton Newman (2009)

LEARNING OUTCOMES

- Describe and explain the role of psychosocial and behavioural factors in rheumatology.
- Describe and explain the biopsychosocial aspects of (rheumatic) diseases.
- Recognise the psychosocial consequences of rheumatic diseases in clinical practice.
- Describe the psychological (cognitive, affective, and behavioural—for example, coping abilities), and social determinants (stress) and moderators (e.g., social support) of well-being and functioning in rheumatic diseases.
- Demonstrate a basic understanding of the interactions among the rheumatic disease process and psychosocial variables.
- Screen for possible psychological problems in patients.
- Show a basic knowledge of psychological assessment tools.
- Describe what kind of psychological assistance rheumatologists and clinical and health psychologists can offer.
- Apply knowledge about psychological interventions in rheumatology in the treatment of emotional distress and pain in patients with rheumatic diseases.

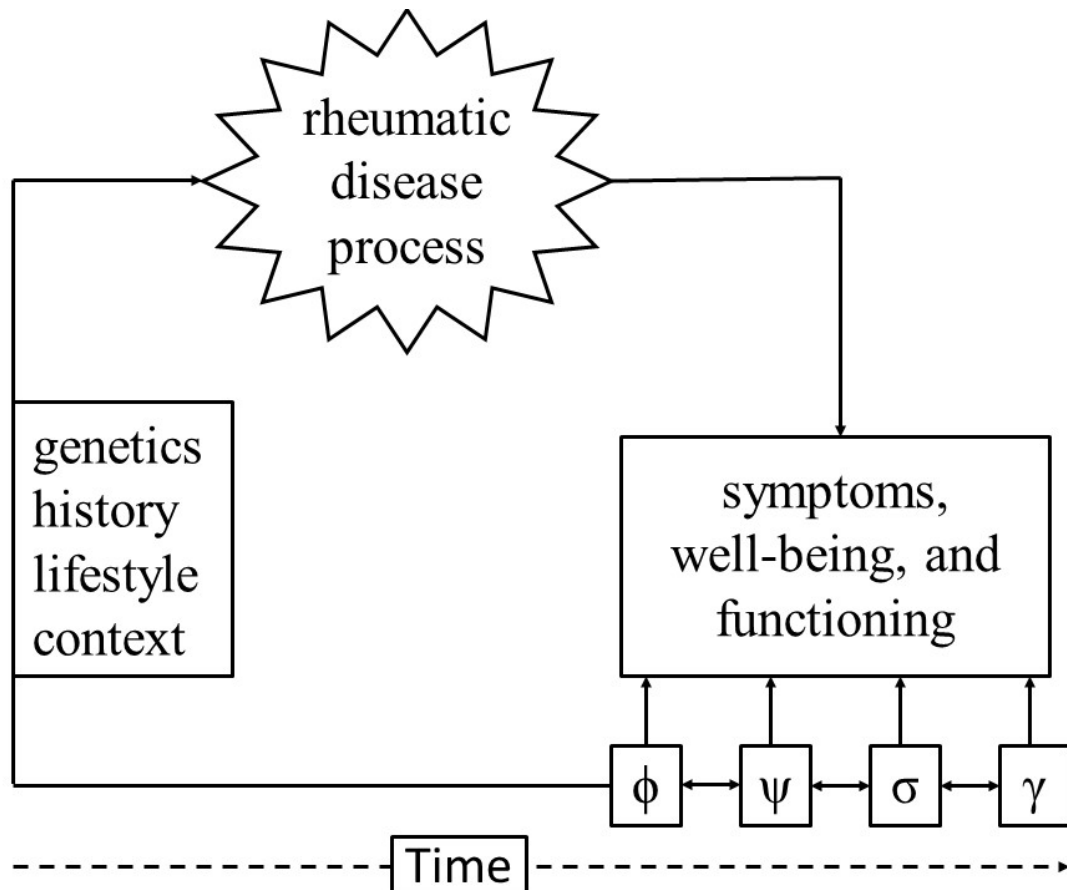
1 Introduction

It is important that clinicians pay attention to the psychosocial, behavioural, and contextual as well as biological dimensions of rheumatic diseases, as these processes are inextricably linked and interact impacting on the perception and response to symptoms and related disability. The disease process has psychosocial consequences and, in turn, psychosocial processes impact on the disease process (Figure 1). Moreover, pre-existing genotypes and prior learning history serve as a background against which the disease is filtered. Behavioural (e.g., avoidance of physical exercise), cognitive (e.g., pessimistic thoughts, fear of activity), emotional (e.g., depression or anxiety) and contextual factors (e.g., availability of emotional support and financial resources, characteristics and limitations of the physical environment) all impact on the disease and illness processes. This set of psychological processes directly impact on symptoms such as pain and fatigue (e.g., hormonal activation, descending pain modulatory effects of brain mechanisms affecting pain perception, avoidance of physical activity) or indirectly on disease activity (e.g., as determinants of adherence to pharmacological treatment, willingness and motivation to engage in activity, and of the likelihood of attending the physician in the event of a disease exacerbation). The Common-sense Model of Illness (Leventhal et al, 1984; Cameron, 2003; Hagger & Orbell, 2003; expanded as the Perceptual-Cognitive Model of Self-Regulation, Leventhal, 1998 and elaborated in Section 2.7 below) is one means of understanding how people try to deal with their disease and accompanying symptoms.

As will be detailed below, many studies have shown that the symptoms and other consequences of the rheumatic disease process are influenced by the way in which people interpret, respond to, and manage their illness and how others respond to their circumstances and needs. This review will describe the influence that rheumatic disease has on psychological wellbeing and physical and emotional functioning, but also the influence that psychosocial factors have on such aspects of management as adherence to recommended treatment and on disease outcomes such as pain, physical and emotional functioning, and health related-quality of life. The possible impact of stress on the rheumatic disease process is discussed in one of the in-depth discussions of this course. Finally, the review will describe methods for assessing patients with rheumatic diseases and provide an overview of treatment of patients' psychosocial problems accompanying these diseases.

Figure 1. Why clinicians should attend not only to the medical dimension but also to the psychological and contextual dimensions of rheumatic diseases.

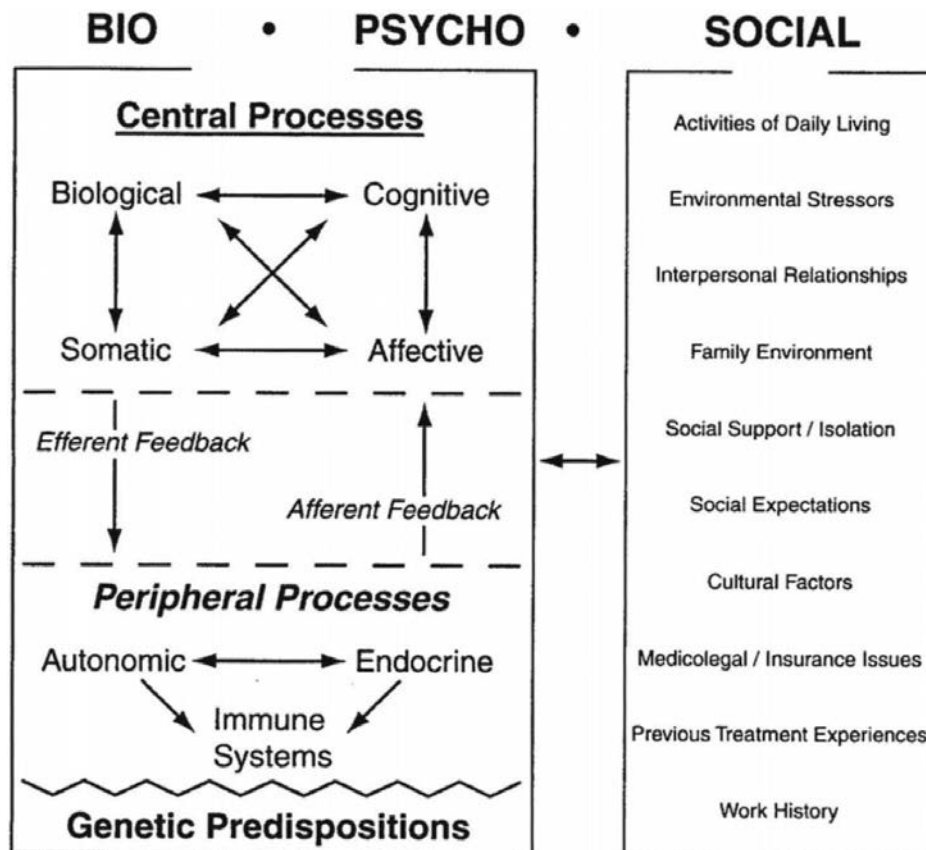
First, the rheumatic disease process itself will impact symptoms, well-being, and functioning. Second, also physiological (ϕ —for example, hormones), psychological (ψ —for example, strategies to cope with problems), social (σ —for example, support or rejection), and contextual (γ —for example, environmental limitation on activity, financial resources available) variables will impact symptoms, well-being, functioning and response to treatment. Third, physiological, psychological, social and contextual variables may impact the rheumatic disease process, itself.



2. Biopsychosocial model

The simplistic model of the psychosocial and behavioural dimensions of rheumatic disease suggests a linear relation, in which the disease severity and damage determine the degree of physical impairment, which in turn influence the illness, disability, and the patient's psychological well-being. This model, is not wrong but rather incomplete. It is not supported by research. A much more complex interrelationship occurs between the disease and its outcomes including modulation from psychosocial factors, genetics, prior experiences, and learning history (Flor & Turk 2011; Figure 2).

Figure 2. A conceptual model of the biopsychosocial interactive processes involved in health and illness.
 From “Comorbidity of Chronic Mental and Physical Health Conditions: The Biopsychosocial Perspective,” by R. J. Gatchel, *American Psychologist*, 59, 792–805. Copyright 2004 by the American Psychological Association.



The terms ‘disease’ and “impairment” have been used to refer to pathological change in the body and the term ‘illness’ and “disability” to refer to the subjective experience of disease (Flor & Turk, 2011). Whereas disease and associated impairments can be examined from a biological point of view, the study of illness and disability from an exclusively biological point of view is insufficient. The study of illness and disability is more fruitful from a Biopsychosocial perspective. A fundamental assumption of this Perspective is that health, illness, and disability are consequences of the synergistic interplay of biological, psychological, social, and environmental factors, which influence the perceived intensity of chronic pain and other symptoms, the degree of disability, and the level of inflammation and other biological factors.

The distinction between disease and illness is analogous to the distinction that can be made between nociception and pain. Nociception involves the stimulation of nerves that convey information about potential tissue damage to the brain. In contrast, pain is the subjective perception that results from the transduction, transmission, and modulation of sensory information. This input may be filtered through an individual’s genetic composition, prior learning history, current psychological status, and sociocultural influences (Gatchel et al, 2007; Flor & Turk, 2011).

As an example, the basic psychobiological mechanisms of chronic pain are influenced by learning such as classical (respondent, Pavlovian) conditioning (reflex-like learning); operant conditioning (learning by approaching positive stimuli and avoiding negative stimuli); observational learning (learning through observation of others), emotional processing, and cognitions (beliefs, attitudes, expectations, meaning analysis). These factors influence sensitisation of central and peripheral responses affecting chronic pain and, in inflammatory rheumatic diseases, hyper-reactive immune responses. Positive interactions among biological, psychological and social factors in chronic pain diseases can provoke healthy mechanisms of pain inhibition and self-regulation in immune response.

A way to understand the Biopsychosocial model is to contrast it with the biomedical (somato-psychic) model, which maintains that illness can be explained solely with biological disease processes independent of psychological and social processes. Independent of psychosocial processes that may result as consequences to physical pathology and the psychogenic model that attributes physical symptoms to psychopathological perturbations. Although the biomedical and psychosomatic models have undeniable benefits, they also have several limitations (Engel, 1977; Taylor, 2003).

A Biopsychosocial perspective incorporates the myriad psychological, social, and contextual factors, in conjunction with biological influences that contribute to the experience, maintenance, and exacerbation of symptoms, as well as response to symptoms and treatments described above. Given the importance of this range of factors, to adequately care for individuals with rheumatic diseases, despite the specific diagnosis, psychological and social-contextual factors, in addition to biological ones, must each be considered and addressed. It is important to acknowledge that rheumatic diseases are chronic conditions, and thus the interplay of physical, psychosocial, behavioural, and contextual factors will evolve over time and should not be viewed as static (Adams & Turk, 2015).

In support of the complex set of factors involved is the wide variability observed in how individual react to ostensibly the same disease and symptoms as well as respond to identical treatment regimens. The longitudinal aspect of person (not just symptom) management and adjustment to illness mean that psychosocial factors are potential causes of symptoms as well as modifiers of symptoms and responses to symptom presence, identifying and dispelling the patient-uniformity myth (e.g., all patients with the same diagnosis are homogeneous requiring a common treatment approach), and acknowledging the importance of environmental context (Adams & Turk, 2015). Although characterization of patient populations complicates the burden of classification (Fillingim et al 2014), it strengthens the potential identification of underlying mechanisms, and helps to guide treatment plans. Research and clinical observation have consistently made us aware that no single treatment works for everyone despite comparable diagnoses. For example, individuals presenting with identical rheumatic diagnoses exhibit a great deal of variability in the degree of pain, number and nature of physical symptoms, and psychological distress that they experience (e.g., Adams & Turk, 2015).

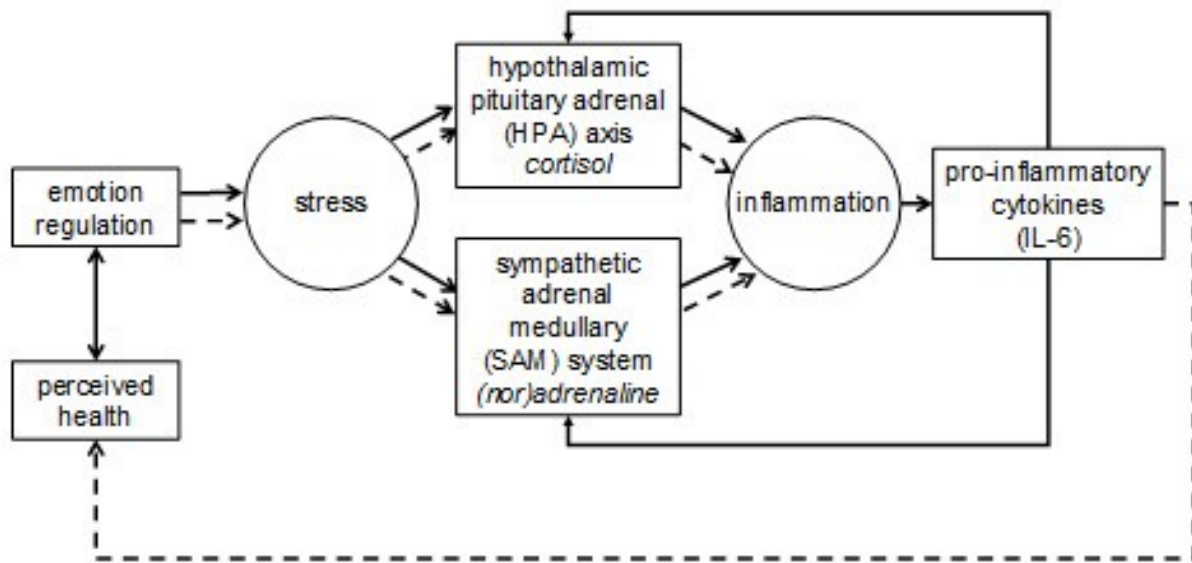
Although we emphasize a Biopsychosocial approach to symptoms, some maintain a view that psychosocial features are direct causes of symptoms. Even in cases in which symptoms occur after some psychological or social perturbation is reported, there is little evidence to support the notion that any psychosocial factor is the sole cause of rheumatic diseases symptoms. Moreover, many who experience comparable events and physical pathology do not develop symptoms and, as noted, even when symptoms do occur there is wide variability in how individuals respond. These psychosocial factors do appear to have an impact on perceptions of symptoms, impact of a disease, and the behaviours of individuals in response to their symptoms. There is little question, however, that psychosocial factors may magnify and maintain symptoms. In the absence of cure, living with a persistent set of symptoms, as characterized by rheumatic diseases, is challenging and the importance and weight of psychosocial factors will vary as individuals adapt and adjust to their persistence over time. The distinction between the causal, moderating, and modulating roles of psychosocial factors is critical for understanding and appropriately treating patients. It is vital that this message be shared with patients who may have preconceived notions about the role of psychosocial factors in their lives and may resist consideration of them if they perceive that these factors are being presented to invalidate their experiences of physical symptoms and contribute to the stigma often associated with these conditions (Adams & Turk, 2015).

2.1 Physiological stress systems

Several possible pathways have been proposed to explain how psychological factors influence disease outcome. One proposal is that psychological factors may have a direct influence on disease through alteration of normal physiological processes. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) is a proposed pathway by which perceived or actual stress may have an impact on inflammation (Figure 3; Elenkov et al, 2000; Van Middendorp et al, 2005).

The HPA axis and the SNS are critically involved in the inflammatory process, but can also be activated by stress reactions or be downregulated after persistent physical or emotional stress. Cortisol and catecholamines including norepinephrine (noradrenaline) are end-products of the HPA axis and the SNS systems, respectively. Cortisol and catecholamines have shown both immunosuppressive and immuno-stimulating effects, depending on their concentration and receptor binding capacity. Under chronic inflammatory conditions the stress regulatory system is compromised. Stress and inflammation may amplify sensitisation of pain, and a vicious spiral of stress, pain, and inflammation may occur (Fischer et al, 2016, McEwen & Kalia, 2010; Straub & Kalden, 2001).

Figure 3. Diagram of the bidirectional relationship between psychological factors and inflammation. Solid lines represent positive feed forward, broken lines represent negative feedback (adapted from Van Middendorp et al, 2005)



2.2 The role of cytokines

The unfavourable consequences of the disease process for psychological adjustment are, among other factors, mediated by cytokines, small proteins that serve to regulate the immune system (De Ridder et al 2008). During inflammation, pro-inflammatory cytokines such as tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6) activate the neuroendocrine stress system. Pro-inflammatory cytokines that signal the brain may also be involved in changing how individuals perceive their health, by reducing psychological, social, and physical wellbeing and functioning-so-called sickness behaviour (Brydon et al, 2009; Dantzer, 2001).

Cytokine induced behavioural effects of inflammation are a common phenomenon in both animals and humans. The administration of inflammatory agents in animals induces a reduction of physical, exploratory, and social behaviour, as well as food and water intake, and it leads to impaired learning and memory. Human sickness behaviour comprises a constellation of non-specific responses, consisting of weakness, malaise, inability to concentrate, depressed mood, lethargy, little interest in the surroundings, and reduced appetite. Both animals that are experimentally injected with an inflammatory agent and humans that have an inflammatory disease are to a certain extent able to resist sickness behaviour depending on, among other factors, motivation and the way they attempt to cope.

2.3 The role of the interaction between heart and brain

Perhaps the cardinal symptom of rheumatic diseases is pain. Pain intensity not only depends on peripheral processes such as inflammation and tissue damage, but also neuronal, immune and neuroendocrine processes are critically involved in pain.

An emerging body of evidence provides support for an important interaction between pain processing and cardiorespiratory regulatory systems (e.g., Bruehl & Chung, 2004; Thieme et al, 2015). It is generally accepted that the stimulation of carotid sinus and cardiopulmonary baroreceptor afferents, which are activated by dynamic changes of blood pressure (BP) and respiratory rate, reduce the pain. It is termed as Baroreflex Sensitivity (BRS). The activated baroreceptors give their signals to the brain stem terminating, in the Nucleus Tractus Solitaries (NTS, Wirtelak, 1997) - the head of the n. vagus that can activate the parasympathetic nervous system. The NTS is responsible both for the inhibition of pain and anxiety besides the improvement of sleep and BP. In healthy individuals, a functional interaction of the cardiovascular and pain regulatory systems has been established whereby elevation in resting arterial blood pressure is related to reduction in acute pain sensitivity. The activation of carotid sinus and cardiopulmonary afferents attenuates pain.

Studies have also shown that persistent pain conditions may be mediated in part by impairments in this interaction between BP and pain sensitivity (e.g., Thieme & Turk, 2006). Diminished baroreceptor sensitivity may have an important impact on pain chronicity (Bruehl & Chung, 2004) and is influenced by classical and operant conditioning (Rau & Elbert, 2001). The permanent stress-related increase of BP leads to a lack of dynamic changes of the pressure in the carotis sinus. The carotid baroreceptors learn not to react anymore. The NTS does not get the information and stops the inhibition. The diminished BRS and NTS activation explain the hypertensive response and have an influence on the development of chronicity in pain.

2.4 Personality

Personality characteristics, the enduring psychological attributes of a person, have in the past been postulated as a cause of arthritis as well as a possible explanation for other aspects of how patients manage their disease. These include individual differences in the ability to cope with the demands of disease and in the adherence to recommended treatment. However, prospective studies of personality as a cause of rheumatoid arthritis (RA) have proved impossible to perform and the elevated levels of neuroticism and lower levels of self-esteem observed soon after diagnosis are now considered to be a reaction to and therefore a consequence of the disease (Krol et al, 1998) that may evolve over time. Neuroticism, a 'proneness to distressing emotional states', has been shown to influence perception of symptoms and wellbeing in RA (Evers et al, 2002; Persson & Sahlberg, 2002). Moreover, personality characteristics such as a self-sacrificing defence style may influence symptoms. For example, pain was associated with impaired physical health related quality of life only in patients with a self-sacrificing defence style (Bai et al, 2009). However, mediating and moderating symptoms cannot be taken as causal mechanisms.

2.5 Behavioural Conceptualizations – Behavioural Learning

Pain is an unavoidable and necessary part of human life. No learning is required to activate nociceptive receptors. However, pain is a potent and salient experience. Beyond mere reflexive actions, people must learn

to avoid, modify, or cope with noxious stimulation. There are three major principles of behavioural learning that help us understand acquisition of adaptive as well as dysfunctional behaviours associated with pain.

2.5.1 Classical (Respondent) Conditioning

In his classic experiment, Pavlov discovered that a dog can be taught, or “conditioned,” to salivate at the sound of a bell by pairing the sound with food presented to a hungry dog. Salivation of dogs in response to food is a natural response, however, by preceding the feeding with the sound of a bell, Pavlov’s dogs learned to associate the sound of the bell with an imminent feeding. Once this association is learned, or “conditioned,” the dogs were found to salivate at the mere sound of the bell even in the absence of the food.

The influence of classical conditioning can be observed in pain patients. Consider physical therapy, a mainstay of treatments for chronic pain patients, where treatment may evoke a conditioned fear response in patients. A patient, for example, who experienced increased pain following physical therapy, may become conditioned and experience a negative emotional response to the presence of the physical therapist, to the treatment room, and to any contextual cues associated with the nociceptive stimulus. The negative emotional reaction may lead to tensing of muscles and this in turn may exacerbate pain and; thereby, further strengthen the association between the presence of the physical therapist and pain.

Once a pain problem persists, fear of motor activities may become increasingly conditioned, resulting in avoidance of activity in the anticipation of avoidance of pain. Avoidance of pain is a powerful rationale for reduction of activity, where muscle soreness associated with exercise functions as a justification for further avoidance. Thus, although it may be useful to reduce movement in the acute pain stage, limitation of activities can be maintained not only by pain but also by anticipatory fear that has been acquired through the mechanism of classical conditioning. Thus, cognitive processes may interact with pure conditioning. It is the anticipation that motivates a conscious decision to avoid specific behaviours or stimuli.

In chronic pain, many activities that were initially neutral or even pleasurable may come to elicit or exacerbate pain. Consequently, they are experienced as aversive and actively avoided. Over time, a greater number of stimuli (e.g., activities) may be expected to elicit or exacerbate pain and will be avoided. This process is referred to as stimulus generalization. Thus, the anticipatory fear of pain and restriction of activity, and not just the actual nociception, may contribute to disability. Anticipatory fear also can elicit physiological reactivity that may aggravate pain. Consequently, conditioning may directly increase nociceptive stimulation and subsequently the perception of pain.

The conviction that patients hold that they should remain inactive is difficult to modify, as long as activity-avoidance succeeds in preventing aggravation of pain. By contrast, repeatedly engaging in behaviour—exposure—that produces progressively less pain than was predicted (corrective feedback) will be followed by

reductions in anticipatory fear and anxiety associated with the activity (Fordyce, Shelton, & Dundore, 1982; Vlaeyen, Kole-Snijders, Boeren, & van Eck, 1995). Such transformations add support to the importance of a quota-based physical exercise program, with patients gradually and progressively increasing their activity levels despite fear of injury and discomfort associated with use of deconditioned muscles. This exposure, in the absence of anticipated pain, provides the corrective feedback that should be positively reinforcing and increase the likelihood of continuation of previously avoided activities.

2.5.2 Operant Conditioning—Contingencies of Reinforcement

The effect of environmental factors in shaping the experience of people with pain was acknowledged long ago (Collie, 1913). However, a new era in thinking about pain began with Fordyce's (1976) extension of operant conditioning to chronic pain. The main focus of operant learning is modification in frequency of a given behaviour -- increasing desirable behaviours and extinction of maladaptive behaviours. The fundamental principle is that if the consequence of a given behaviour is rewarding, its occurrence increases; whereas if the consequence is aversive, the likelihood of its occurrence decreases.

When a person is exposed to a stimulus that causes tissue damage, the immediate behavioural response is withdrawal in an attempt to escape from noxious sensations. Such reflexive behaviours are adaptive and appropriate. Behaviours associated with pain, such as limping and moaning, are called pain behaviours. Pain behaviours include overt expressions of pain, distress, and suffering. A critical defining feature of overt behaviours is that they are observable and thus have a communicative function. If behaviours are observable they are capable of evoking responses and it is the consequences following the behaviour that are particularly important as they can serve to maintain or diminish the likelihood of the behaviour recurring. These pain behaviours can become subjected to the principles of operant conditioning. These behaviours may be positively reinforced directly, for example, by attention from a family member, acquaintance, or health care provider. The principles of learning suggest that behaviours that are positively reinforced will occur more frequently. Pain behaviours may also be maintained by the escape from noxious stimulation by the use of drugs or rest, or the avoidance of undesirable activities. In addition well behaviours (e.g., activity, working) may not be positively reinforced, and the more rewarding pain behaviours may therefore be maintained.

The following example illustrates the role of operant conditioning: When back pain flares up, the individual may lie down and hold her back. The significant other may observe the behaviour and may respond by offering to rub the person with pain back. This response may positively reward the individual and the pain behaviours (i.e., lying down) may be repeated even in the absence of severe pain. In other words, the pain behaviours are being maintained by the learned consequences. The individual's pain behaviours may be negatively reinforced if they permit avoidance of undesirable activities. For example, the significant other may suggest that they cancel the evening plans with a relative, an activity that individual with pain may preferred to avoid in the

past. In this situation, the significant other her husband provided extra attention, comfort, and the opportunity to avoid an undesirable social obligation.

Table 1 describes examples of basic operant principles in chronic pain. The operant learning paradigm does not explain the aetiology of pain or initiation of the behaviour but rather focuses primarily on the maintenance of pain behaviours and deficiency in well behaviours. Adjustment of reinforcement schedules will likely modify the probability of recurrence of pain behaviours and well behaviours.

Table 1. Principles of Operant Conditioning

Schedule	Consequences	Probability of the behaviour recurring
Positive reinforcement	Reward the behaviour	More likely
Negative reinforcement	Prevent or withdraw, avoidance	More likely
Punishment	With negative emotions and much attention	More likely
Punishment	With little attention, ignoring the behaviour	Less likely
Neglect	Prevent or withdraw positive results	Less likely

It is important not to make the mistake of viewing pain behaviours as being synonymous with malingering. Malingering involves the patient consciously and purposely faking a symptom such as pain for some gain, usually financial (secondary gain). In the case of pain behaviours, there is no suggestion of conscious deception but rather the unintended performance of pain behaviours resulting from environmental reinforcement contingencies. Contrary to the beliefs of many third-party payers, there is little support for the contention that outright faking of pain for financial gain is prevalent (Craig, Hill, & McMurtry, 1999).

2.5.3 Social-Learning Processes

From the social-learning perspective, the acquisition of pain behaviours may occur by means of observational learning and modelling processes. That is, people can acquire behavioural responses that were not previously in their repertoire by the observation of others, particularly others who they view as similar to themselves.

Children develop attitudes about health and health care, and the perception and interpretation of symptoms and physiological processes from their parents and social environment. They learn appropriate and inappropriate responses to injury and disease and thus may be more or less likely to ignore or over-respond to symptoms they experience based on behaviours modelled in childhood. The culturally acquired perception and interpretation of symptoms determines how people deal with disease states. The observation of others in

pain is an event that captivates attention. This attention may have survival value, may help to avoid experiencing more pain, and may help to learn what to do about acute pain.

From earliest years, infants, toddlers, and young children are exposed to numerous painful episodes from bumps and falls. Thus, they have plenty of opportunity to observe the reactions they receive. Children of chronic pain patients may make more pain-related responses during stressful times than would children with healthy parents. These children tend to exhibit greater illness behaviours (e.g., complaining, days absent from school, visit to school nurse) than children of healthy parents (Richard, 1988). Models can influence the expression, localization, and methods of coping with pain. Physiological responses may even be conditioned during observation of others in pain (Vaughan & Lanzetta, 1980). Expectancies and actual behavioural responses to nociceptive stimulation are based, at least partially, on prior experience either direct or from observation of others. This may contribute to the marked variability in response to objectively similar degrees of physical pathology observed.

2.6 Behavioural Principles

Video 1 - Pain behaviours in a Patient with dysfunctional Maladaptation

Video 2 - Pain Behaviors in a patient with interpersonal-distressed Maladaptation

Pain, even though originally a reflex, is maintained through reinforcement controlled by operant conditioning formulated by Wilbert Fordyce (1976). He suggested a paradigm shift by expanding the concept of pain from biological processes to include also the influence of "...social/contextual factors that might be little (if at all) related to neurophysiological parameters ...".

Pain behaviours are overt expressions of pain, distress, and suffering such as slowed movement, bracing, limping, and grimacing. Pain behaviours have a communicative function and signal the presence of pain to others. A central feature of pain behaviours is that they are observable, and therefore capable of eliciting a response from significant others. From an operant conditioning perspective, increased pain behaviours result from reinforcing responses by significant others. For example, solicitous responses by significant others have been found to be positively associated with higher ratings of pain severity, more pain behaviours, greater disability and decreased activity levels (e.g., Flor et al, 1995).

Pain behaviours arise through both positive (e.g., excessive solicitous spouse response to pain) and negative reinforcement (e.g., avoidance of unpleasant activities, catastrophizing) subconscious behaviour (Table 1, Box 1). Pain behaviours correlate with an amplified perception of pain intensity that provokes neurophysiological changes influencing the development and maintenance of pain memory (Flor et al, 2002). Operant learning

has been shown to reduce problematic symptoms and behaviours ranging from mental problems such as anxiety and mood disorders (Thieme et al, 2004), to physical problems associated with medication misuse (Turk et al, 1996), deficient activity levels (Romano et al 1995), excessive use of doctor visits (Thieme et al, 2003), avoidance behaviours (Nicassio et al 1997) and amplified pain perception in FM patients with dysfunctional psychosocial adaptation (e.g., Thieme et al, 2005).

Box 1 Operant factors:

Pain behaviour (overt expressions of pain, distress, and suffering)

Betty used to enjoy life, but since she has RA, she only wants to rest. John, her husband, goes to festivities in the family, but when he suggests that she accompanies him or even gets up from the couch and goes outside, Betty answers “that is not good for me, it will make my condition worse, just leave me alone, only rest will help...”. Such kinds of learned cognitions are termed ‘catastrophizing’. Several studies have shown that catastrophizing has a big influence on the course of different pain diseases. Partners and health-care providers can also positively reinforce pain behaviour by pain-related attention and negatively reinforcing pain behaviour by encouraging avoidance of potentially undesirable activities (e.g., performing household chores). For instance, when someone only offers instrumental help or pays attention in case of pain behaviour like moaning, slowing down, or avoiding activities, this behaviour is strengthened and may occur more often in the future. In the operant therapy (OT), patients learn to extinguish (i.e., unlearn) their pain behaviour and to develop healthy behaviour (paced activity, interpersonal interactions) instead; even when experiencing pain. Their significant others are taught to give solicitous responses to the learned healthy behaviour of their diseased partner while ignoring their inappropriate and maladaptive pain behaviours (Bradley et al, 1987, Flor & Birbaumer, 1993, Thieme et al, 2003, 2006).

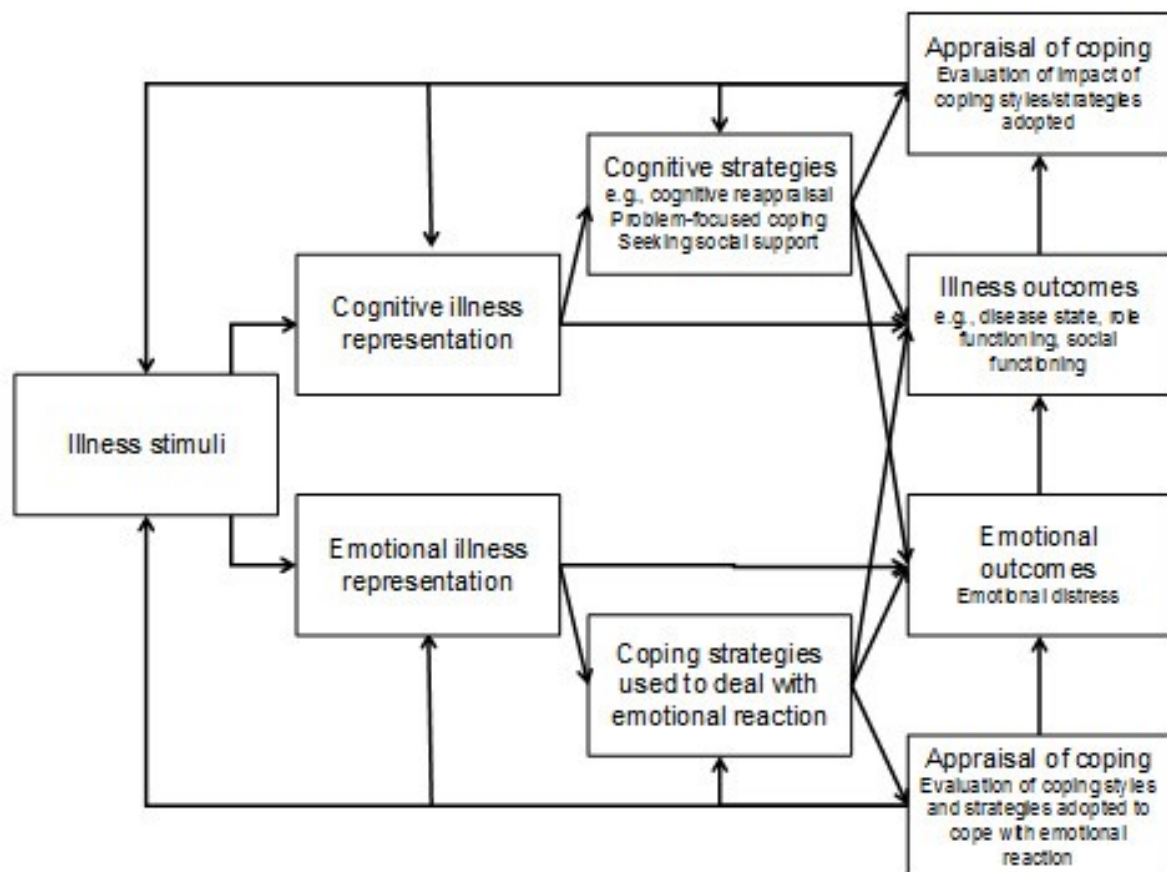
2.7 Illness beliefs and cognitive factors

As outlined in Figure 4 and Box 2, the Perceptual-Cognitive Model of Self-Regulation (Leventhal et al 1998), expanded on the Common-Sense Model of Illness (Leventhal et al, 1984; Cameron et al, 2003), maintains that how people think about their condition influences how they cope with it—their emotional and behavioural response (Turner et al, 2000). There is good evidence to support this view. A cross-sectional study with patients with multiple chronic pain conditions demonstrated that illness beliefs and coping strategies associated with levels of daily functioning (Scharloo et al, 1998) and social support, assessed very early in the disease process, can affect long-term functional disability and pain in RA (Evers et al, 2003).

In support of the Perceptual-Cognitive Model of Self-Regulation, longitudinal studies of RA patients (Scharloo et al, 1999, Van Hoogmoed et al, 2010), demonstrated that illness perceptions and coping strategies contributed to fatigue and health outcomes. Beliefs in the adverse consequences of the disease was associated with more visits to the outpatient clinic, greater tiredness, and higher anxiety scores. Less perceived control and less expression of emotion were associated with more hospital admissions. High scores on coping involving fostering reassuring thoughts were associated with more functional disability. More passive coping was associated with more functional disability and higher anxiety. More perceived symptoms were associated

with more pain, more tiredness, and more depression. More avoidant coping was associated with more tiredness. Belief that the illness will last a long time was associated with higher anxiety. The effect of illness beliefs on disability and quality of life appears to be relatively independent of disease activity (e.g., Graves et al, 2009).

Figure 4. The Perceptual-Cognitive Model of Self-Regulation (Leventhal et al. 1998), expanded on the Common-Sense Model of Illness (Leventhal et al, 1984; Cameron et al, 2003) Adapted from Hagger & Orbell, 2003.



2.7.1 Fear avoidance

Patients' fears about activity increasing pain and other symptoms and causing damage, for example, are likely to intensify actual and perceived limitations physical ability, which are not necessarily a consequence of the severity of their disease or impairments. The Fear-Avoidance Model postulates that pain-related fear and avoidance of physical exercise are essential features of the development, evolution, and maintenance of physical disability for a substantial number of patients with musculoskeletal pain (Vlaeyen & Linton, 2000). In the last decades, an increasing number of investigations have corroborated the interactions among beliefs, emotional response, and behaviours described in the Fear-Avoidance Model (Crombez et al, 2012; Wouters et al, 2012).

Box 2 Perceptual-Cognitive Model of Self-Regulation (Leventhal et al, 1998)

Common-sense Model of health threats distinguishes illness representations and coping procedures:

Illness Representations:

1. Content defines the nature of health threats:

- Identity, the label of the threat—for example, fibromyalgia and its symptoms
- Time line, the prognosis and changeability of the problem
- Cause, the supposed origin—for example, somatic/genetic or stress-induced
- Consequences, the effects such as reduced functioning or work disability
- Cure—control, the extent to which the health problem can be cured, prevented, reduced, or kept from progressing

2. Organization of Representations in acute pattern (flu), cyclic (allergy) and chronic conditions (RA)

Coping Procedures:

- Outcome Expectancies with the dimensions: goal-relevance, time lines, dose efficacy beliefs
- Risk and benefits associated with specific classes of procedures (for example general vs. treatment-specific beliefs affecting adherence to medication protocols)

These beliefs will affect the actions with respect to management of the disease and its consequences.

The beliefs are measured with the revised Illness Perception Questionnaire (IPQ-r, Moss-Morris et al, 2002)

Disease representation and coping procedures share a common identity!

Representations of disease can overlap with representations of the self:

- Attributes of the self can define risk: Perceived vulnerability for breast cancer defines the risk.
- Attributes of the self can moderate procedures for self-regulation - for example, age can moderate the self-regulation process.

2.7.2 Cognitive mediators: Self-efficacy and catastrophizing

Self-efficacy is a person's confidence in their ability to successfully execute and accomplish a given task (Bandura, 1997). Patients' self-efficacy to perform activities of daily living at baseline is a significant predictor of disability as illustrated in a study that assessed activity 12 months from initial assessment (Holm et al, 1998). Converging lines of evidence indicate that perceived self-efficacy operates as an important cognitive factor in adaptive psychological functioning (e.g., Benyon et al, 2010; Sarda et al, 2009), disability (e.g., Benyon et al, 2010; Busch et al, 2007; Sarda et al, 2009), and treatment outcome (e.g., Huffman et al, 2005).

In addition to pain, cognitive-behavioural mechanisms have been shown to directly affect disability. The interference of chronic pain with activities of daily living was, after controlling for current pain severity, accounted for by catastrophizing (a combination of excessively focusing on pain sensations, thinking that something serious might happen, and the perception of not being able to cope with the pain situation - a feeling of helplessness), fear of pain, guarding, and control beliefs (Karoly et al, 2007). Catastrophizing is a

significant mediator of emotional and behavioural reactions to nociceptive sensations and physical impairment. The combination of both situation-specific pain-related and general cognitive variables explained up to 60% of the variance in pain and disability in studies of chronic back pain and RA patients (Edwards et al, 2006, 2011; Flor & Turk, 1988). That means catastrophizing has an important impact on the course of the disease replicated in studies for OA, and fibromyalgia (FM).

2.7.3 Hypervigilance

Hypervigilance for symptoms represents an attentional bias that many people with rheumatic diseases exhibit. An attentional bias is a selective attention towards specific information, most often in relation to threatening information. People who experience recurrent symptoms may develop a pattern of behaviour in which they are constantly on high alert for and anticipate future pain episodes, flare-ups, and increases in pain intensity. This hypervigilance may contribute to patients' avoidance of activity all together or they may cease activity at the earliest sign of symptoms as proposed in the Fear-Avoidance Model.

Hypervigilance for symptoms has been associated with increased symptom intensity, disability, and pain-related health care utilization in a variety of populations of patients with chronic pain (e.g., FM, RA, back pain, Fillingim & Edwards, 2005). It is important to bear in mind that for the individual with the symptoms, being hypervigilant to pain makes perfect sense – paying attention is an important survival mechanism. This is true in the short-term; to protect ourselves against threats. Rheumatic patients may require ongoing education about the difference between monitoring symptoms and excessive focus on symptoms.

2.7.4. Psychological flexibility-rigidity

Psychological flexibility refers to one's ability to act in accordance with his or her own set of values, during interfering thoughts, feelings, or bodily sensations. In acting in alignment with one's values, individuals persist in behaviours that move them toward their broader goals, and need to change behaviours that move them further away from their values. Studies of psychological flexibility demonstrate that higher flexibility is adaptive. Higher psychological flexibility is associated with better psychological outcomes and higher quality of life. Low levels of flexibility, psychological inflexibility, are associated with avoidant coping methods like denial, behavioural disengagement, and self-blame (Adams & Turk, 2015).

In the context of patients with rheumatic diseases, psychological flexibility may be manifested by a person's ability and dedication to maintain involvement in meaningful activities and acceptance that, despite ongoing symptoms throughout their lives, they still strive for and may experience a full life. On the other hand, psychological rigidity is reflected in patients who withdraw from their favourite activities, since they believing that they cannot be active in hobbies. These patients may also obsessively seek ways to eradicate and avoid their symptoms completely, often spending a great deal of time in the search, and to the detriment of actively

engaging in their lives. Obviously, balance is paramount. The Serenity Prayer attributed to the theologian Reinhold Niebhur captures this quite well.

“Give me the serenity to accept things I cannot change, the courage to change the things I can, and the wisdom to know the difference.” [emphasis added]

2.8 Health-Related Quality of Life

Health-related quality of Life (HRQoL) is a relatively new concept. For many years, medical care was directed at the disease and at survival. Nowadays, more care is taken of the patient’s quality of life. Most definitions of HRQoL refer to four components: physical functioning, psychological status, social functioning, and symptoms of the disease or treatment (Taylor, 2003). A more elaborate definition of quality of life is used by the World Health Organization: “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (Skevington et al, 2004). RA patients show a lower HRQoL than osteoarthritis (OA) (Wysocka-Skurska et al, 2016), and when musculoskeletal diseases coexist (Picavet, 2004).

Thus, how satisfied or bothered people are with their HRQoL is a highly individual matter. Besides being directed at treatment of disease and symptoms, care should also attend to promoting psychological, physical, and social functioning.

2.8.1 Focus on functioning

Traditionally, rest was considered as appropriate response to a chronic inflammatory disease; currently, exercise therapy is considered a better recommendation (De Ridder et al 2008). Even in chronic inflammatory diseases such as RA, careful long-term intensive exercise has been shown to improve functional ability and emotional status without detrimental effects on disease activity or radiographic damage (De Jong et al 2003; Smidt et al 2005). The challenge of psychological adjustment is often to help the patient to go against the ‘appeal’ of sickness behaviour by overcoming fatigue and depressed mood through exercise, and engaging in activities that promote HRQoL (Box 3).

Based on rank ordering across the HRQoL dimensions of several chronic conditions, physical functioning is especially severely impaired in people with arthritis and other musculoskeletal conditions, but the impact on mental wellbeing is less severe (Alonso et al, 2004; Sprangers et al, 2000). Mental wellbeing and physical functioning in arthritis are related; individuals reporting coexisting psychological distress have poorer scores on physical functioning than those without psychological distress (Hill et al, 2007). Once again, focusing only on the physical aspect, leaves the psychological aspect untreated and may lead to unsuccessful treatment and overtreatment of the physical aspects of the condition.

Box 3 A case for psychology

Traditionally, mental health professionals focused on patients who were unable to adjust adequately to the consequences of chronic diseases. In the past decades, the emphasis on the reasons why people fail to achieve a healthy adjustment has shifted to the identification of factors that help patients make that adjustment. To promote psychological adjustment, individuals with chronic diseases are encouraged to remain active, to acknowledge and express their emotions in a way that allows them to take control of their lives, to engage in self-management, and to try to focus on potential positive outcomes of their illness. Individuals who can use these strategies have the best chance of successfully adjusting to the challenges posed by a chronic illness (De Ridder et al. 2008). Stress resilience factors, and interventions to ease stress and enhance resilience, are gaining increasing attention for the treatment of rheumatic conditions. Cognitive-behavioural and social risk and resilience factors predict the long-term physical and psychological functioning of individuals with rheumatic conditions. Furthermore, screening is useful in clinical practice to identify and select individuals at risk. Stress-management and resilience interventions offer promising ways to improve the long-term functioning. These treatment methods can be especially useful when they are tailored to the specific risk and resilience factors of individuals with chronic diseases, to increase efficiency and availability of treatments, and to optimize patient empowerment in rheumatic conditions.

2.8.2 Life roles

Fatigue, and decreased muscle strength and endurance, along with pain are among the consequences of rheumatic disease that may hamper work, relationships, leisure time, and social activities. Patients with rheumatic diseases will often need to adjust to their life roles. A longitudinal study showed that within the first 3 years almost 50% of patients with RA and more than 25% of individuals with more than 5 years of RA report emotional distress predicted by disability. Disability in valued life activities is very common among individuals with rheumatic diseases. The emotional distress is also associated with alteration of their recreation time, the experienced difficulties in their roles as spouse and parent (Bacconnier et al, 2014). Questionnaire data for 1,210 RA patients at six hospitals in Britain, finds that 46% would like to have discussed the psychological impact of their disease but were never asked about it (Dures et al. 2014). Such role function is measured in the SF-36 and social relationships in the WHOQOL and AIMS.

2.8.3 Work

Work disability and a reduction of family income is a common outcome of rheumatic diseases (Wolfe et al, 2005, Kobelt et al, 2009). In RA, one study showed that education level, body mass index, ESR, rheumatoid factor, pain, and disability assessed with the HAQ, and physical demands of the job were independently associated with work disability (Wolfe et al 2005). A systematic literature review revealed that biomedical variables do not consistently predict work disability in RA; much more important were physical job demands,

low functional capacity, old age, and low education (De Croon et al, 2004). A Swedish study compared RA patients with healthy controls found that low decision latitude was associated with an increased risk of developing RA. Furthermore, some evidence suggests that those with high psychological job demands had a decreased risk of RA (Bengtsson et al, 2009). These results indicate that to deal with work disability in RA the misfit between individual capability and job demands needs to be addressed.

Encouragement to remain in work is an important feature of overall care to individuals with rheumatic disease, and it is important to appreciate that if a patient will be able to continue work will depend on the appropriateness of individual adjustments and the possibility of altering the demands of the work situation (Henriksson et al, 2000). Work accommodations can assist in both job performance and with satisfaction while keeping energy for home and free time and having acknowledgement and help from management and colleagues (Bossemma et al, 2012). When appropriate given age and physical limitations, individuals with chronic diseases should be encouraged to negotiate with employers to improve the match between job demands and capabilities.

2.8.4 Interpersonal relationships

It might be expected that having a painful and potentially disabling chronic disease would have significant negative effects on personal relationships. However, this is not necessarily the case. For example, in one study when asked if they had experienced any interpersonal benefits because of their disease, 71% of people with RA described interpersonal benefits such as ‘appreciation of support from loved ones’ and ‘increased compassion/empathy’, whereas 16% reported another type of benefit (new outlook on life or self), and 13% reported no benefits (Danoff-Burg & Revenson, 2005). Interpersonal benefit-finding predicted lower levels of disability at a 12-month follow-up but not levels of psychological distress or pain. Although the results likely reflect real positive consequences of the disease, caution needs to be exercised in that some patients might focus on positive aspects of their situation in order to protect themselves from painful emotions or deny the severity of their illness and its consequences.

Sexuality is an area often neglected by health professionals; rheumatic diseases impact on the sexual lives of a large minority of those affected and this is a problem that patients and health professionals are reluctant to discuss face-to-face (Hill et al, 2003).). In RA, one-third of individuals report that their sexual activity is influenced by higher levels of fatigue, mental distress, functional limitations, and lower levels of self-efficacy (Helland et al, 2008). They also reported that they are less sexually active than controls and a considerable number of both male and female patients have trouble with their joints during sexual activities, but patients do not differ from controls regarding sexual satisfaction (Van Berlo et al 2007). In FM, especially the psychological aspect of the sexual response cycle (sexual desire and satisfaction) is more disturbed than normal (Prins et al, 2006; Tikiz et al, 2005).

Rheumatic diseases not only have significant impacts on the identified patient. Early results of an ongoing study (K. Thieme) show a higher rate of depression in spouses and more cardiovascular and cancer diseases in spouses who are very solicitous towards their patient-partner.

2.9 Coping

Coping refers to the cognitive, behavioural, and emotional processes by which people attempt to limit the impact of a stressor such as having a rheumatic disease. The coping process involves appraisal of the level of 'threat' posed by the stressor and of one's resources to deal with it (Box 4). If a person feels that he or she is inadequately resourced to deal with the threat, a stress response arises that involves physiological arousal, feelings of anxiety and distress, and stress-related behaviour. Coping strategies have been divided into two broad categories (Lazarus & Folkman, 1984): problem-focused coping (change aspects of the stressful situation) and emotion-focused coping (managing the emotional response that the stressor evokes).

Box 4 Primary and secondary appraisal

Not all individuals respond in the same way to stressors of the disease or life stressors. In order for stress to be evoked for the person, two cognitive events must occur.

1. Primary appraisal: the perception that the event is a threat to one's personal goals—for example, stress may occur when the patient realises that the disease will prevent a successful career.
2. Secondary appraisal: the evaluation that one does or does not have the resources to cope with the demands of the threat—for example, when the patient realises that to be able to live a happy, less ambitious life or to adapt the circumstances at work will reduce stress.

An individual's predominantly used means of coping are likely to change over the course of the disease, as the demands of the disease change and people develop (or fail to develop) resources to deal with them.

Individuals with a diagnosis of early RA report greater future denial than those with established RA, suggesting that denial may be a strategy used for coping in the early stages after receiving a diagnosis (Treharne et al, 2004).

Some patterns of coping have been found to be related to outcomes in rheumatic disease. For example, catastrophizing has been identified as an important strategy in how people cope with pain. In a review, the authors concluded that catastrophizing appeared to be positively related to pain severity and pain-related disability, affective distress, muscle and joint tenderness, and poor pain-treatment outcomes across different rheumatic diseases (Edwards et al, 2006). Proposed explanatory pathways included maladaptive influences on the social environment and amplification of the central nervous system's processing of pain.

The use of passive coping strategies—exerting little control to manage a problem, relying on hoping without taking any action - has generally been associated with poorer outcomes. For example, the use of passive coping strategies and high expectations of disability (Ferrari & Russell 2010) in RA. In a longitudinal study in

patients with a recent diagnosis of RA, passive pain coping predicted functional disability at 3-year but not 5-year follow-up (Evers et al, 2003). This finding suggests that early coping skills training can help people adopt more appropriate strategies to deal with the consequences of the disease. In contrast, the use of more active coping strategies—exerting control to manage a problem—has been shown to be more likely to result in positive outcomes (Buckelew & Parker, 1989).

While the use of active coping strategies is usually found to be helpful, in situations where it is not possible to change the source of stress, continued attempts to solve the problem may result in heightened distress. Expression of emotions may lead to better psychological and physical adjustment as has been found in a variety of chronic conditions (De Ridder et al, 2008).

2.10 Social support

Support from friends and family is potentially an important influence on how well people manage and cope with their disease. In research, this support has been termed ‘social support’ and has been conceptualised both structurally—that is, the size and composition of a person’s social network; and functionally—that is, how a person perceives and evaluates the adequacy of their support network. It is the latter, which appears to be most closely related to health (McNally & Newman, 1999). In a large study as many as 49% of patients with FM were found to report a high degree of loneliness, while the percentages for patients with ankylosing spondylitis or rheumatoid arthritis were 32 % (Kool & Geenen, 2012).

Following Social Support Theory, receiving support from others is generally beneficial to mental and physical health and it may buffer the harmful impact of stressors of the disease or external stressors (Cohen & Wills 1985). In confirmation of this buffering hypothesis, mastery, having many diffuse social relationships and receiving emotional support appeared to mitigate the influence of arthritis on depressive symptoms (Penninx et al, 1997). The important part that social support can play in chronic disease was also shown in a review which concluded that adherence to medical treatment is higher in those from cohesive families but lower in those from families that are in conflict (DiMatteo, 2004).

A review of the empirical literature in several chronic illnesses observed a modest positive relation between social support and self-management (Gallant, 2003). In one prospective study, perceived social support measured at baseline predicted pain 3 years and 5 years later (Evers et al, 2003). Studies have shown that the psychological adjustment of women with RA might be related to the beneficial or problematic spousal support the patient receives from her husband. When the spouse underestimated fatigue (11%), or underestimated (39%) or overestimated physical limitation levels (34%), the person with RA received problematic support such as the spouse find it hard to understand the way the person feel (Lehmann et al, 2011). In contrast, women who reported their spouse as being supportive engaged in more adaptive coping strategies. There is evidence from prospective studies that illness cognitions of more helplessness and less acceptance, more passive coping

with pain or stress, and lower levels of social support predict decreased physical, psychological, and social functioning in individuals with RA in the long-term (e.g., Evers et al. 2002).

A distinction needs to be made between positive support and negative support—that is, care with a negative outcome. Some spouses or other social agents have good intentions, but nevertheless offer an unhealthy kind of social support. Spouses who, for instance, in an assertive and lecturing way ‘know’ what is best for the patient can take away a feeling of independence and control (Kool et al, 2009). Lack of reciprocity in a relationship, both receiving more support than one has provided (over-benefit) and providing more support than one has received (under-benefit) are psychologically distressing (Gleason et al, 2003). Inappropriate and overprotecting support of spouses for patients has been associated with reduced wellbeing and functioning (Hagedoorn et al, 2006; Joekees et al, 2007; Kool et al, 2006). In women with RA, both problematic support and unavailability of support were significantly related to poor family functioning and lower life satisfaction. Both greater problematic support and lower family functioning were (together with higher symptom severity) associated with depressive symptoms (Coty & Walston, 2010).

Also, solicitousness—that is, taking over tasks that the patient could still do—has been shown negative social support (Newton-John, 2002). Self-report data support the hypothesis that spouse-solicitous responses to pain behaviours in patients with chronic pain may contribute to the maintenance of pain behaviours (i.e., overt expressions of pain, distress, and suffering) and disability. In an observational study, spouse-solicitous responses to non-verbal pain behaviours during a household activity were significant predictors of non-verbal pain behaviour in dysfunctional maladapted FM patients who reported greater pain and pain-related interference (Thieme et al., 2005). In this study, spouse-solicitous responses did not predict psychosocial dysfunction or total self-reported pain behaviours.

Considering the different psychosocial aspects associated with chronic pain, there is a heterogeneity of psychosocial adaptations observed among chronic pain patients that is independent on diagnoses. Research by Turk and colleagues (1994) that considers patterns with different levels of pain, interference, physical functioning, spouse responses, pain behaviours and comorbidity (Thieme et al 2004, 2005) has identified several patterns that have been related to chronicity following acute injuries to responses to treatments (e.g., Bergstrom et al, 2011; 2012; Litt & Porto, 2013; Thieme et al 2004, 2006; Verra et al 2009). The subgroups identified are described in box 5.

Box 5 Heterogeneity in Psychosocial Adaptation

Compared to other chronic pain patients:

- *Dysfunctional subgroup* exhibits the highest level of pain, physical disability, and solicitous spouse behaviour and less physical activity. Those patients show significantly more frequently anxiety disorders because of a learned avoidance behaviour reinforced by a solicitous spouse behaviour (see case report 2).
- *Interpersonal-distressed subgroup* reports significantly lower levels of pain, disability, and marital satisfaction. That goes along with a higher level of negative spouse responses on the patient's expression of pain. Those patients learn to show pain behaviours to a little amount with the consequence of a reduced perception of their pain. Instead, they develop more frequently depressive episodes because of a loss of social support (see case report 1).
- *Adaptive Coper subgroup* display a low pain intensity, emotional distress, and interference of pain with daily life and activities associated with distracting spouse behaviours. They show less pain behaviours and a low amount of psychiatric comorbidities such as anxiety and depression.

2.11 Emotion regulation strategies

Psychological adjustment to chronic disease and its consequences depends on coping styles and cognitions (attitudes, beliefs, appraisals, expectancies, interpretation of meaning), but also on the common emotion regulation strategies of a person. Prospective studies generally show that the regular use of avoidant non-expressive styles of emotion regulation, such as alexithymia (having difficulty identifying feelings and distinguishing between feelings and the bodily sensations of emotional arousal and difficulty describing feeling to others), being ambivalent about expressing emotions, emotional repression (being unaware of emotions) and emotional control (avoiding the expression of emotions) are disadvantageous for psychological adjustment and survival, whereas acknowledging and intensely experiencing emotions is suggested to be beneficial for adjustment as long as the emotions are expressed and dealt with (De Ridder et al, 2008). Although expressing emotions is generally adaptive, the mere uncontrolled expression of emotions without processing can be maladaptive.

In a prospective study in patients with RA, alexithymia, and ambivalence over expression of emotions predicted an increase of perceived disease activity 4 months later (Van Middendorp et al, 2005). Measures of alexithymia often co-vary with measures of emotional distress. In a study of female patients with different painful rheumatic conditions and healthy controls no difference in alexithymia was found between the two groups after controlling for anxiety and depression. However, patients had significantly lower scores on the subscale "self" of the Levels of Emotional Awareness scale, indicating a lower capacity to describe their own emotional experience (Baeza-Velasco et al, 2012). Inconsistent evidence for the beneficial effects of emotional expression interventions have been observed in RA (Kelley et al, 1997; Lumley et al, 2011; Van Middendorp et al, 2009; Wetherell et al, 2005) and FM (Lumley et al, 2008).

2.12 Self-regulation

The Perceptual-Cognitive Model of Self-Regulation (Leventhal et al, 1998) ‘common-sense’ perspective of their illness), described earlier (Figure 4 and Box 2), provides a framework through which they understand it and respond to it. This framework, or illness representation, is influenced by many factors, including their experience and knowledge about the illness and information they receive from healthcare professionals, the media, family and friends. The illness also generates an emotional response based on beliefs, expectations, and meaning ascribed to the disease and symptoms. The coping behaviours (i.e., attempts to control or avoid physical and emotional symptoms), including whether they choose to adhere to recommended treatment, that people select to manage their illness are then influenced by both their cognitive representations and their emotional state. People evaluate how effective their coping behaviours have been in managing their illness and this appraisal can then in turn lead to changes in their illness representations and their behaviours. An important feature of this model applied to chronic illnesses is evolution over time. The illness representation will be affected by the effects of the patients’ coping efforts and the disease trajectory.

3. Impacts of rheumatic disease

A survey by the European League Against Rheumatism (EULAR) showed that 70% of people with a rheumatic disease and their carers indicated that their condition affects them emotionally and has a negative impact on their mood often. Yet, only 35% of them raise this issue with their doctor. The sometimes-uncontrollable nature of rheumatic diseases as well as their unpredictable course may make patients more vulnerable to emotional distress. An important psychological dimension of rheumatic disease is the role that several psychological variables have as moderators and mediators of in disease outcomes such as symptoms and physical function.

3.1 Fatigue

Severe fatigue is an extremely prevalent and debilitating symptom in many rheumatic diseases, affecting between 40–60% of patients with a single inflammatory rheumatic disease such as RA, (systemic lupus erythematosus (SLE), ankylosing spondylitis, Sjögren’s syndrome, psoriatic arthritis, and scleroderma, and around 80% of patients with FM. Fatigue may be present regardless of disease activity, and there is no or only a minimal association between fatigue and indicators of the severity of the inflammatory disease as such (Hartkamp et al, 2011; Stebbings & Treharne, 2010). Fatigue is most often associated with pain, sleep disturbances, depression, and negative illness perceptions (Stebbing & Treharne, 2010).

The complexity of fatigue in patients with rheumatic diseases has been emphasised. The Bristol RA Fatigue Multidimensional Questionnaire (BRAFMQ, Nicklin et al, 2010) developed specifically to assess fatigue in

patients with RA, identifies four dimensions of fatigue: physical fatigue, emotional fatigue, cognitive fatigue (concentration problems, lack of mental energy), and daily life consequences of fatigue. Another study identified four patterns of fatigue among patients with RA: 'little impact of fatigue', 'good coping and bad sleep', 'search for balance', and 'high distress' (Nikolaus et al, 2010a). Younger women with RA and with multiple daily roles seem to be particularly vulnerable to the negative impact of fatigue (Nikolaus et al, 2010b).

As fatigue levels decrease in the first hours after awakening and increase throughout the remainder of the day (Goodchild et al, 2010; Van Oers et al, 2010), patients with rheumatic diseases may function best around noon. Fatigue and sleep influence one another. In a study of patients with RA and patients with Sjögren's syndrome, evenings characterised by high fatigue related discomfort were followed by nights with less sleep and worse sleep efficiency. Moreover, nights of poor sleep tended to be followed by days with more severe fatigue compared with the individual's average (Goodchild et al, 2010).

The pathophysiology of fatigue is complex and multifactorial. Among biological factors cytokines, oxidative stress, mitochondrial dysfunction have been investigated (Norheim et al, 2011). Genetic markers of fatigue has also been found for rheumatic disease; e.g., signals of association with primary Sjögren's syndrome (pSS) were detected for one SNP in SLC25A40 and two SNPs in PKN1 in a pSS case versus control analysis (Norheim et al, 2013).

3.2 Affective Distress - Depression

The UK National Institute for Health and Clinical Excellence (NICE) underlines that individuals 'with significant physical illnesses causing disability' have an increased propensity to have high levels of depressed mood (NICE guidelines). Systematic review and meta-analysis compared levels of depressed mood in people with RA, OA, and FM and in healthy controls (Dickens et al, 2002, Matcham et al, 2013). The depressed mood levels of people with RA were significantly higher than the levels of healthy controls (the difference was small to moderate) and of people with OA (the difference was very small), whereas people with FM had higher depressed mood levels than those with RA (the difference was small). A Meta-analysis with 72 studies revealed the prevalence of major depressive disorder to be 16.8% (95% CI 10%, 24%). According to standardized questionnaires, as the Patient Health Questionnaire (PHQ-9, Kroenke et al, 2001), the prevalence of depression was 38.8% (95% CI 34%, 43%), and prevalence levels according to the HADS was 34.2% (95% CI 25%, 44%) for medium and 14.8% (95% CI 12%, 18%) for severe episode of depression. (Matcham et al, 2013). However, the rheumatologists should be aware that loss of appetite and movement might be rather a function of pain than of depression.

Since the prevalence of rheumatic diseases is also higher in women than men, there is a good chance that the rheumatologist will be confronted several times each year by a patient who needs help for depression. In the

case of Judy (Box 6), a referral to a mental health professional would probably show that she is significantly depressed and would benefit for treatment of her depression.

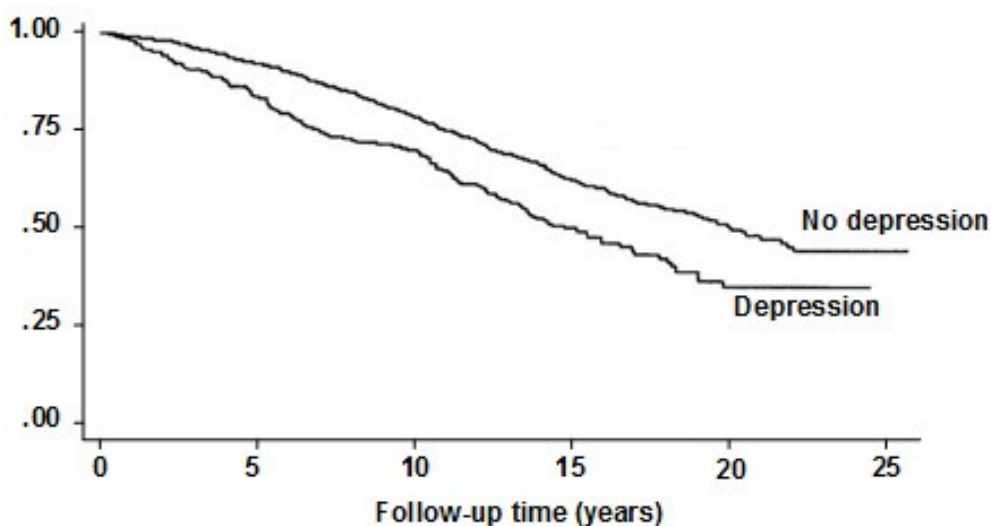
Box 6 A case of depression

Most often Judy came alone to the consultation, but this time her partner Bill came with her. Bill explained: “Lately, Judy just lies down on the couch much of the time. Especially in the morning, she’s seems unable to do anything. Then, she just lays there, she does not read the paper, she does nothing at all. She seems to have no energy or interest in doing any of the things she used like to do” Judy has lost weight in the past months. She awakens very early in the morning; sometimes after having slept for only a few hours. She says she feels worthless and guilty about not being motivated to do the household tasks. She’s glad that the children have all left home “having them around would only make things worse.”

3.2.1 Depression Mortality

Depression has been found to be an independent predictor of mortality in RA. Ang et al (2005) followed 1290 patients for 18 years and found that the hazard ratio of clinical depression on mortality was 2.2 (95% CI 1.2 to 3.9; $p=0.01$) Figure 5. In a meta-analysis of 25 studies, a hazard ratio of depression on mortality between 1.6 and 2.1 was observed and the relative risk in subclinical depression was not substantially smaller than in clinical depression (Cuijpers & Smit, 2002).

Figure 5. Survival over 20-year follow-up of patients with rheumatoid arthritis with and without depression. Reprinted with permission from Ang et al 2005.



3.2.2 Prediction of depression

It is important to appreciate the factors that appear most important in causing depression in rheumatic disease and the extent to which they are modifiable. An obvious hypothesis is that the disease and its consequences may be risk factors for depression: this has been partly confirmed. Depression is often not directly predicted by clinical markers of disease severity, although such a relation has been found in some

studies (Cadena et al, 2003; Martindale et al, 2006). Low socioeconomic status, female sex, younger age, race/ethnicity, higher pain, and functional limitation, as well as poor clinical status appear to be important predictors of depression among persons with RA. Systemic inflammation may also be associated with, cause, or contribute to depression in RA (Margaretten et al, 2011). Longitudinal studies of people with RA show that cognitive and behavioural variables are also important. In one study, the course of depression was predicted by physical disability associated with helplessness cognitions and passive coping (Covic et al, 2003). In another study, disability, pain and beliefs about the consequences of arthritis and coping strategies were the most important predictors of depression (Sharpe et al, 2001).

In people with OA, the strongest risk factors for depression were pain and having few social contacts, followed by physical limitation of the lower body, physical limitation of the upper body, a younger age, and a high body weight (Rosemann et al, 2008). In addition, concerns about physical appearance were, together with levels of disability, predictive of depression in people with RA and in patients with systemic lupus erythematosus (SLE). Concerns about appearance were also found to mediate the relationship between disability and depression (Monaghan et al, 2007).

The relation between depression, symptoms, and physical functioning is complex. It might be expected that a painful, disabling and, to a certain extent, uncontrollable and unpredictable illness could lead to depression, and this relationship gains support from the studies above. However, the relation is not necessarily unidirectional; depression will influence other outcomes in rheumatic disease such as functional abilities.

3.3 Emotional Distress - Anxiety

Anxiety is a major mental health problem that the rheumatologist may confront. The presentation may vary. Negative features of physical limitations or appearance may lead to fear of being evaluated negatively by others. Patients may also have intense anxiety about the presence or severity of physiological symptoms. Intense anxiety and worries (Box 7) are a severe threat to wellbeing and functioning. It is not uncommon to find anxiety combined with depression.

The classification of anxiety disorders (for example, phobias, generalised anxiety disorder, panic with agoraphobia) is according to DSM criteria (Diagnostic and Statistical Manual of the American Psychiatric Association, DSM-5, American Psychiatric Association, 2013) but, as with depression, many people experience heightened feelings of anxiety without meeting the diagnostic criteria for an anxiety disorder. State anxiety refers to an unpleasant emotional arousal in response to a perceived threat, while trait anxiety refers to stable individual differences in a predisposition to state anxiety in anticipation of threatening situations (Spielberger et al, 1983). State anxiety may be a perfectly normal response, but trait anxiety is troublesome for the individual.

Box 7 A case of generalised anxiety

Joanne is the kind of person who is easily worried. She feels stressed almost all the time. She is anxious that her children will be involved in a car accident. When she must stay at home because of her arthritis, Joanne hides from her neighbours, because she does not want them to judge her to be a malingerer. When she has a discussion with her husband, she is afraid that he will leave her for another woman. When there is a problem about insurance on the television, she starts worrying about her own insurance. She is worrying all the time; even when she should be sleeping she is worrying. Therefore, she is easily irritated and fatigued. She envies other people who appear to live their life careless, without any worries.

The core problem for Joanne is that her social, occupational and other important areas of functioning are hampered by excessive, difficult to control anxiety and worry about many events or activities, occurring more days than not. She probably has generalised anxiety disorder.

People with rheumatic disease likely experience anxiety from time to time, because uncertainty about the course and progression is an integral aspect of the disease.

3.3.1 Prediction of anxiety

It appears that anxiety remains stable or decreases slightly over the early years of RA (Evers et al, 2002; Treharne et al, 2007). In one study, disease duration at baseline did not predict the level of concurrent anxiety but greater inflammation, and a longer disease duration at baseline did predict improvement in anxiety by the 1-year follow-up (Treharne et al, 2007). In another study, neither clinical status (erythrocyte sedimentation rate and joint count), pain and self-reported functional disability nor coping or social support predicted anxiety (Evers et al, 2002). The anxiety in rheumatic disease has been shown to be related to an increased sympathetic response associated with diminished BRS and NTS activation (Osailan et al, 2016); beta-blockers may reduce pain and anxiety to 10% (Schneider, 1997).

3.3.2 Prevalence of anxiety disorders

Although fewer studies in rheumatic disease have examined anxiety than depression, some suggest that anxiety is the more prevalent condition. For example, in a cross-sectional study the percentages with an anxiety disorder (panic with agoraphobia, panic without agoraphobia, social phobia, simple phobia, and generalised anxiety disorder) totalled 13% of those without arthritis compared with 20% of those with arthritis (McWilliams et al, 2008). During a longitudinal study extending over 10 years, 30% of patients with RA had increased levels of anxiety at baseline and the prevalence during follow-up varied between 23–25%, whereas 10% of the patients scored within the range for depression with follow-up prevalence varying between 5–13% (Odegard et al, 2007).

In people with RA and OA, state anxiety in RA have normative scores, but trait anxiety, indicating persistently raised anxiety levels, is higher—especially in people with RA who reported comorbid depression (VanDyke et al, 2004). Those with OA did not differ from normative samples on either state or trait anxiety. The difference between RA and OA is interesting, given that they do not differ greatly in rates of depression. This may reflect the greater uncertainty of living with RA, whereas the findings for depression may be at least partly explained by similar levels of pain. Anxiety is also common in other rheumatic disease, such as SLE (Bachen et al, 2009), and in FM, especially in patients with a dysfunctional pain profile (Thieme et al, 2004).

3.3.3 Pain - Psychological Distress Relationship

The relation between pain and emotional distress is not unidirectional. While greater pain has been linked to depression, a history of clinical depression has also predicted current reports of greater pain. Pain reports of participants with RA in stress-induction tests were compared in those who had no history of depression, those who had had one major depressive episode, and those who had experienced two or more episodes (Zautra et al, 2007). The latter group reported most pain, both at entry into the study and in response to the stress induction test compared to the other groups. Similar results were observed for fatigue. People with RA who had a history of affective disorder (major depression or generalised anxiety disorder) reported higher levels of fatigue than those with no previous affective disturbance (Jump et al, 2004).

In a prospective study, baseline variables that predicted fatigue at a 12-month follow-up were less helpful at home, more anxiety and more disability for patients with RA, and more anxiety and less physical activity for a control group (Mancuso et al, 2006). In RA, although an association was observed between psychological distress and disease activity measured at the same time, prospective analyses did not support the notion that psychological distress is a risk factor for future exacerbation of disease activity (Overman et al, 2012)

4. Psychological assessment

We have emphasized the range of psychosocial and behavioural factors that are important in chronic diseases. Optimal treatment of individuals with these conditions will require attention be given to how these factors influence each individual affected. Initially, this will require some assessment of the set of factors described above. A number of tools are available to assess the nature and severity of the psychological impact and the resources available to patients with rheumatic diseases. These may be useful for the clinician to screen patients both for psychological disturbance as well as to gain a greater understanding of patients' beliefs and behaviours. Although a rheumatologist may not have the time or expertise to perform a comprehensive assessment, he or she should be familiar with available measures that may be used by mental health professionals to whom patients may be referred for such an assessment. Not every patient will require an extensive assessment as described but initial screening may help determine which patients might, indeed, benefit from such evaluation.

4.1 Depression

Depression is important because the distress indicates that people are suffering, but also has further implications for how people can manage their rheumatic disease and their physical functioning and, thus, for their health outcome. The NICE guidelines for screening are useful to apply in the first instance in a clinical interview. Several more detailed questionnaire measures are available that can be used to assess the level of depressed or anxious mood and screen for possible clinical 'caseness' (Box 8). The Patient Health Questionnaire (PHQ-S; Kroenke et al, 2001) is a brief, self-administered depression questionnaire, which scores each of the nine DSM-5 criteria as '0' (not at all) to '3' (nearly every day).

4.1.1 Depression Diagnosis

The rheumatologist must always be alert to the possibility of a patient being depressed. There are several brief screening questionnaires exist to assist in the identification of depressed mood (box 9). These are efficient and can be one basis for determining whether a more extensive evaluation by a mental health professional might be appropriate. These brief measures can be used throughout treatment to monitor changing status.

The criteria of the (DSM-5 (American Psychiatric Association, 2013) are used for the classification of mental disorders into qualitatively different diagnostic categories (Box 8, 9). Diagnosis of clinical depression requires a clinical interview performed by an appropriately qualified practitioner such as a psychiatrist or clinical psychologist. Mood varies on a spectrum from high to low and from transient emotional states to a more enduring predisposition to stable negative mood. Moreover, depressed mood may occur without the usual co-existing vegetative symptoms, such as sleep disturbance, change of appetite and low energy.

Box 9 Screening for depression

Diagnosis of clinical depression requires a clinical interview performed by an appropriately qualified practitioner such as a psychiatrist or clinical psychologist. Several screening questionnaires exist to assist in the screening for depressed mood. These instruments also provide cut-off scores that are suggestive of clinical depression and, therefore, the need for further investigation.

1. The 14-item Hospital Anxiety and Depression Scale (HADS) with an anxiety subscale (HADS-A) and a depression subscale (HADS-D; Zigmond & Snaith, 1983)
2. The 5-item Mental Health Inventory (MHI-5; Berwick et al, 1991)
3. The 20-item Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977)
4. The 21-item Beck Depression Inventory (BDI-II; Beck et al, 1996)
5. The 9-item Patient Health Questionnaire (PHQ-2; Kroenke et al, 2003)

Rheumatologists should screen for depression in their regular clinical interview by using two key questions concerning mood and interest, as recommended by the NICE guidelines:

'During the last month, have you often been bothered by feeling down, depressed or hopeless?'

and

‘During the last month, have you often been bothered by having little interest or pleasure in doing things?’

Box 8 The diagnosis Major Depression per the criteria of DSM-5

Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks.

- Mood represents a change from the person's baseline.
- Impaired function: social, occupational, educational.
- Specific symptoms, at least 5 of these 9, present nearly every day:
 1. Depressed mood or irritable most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
 2. Decreased interest or pleasure in most activities, most of each day
 3. Significant weight change (5%) or change in appetite
 4. Change in sleep: Insomnia or hypersomnia
 5. Change in activity: Psychomotor agitation or retardation
 6. Fatigue or loss of energy
 7. Guilt/worthlessness: Feelings of worthlessness or excessive or inappropriate guilt
 8. Concentration: diminished ability to think or concentrate, or more indecisiveness
 9. Suicidality: Thoughts of death or suicide, or has suicide plan.

Depressive Episode Criteria (may be part of Major Depressive Disorder OR an isolated episode)

A - Criteria

1. Depressed Mood
2. Loss of interest and enjoyment in usual activities
3. Reduced energy and decreased activity

B - Criteria

1. Reduced self-esteem and confidence
2. Ideas of guilt and unworthiness
3. Pessimistic thoughts
4. Disturbed sleep
5. Diminished appetite
6. Ideas of self-harm

Severity of Depressive Episode:

- Mild: > 1 from column A plus 1-2 from column B. Or 5-6 sx but mild in severity and functional impairment.
- Moderate: > 1 from column A plus 2-3 from column B. Or 7 – 8 sx but moderate functional impairment.
- Severe: All 3 from column A plus > 3 from column B. Or fewer sx but any of these: severe functional impairment, psychotic sx, recent suicide attempt, or has specific suicide plan or clear intent.

4.2 Anxiety

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) assesses both depressed mood (seven items) and anxious mood (seven items), and there are several screening questionnaires that can be used to assess anxiety alone—for example, the State-Trait-Anxiety Inventory (STAI) that assesses state anxiety (20 items) and trait anxiety (20 items) (Spielberger et al, 1983). The SCL-90 Symptom Checklist includes a 10-item anxiety subscale among other dimensions of emotional symptoms (Arrindell & Ettema, 2003).

4.3 Pain-related fear

Instruments used to study anxiety and fear responses related to chronic pain are the Pain Anxiety Symptoms Scale (PASS, McCracken et al, 1996), the Fear Avoidance Beliefs Questionnaire (FABQ), the Fear of Pain

Questionnaire (FPQ), and a version of the STAI with variables related to pain severity, perceived disability, and pain behaviour (Spielberger et al, 1983).

4.4 Cognitions

To assess how patients think about their condition the revised Illness Perception Questionnaire (IPQ-r) could be used (Moss-Morris et al, 2002). In addition, the Illness Cognition Questionnaire (ICQ, Eves et al, 2001) assesses three illness cognitions: helplessness as a way of emphasising the aversive meaning of the disease; acceptance as a way to diminish the aversive meaning; and perceived benefits as a way of adding a positive meaning to the disease. To assess pain catastrophizing, the 14-item Pain Catastrophizing Scale can be used (Van Damme et al, 2002). The three factors of this scale are rumination, magnification, and helplessness.

4.4.1 Self-efficacy

To measure self-efficacy, the Arthritis Self-Efficacy Scale (ASES) could be used (Lorig et al, 1989). This 20-item questionnaire assesses self-efficacy in three domains: pain, function, and other arthritis symptoms such as fatigue.

4.5 Coping

To assess how patients are attempting to cope with their condition the Brief COPE (Carver, 1997) could be used (Box 10).

Box 10 Assessment of coping

The brief COPE assesses with 28 items the following 14 coping strategies:

- Self-distraction
- Active coping
- Denial
- Substance use
- Use of emotional support
- Use of instrumental support
- Behavioural disengagement
- Venting
- Positive reframing
- Planning
- Humour
- Acceptance
- Religion
- Self-blame

4.5.1 Coping with pain

Commonly used questionnaires to assess coping with pain are the Coping Strategies Questionnaire (CSQ; Rosenstiel et al, 1983) and the Vanderbilt Multidimensional Pain Coping Inventory that measures 11 coping strategies: problem solving, positive reappraisal, distraction, confrontative coping, distancing or denial, stoicism, use of religion, self-blame, self-isolation, wishful thinking, and disengagement (Smith et al, 1997).

4.5.2 Catastrophizing

Additionally, to the Pain Catastrophizing Scale (van Damme et al, 2002), the 32-item Pain-Related Self-Statements Scale (PRSS; Flor et al, 1993) can be used with the subscales 'active coping' (for example, 'I can handle my pain') and 'catastrophizing' (for example, 'I am a hopeless case').

4.6 Social support

There are many instruments to assess the social resources in the environment of patients. The multidimensional scale of perceived social support includes one social support scale (Zimet et al, 1988). The short form the Social Support Questionnaire measures two dimensions of social support: availability and satisfaction (Sarason et al, 1987). The MOS Social support Survey assesses emotional/informational support, affective support, instrumental support, and positive social interaction (Sherbourne et al, 1991). A negative social attitude towards patients with rheumatic diseases can be assessed with the Illness Invalidation Inventory (3*I) that includes two scales: lack of understanding and discounting (Kool et al, 2010).

4.7 Quality of Life

Four questionnaires are commonly used to assess quality of life in rheumatic diseases (Box 11). Two instruments to assess generic quality of life in rheumatic diseases are the 36-item questionnaire short-form 36 (SF-36) and the 100-item WHO Quality of Life (WHOQoL) questionnaire (Kuyken et al, 1995); a brief 24-item version of this questionnaire has also been developed (Skevington et al, 2004).

Besides generic questionnaires, assessment instruments that are more specific for rheumatic diseases have been developed, such as the 45-item Arthritis Impact Measurement Scales (AIMS; Meenan et al, 1992) and the Health Assessment Questionnaire (HAQ; Fries et al, 1980) and its derivatives (the modified HAQ, clinical HAQ, and multidimensional HAQ).

For some rheumatic disease, specific instruments have been developed. The Fibromyalgia Impact Questionnaire (FIQ-R) measures the impact of FM in the domains of physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and wellbeing (Burckhardt et al, 2009). The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is used to evaluate pain, stiffness and functional limitation in OA (Bellamy et al, 1988).

Box 11 The Dimensions of Quality of Life

Four instruments that are commonly used in rheumatic diseases

The Short-Form 36 (SF-36)

1. Physical functioning
2. Role limitations because of physical problems
3. Bodily pain
4. General health
5. Vitality
6. Social functioning
7. Role limitations because of emotional problems
8. Mental health

WHO Quality of Life (WHOQoL)

1. Physical
2. Psychological
3. Level of independence
4. Social relationships
5. Environment
6. Spirituality/religion/personal beliefs

Arthritis Impact Measurement Scales (AIMS)

1. Mobility
2. Physical activity
3. Dexterity
4. Household activities
5. Activities of daily living
6. Anxiety
7. Depression
8. Social activity
9. Pain

Health Assessment Questionnaire (HAQ)

1. Disability
2. Pain

5. Treatment and Psychological intervention

Most rheumatologists will not have the time or expertise to provide in depth psychological interventions for their patients beyond education and encouragement for self-management and responsibility, they need to be familiar with some of the options available and that may be offered to patients they refer to mental health professionals. Some of the most commonly used psychological interventions and their rationales are outlined below.

5.1 Education

Patient education is designed to help individuals understand the nature of their disease, what to expect, and the importance of their role in the self-management of their disease, symptoms, and life with the disease. Education may include advice about activity and some basic self-management skills. More intensive treatment may go into much more depth and include practice and guidance and not just didactic information.

A systematic review of patient education in RA found significant short-term effects of education on disability, joint counts, patient global assessment, psychological status, and depression, and a trend for pain reduction, but there was little evidence of long-term benefits (Riemsma et al, 2004). Another review found improved knowledge, coping behaviour, compliance, and health effects in the short-term, but only some of the studies showed a positive long-term effect on physical or psychological health (Niedermann et al, 2004). A third review concluded that the summary effect sizes suggested that arthritis education programmes result in small reductions in pain and disability (Warsi et al, 2003). Overall, there is a need to find strategies to enhance the transfer of short-term effects into gains in health status.

5.2 Exercise

Aerobic and strength exercise is a means to improve physical function and mental wellbeing. Patients may avoid exercise because of fear of injury and pain (Vlaeyen & Linton, 2010). In clinical practice, the beliefs of patients about possible negative consequences of physical exercise should be addressed because these may hamper the outcome. Evidence about beneficial effects of physical exercise training for patients with RA, OA, and FM has been accumulating (e.g., Busch et al, 2008; Kettunen & Kujala, 2004; Smidt et al, 2005). Physical exercises are combined with the self-management approaches described below.

5.3 Self-management

It has become increasingly recognised that the bulk of the management of chronic conditions is performed by patients and their families (Newman et al, 2009). The limited contact that healthcare professionals have with individuals with chronic conditions means that a lot of time they are on their own and must learn how to cope with taking the medication, with symptoms such as pain and with consequences such as disability.

Encouraging and supporting people with chronic conditions to take more control of their illness by engaging in self-management behaviours has increasingly become a focus in many health services. One push for this approach is the increasing recognition that with an ageing population and consequent increase in chronic disease, health services must change their treatment model (Hyde 2009).

The term 'self-management' implies that a substantial responsibility is taken by patients; this shift of responsibility from the healthcare professional to the individual for the day-to-day management of their condition is achieved by providing information and skills to the participants (Newman et al, 2001, 2004).

Self-management interventions such as CBT (described below) have been shown to be effective in improving coping strategies and reducing the emotional challenges of the disease (Parker & Hart, 2009). Reviews have reported the beneficial effects of self-management interventions on pain, disability, and psychological well-being, over and above effects already being obtained from medication (Newman et al, 2001).

Probably better outcomes could be obtained when more attention is devoted to the content of widely heterogeneous self-management programmes, how they are delivered, the study design, and the attitudes and beliefs of the participants (Newman et al, 2004).

5.3.1 Lay-led self-management

A widely known self-management intervention is the Arthritis Self-Management Programme (ASMP, Barlow et al, 2000). This community-based group programme, led by lay people who themselves are patients, teaches a variety of skills and aims to enhance participants' self-efficacy to deal with their condition. In patients with RA and OA, the ASMP led to positive outcomes with respect to a range of health behaviours (e.g., cognitive symptom management, communication with physicians, dietary habit, exercise, and relaxation) and depression, whereas a trend towards decreases in fatigue and anxiety were noted (Barlow et al, 2000). The findings suggest that the ASMP is effective in promoting improvements in perception of control, health behaviours, and health status, when delivered in UK settings.

A review summarized that lay-led self-management education programmes may lead to small, short-term improvements in participants' self-efficacy, self-rated health, cognitive-symptom management, and frequency of aerobic exercise but that there is currently no evidence to suggest that such programmes improve psychological health, symptoms or health-related quality of life, or healthcare use (Foster et al, 2007).

5.4 Operant-behavioural interventions

The aims of Operant Behavioural Therapy (predicated on principles of operant conditioning see Table 1) are to both reduce pain behaviours, and teach healthy and assertive pain-incompatible behaviours. To achieve these aims, several operant learning strategies are used, such as the contingent positive reinforcement of pain-incompatible behaviour and reduced or absent positive reinforcement of pain behaviours, time-contingent intake and reduction of medication, increased bodily activity, reduction of interference of pain with activities, reduction of pain behaviours, and training in assertive pain-incompatible behaviours. Active participation of significant others is necessary since these important partners will learn to reinforce healthy pain-incompatible behaviours of the patient. The reduction of pain behaviours postulates the insight of both patient and spouse

to distinguish between subconscious “unhealthy” pain behaviours and conscious healthy behaviours. Although a treatment in its own right, physical exercise is an essential part of an operant learning program for training of motor perception, increasing personal physical activities and reducing avoidance behaviour, intake of medication, and excessive solicitous spouse behaviour (Thieme et al, 2003, 2006).

5.5 Cognitive–behavioural interventions

5.5.1 CBT and Treatment of Anxiety

There is growing evidence that CBT is effective in reducing anxiety in patients with rheumatic disease. A meta-analytic review indicated that cognitive-behavioural interventions focused on changing negative cognitions and increasing physical activity levels, is beneficial for many patients with RA (Knittle et al, 2010). In rheumatic diseases, CBT typically involves some combination of cognitive restructuring, behavioural interventions (e.g., increasing physical activity, relaxation), and stress management, and it is mostly delivered in 10 to 20 one hour sessions taking place weekly or once every two weeks by trained clinical psychologists (psychotherapists), nurses, or social workers.

5.5.2 CBT and Treatment of Patients with Depression

Many patients with milder depression respond to interventions such as exercise or guided self-help. Although many improve while being monitored without intervention, structured therapies, such as problem-solving, brief cognitive-behavioural therapy (CBT, Box 12), or counselling can be helpful. Antidepressant drugs and long-term psychological therapies can intensify the treatment. An excerpt from the NICE recommendations are provided in Box 12.

Box 13 NICE treatment guidelines - mild depression

For a significant number of people with mild to moderate depression, brief interventions delivered by the primary care team are effective; for others—particularly if they have not responded to the initial brief intervention—more complex interventions, which could be provided in primary or secondary care, are required.

Many patients with milder depression respond to interventions such as exercise or guided self-help, although many improve while being monitored without additional help. More structured therapies, such as problem solving, brief cognitive–behavioural therapy (CBT) or counselling, can be helpful. Antidepressant drugs and psychological therapies, such as long-term CBT or interpersonal psychotherapy (IPT), are not recommended as an initial treatment; these may be offered when simpler methods (for example, guided self-help or exercise) have failed to produce an adequate response.

General measures that can help some patients with mild depression

1. Sleep hygiene and anxiety management.
2. Watchful waiting. For patients who do not want an intervention or who may recover with no intervention, a further assessment should be arranged, normally within 2 weeks.

3. Physical exercise. Structured and supervised physical exercise may help.

4. Guided self-help programmes based on CBT. Appropriate written materials could be provided with limited support from a healthcare professional, who typically introduces the self-help programme and reviews progress and outcome.

Reprinted with permission from: Guidelines for the evaluation and treatment of depression of the National Institute for Health and Clinical Excellence (NICE): <http://www.nice.org.uk/Guidance/CG23#documents>.

Box 12 Cognitive-behavioural therapy (CBT)

A main premise of CBT is that negative, dysfunctional thought processes have a perpetuating role in health problems. The intervention is directed at reduction of symptoms like depression, anxiety and pain and physiological responses through the manipulation of thoughts and behaviour; examples are interventions with one specific aim—for example, relaxation, stress reduction or overcoming of fear-avoidance beliefs to support an exercise intervention and, more commonly, the incorporation of various methods—for example, cognitive restructuring of dysfunctional beliefs or ‘worry’ thoughts, pain coping skills training, activity pacing, stress management training, relaxation exercises, exposure to anxious situations, thoughts and worries, and positive self-talk.

In moderate to severe depression, antidepressants are the mainstay of therapy, preferably in combination with some form of psychotherapy. For several decades, tricyclic antidepressants were the first-line treatment of depression. Nowadays, antidepressant drugs of choice are, in the first instance, serotonin reuptake inhibitors (Ebmeier et al, 2006). To date, no published comparative study of the newer antidepressants such as those aimed at inhibition of the reuptake of serotonin and norepinephrine (noradrenaline) (SNRIs) has enrolled a large enough group of patients to have the power to detect reliably the differences between two effective treatments (Lieberman et al, 2005). Because pro-inflammatory cytokines may promote depression, the blockade of pro-inflammatory cytokines with biologicals such as infliximab, etanercept or adalimumab may turn out to be a new therapy for depression in RA (Fuggle et al, 2014; Rech et al, 2013).

The psychological treatment of depression will vary depending on its severity. Combined treatment involving medication and evidence based psychotherapy typically provides a modest increment over either single treatment alone (Hollon et al, 2002). In both severe and mild depression, to prevent relapse or recurrence, a clinical psychologist may offer CBT or interpersonal psychotherapy (IPT) (Anderson et al 2000; Ebmeier et al, 2006; Hollon et al, 2002). A main premise of CBT is that negative, dysfunctional thought processes have a perpetuating role in depression, whereas IPT is based on the premise that depression occurs in a social and interpersonal context. Review studies indicate greater long-term effectiveness of CBT over tricyclic antidepressants alone. CBT is a mainstay approach to depression (Ebmeier et al, 2006; Feldman, 2007; Kuyken et al, 2007). The capacity to reduce relapse risk after stopping pharmacological interventions is considered one of the major benefits provided by cognitive and behavioural interventions with respect to the treatment of

depression and anxiety disorders (Hollon et al, 2006). Outcomes for IPT are broadly like the outcomes of CBT (Ebmeier et al, 2006).

5.5.3 CBT and Treatment of Pain and Disability

Reviews of cognitive–behavioural interventions concluded that, over the past decade, controlled research has continued to provide support for the efficacy of psychosocial interventions for OA and RA (Astin et al, 2002, Keefe et al, 2002, Morley et al, 1999, 2011). Research has revealed beneficial effects across a number of arthritis outcomes, including pain management, diminished psychological distress, improved marital adjustment, and reduced disease-related symptoms such as joint swelling and fatigue. Patients with shorter disease duration show higher effects from CBT (Astin, et al 2002).

CBT has been included as a treatment option in the case of FM with moderate to large effects (Carville et al, 2008; Hauser et al, 2010; see Box 12), perhaps most in highly distressed patients (Van Koulil et al, 2010, Thieme et al, 2007). A meta-analysis examined the efficacy of randomised controlled trials of cognitive–behavioural interventions in the treatment of RA (Astin et al, 2002). Significant effect sizes (Box 14) were found post-intervention for pain (0.22), functional disability (0.27), psychological status (0.15), coping (0.46), and self-efficacy (0.35). At follow-up (averaging 8.5 months, significant pooled effect sizes were observed for tender joints (0.33), psychological status (0.30), and coping (0.52). Overall, the findings suggested that psychological interventions may be important adjunctive therapies in the management of RA; perhaps the most for patients who have had the illness for shorter duration.

Box 14 Quantifying the effects of therapy: effect size

In a randomised controlled trial, researchers are not only interested in the significance of effects, but also in the magnitude of effects. A commonly used statistic to express the magnitude of effects is the effects size, or *d* statistic. It expresses the difference between groups (for example, the experimental and control group) in standard deviation units. A *d* of 0.30 means that the difference between two groups is 0.30 standard deviation. To interpret the magnitude of effect sizes, the criteria proposed by Cohen (1988) are commonly used:

Small difference: $d = -0.20$ or $d = 0.20$

Moderate difference: $d = -0.50$ or $d = 0.50$

Large difference: $d = -0.80$ or $d = 0.80$

5.5.4 Acceptance and Commitment Therapy (ACT)

Although, the restructuring of cognitions and behaviour is a fruitful approach to help patients to deal with situations that can be changed, the acceptance of the inevitable consequences of the disease should be part of patients' coping repertoire to deal with situations that cannot be changed. In recent years, Acceptance and Commitment Therapy (ACT; Hayes et al, 2006), a variant of traditional CBT, been applied in the treatment of mental problems that may accompany chronic somatic diseases (including several rheumatic diseases). This

therapy helps patients to accept the difficulties that come with a chronic disease and to be committed to make changes in daily life that are in agreements with one's life values.

ACT is an example of a mindfulness based stress reduction (MBSR) therapy. Mindfulness based interventions focus on becoming aware and accepting all thoughts, feelings, and sensations instead of trying to avoid or fight them. Recent reviews have found significant, small to moderate effects of MBSR on psychological distress, pain and coping behaviour (Bohlmeijer et al, 2010; Merkes, 2010; Veehof et al, 2011). Integrating MBSR in CBT may enhance the efficacy of mindfulness-based interventions (Bohlmeijer et al, 2010). A randomized controlled trial examined the effects of a mindfulness-based group intervention in adults with inflammatory rheumatic diseases (Zangi et al, 2012). Significant better improvements in the experimental group as compared to the control group were found in psychological distress, self-efficacy, emotion-focused coping, fatigue, self-care ability, and overall well-being at post-treatment and maintained at 12 months' follow-up. However, there do not appear to be any studies demonstrating that ACT has any better outcomes when compared to CBT in general (Wetherell et al, 2011). An important question that remains is identifying those patients who are most likely to respond to any of the variants of CBT and other psychosocial treatments (Vlaeyen & Morley, 2005).

6. Adherence/Compliance

For any treatment to be effective (pharmacological or nonpharmacological), patients have to adhere to the requirements, in the absence of cure, patients may have to adhere to treatment recommendations for many years.

Adherence to medication and to other aspects of recommended treatment such as exercise are essential for optimising health and well-being in rheumatic disease. A meta-analysis of 22 studies in arthritis found a mean adherence to medication of 81% (95% CI 72% to 89%, DiMatteo, 2004). Non-adherence to medication may be unintentional—for example, misunderstanding the correct dose to take or forgetting to take it—or it may be intentional—for example, not completing a course of medication once the patient feels better. Psychological factors have been found to have an influence on adherence—for example, the beliefs people hold about their illness and treatment have been shown to influence how well they follow advice. These beliefs are formed not only by the information received from healthcare professionals but may also be influenced by the person's own experience of the illness and by the views of other people and the media. Beliefs about the necessity of medication and concerns about the medication itself have been shown to be important (Horne & Weisman, 1999). For example, concerns expressed about medication have been found to be greater in patients with RA who are non-adherent than in those who are adherent (Neame & Hammond, 2005). Better adherence was also predicted by a stronger belief in the necessity of medication and belief that medications are not overused (Treharne et al, 2004). As predicted by the Perceptual-Cognitive Model of Self-Regulation, expanded from the

Common Sense Self-Regulatory Model (Box 4), cognitive and emotional representations of illness are hypothesized to affect adherence. Although this has not been examined in rheumatic diseases, a study in individuals with asthma revealed that beliefs about antecedent causes and about cure-control predicted current adherence and beliefs about the duration of one's asthma predicted intention to adhere in the future (Jessop & Rutter, 2003).

Depression is also an important risk factor for non-adherence. In a meta-analysis, non-adherence was shown to be three times greater in depressed than in non-depressed patients (DiMatteo et al, 2000). The authors of the meta-analysis proposed that this might arise because the sense of hopelessness that typifies depression is likely to influence beliefs about the value of taking medication. Furthermore, people who are depressed often withdraw from those who could provide support, and this in turn may have a negative impact on adherence. The cognitive deterioration which often accompanies depression could also lead to difficulties in adhering to what is often a complex medication regimen.

Discontinuation of medication was examined in 68 patients with RA starting their first DMARD treatment (Wong & Mulherin, 2007). Contrary to the study authors' expectations, discontinuation of the drug within the first year was more likely in older and less anxious patients. Other hypothesised predictor variables, such as depression, relationship with hospital doctors, social support and beliefs about medication did not significantly improve the prediction.

Listening to what a patient really wants will also promote adherence. A principal condition for behaviour change is that one is motivated to change. Self-determination Theory (Ryan & Deci, 2000) emphasizes the importance of keeping therapeutic goals close to the autonomous motivation of people. A behaviour is autonomous when a patient conceives a meaningful rationale for change, values the behaviour, and aligns it with other central values and lifestyle patterns. A common technique aimed at finding motivated behaviour originating from one's own values is motivational interviewing. Another important aspect of autonomy is to work with individualized goals. Therapeutic effects are expected to be better when patients verbalize and strive for their own goals on various domains (i.e., personal care, housekeeping, work/study, hobbies, social, physical activities, and other) and reaching these goals should be rewarding and satisfying. To support intentions to change behaviours and actually fulfil intentions, action plans will help. Action plans detail what specific behaviours will be conducted where, when, and with whom.

6.1. Assessment of Adherence

Adherence can be assessed by several different methods, none of which is without problems. These include pill counts, physiological markers, electronic monitors, and self-report methods. A review concluded that there only slightly higher estimates of adherence were found with self-report than with pill counts (DiMatteo, 2004).

The 19 items Compliance Questionnaire for Rheumatology (CQR, de Klerk et al, 1999) is the only self-report adherence measure created specifically for and validated in rheumatic diseases. A five items version has been found to identify 69 % of low adherers to DMARDS (Hughes et al, 2013). Other self-report measures of medication adherence include the six-item Simplified Medication Adherence Questionnaire (SMAQ; Knobel et al, 2002) and the Brief Medication Questionnaire (BMQ; Svarstad et al, 1999).

6.2 Improving adherence to medication and treatment recommendations

There have been few interventions designed specifically to improve medication adherence in patients with rheumatic diseases (Elliott, 2008). Most interventions have been based on patient education and the teaching of self-management techniques. The effect of group therapy and CBT on medicine adherence is not clear. Those interventions that are effective tend to emphasise developing a daily routine of self-management activities, coping strategies, self-efficacy, and problem solving. It appears that adherence to supervised classes and treatments provided on a one-to-one basis is larger than adherence to home programmes (Kettunen & Kujala, 2004). Research is required to develop evidence-based, pragmatic, patient-centred interventions to improve medication adherence in patients with RA. Practitioners require support and training in the communication of risk and incorporation of patients' beliefs into the consultation process.

7 Daily rheumatology practice

Without doubt, the first task of the rheumatologist is to treat the patient throughout the rheumatic disease process. However, it is important in attempting to achieve overall care for patients that the rheumatologist also has an open mind with respect to the psychosocial aspects of the diseases. The disease process will have psychosocial consequences and psychosocial variables may impact the symptoms and the disease process (Figure 1).

Recognising that patients are experts on their lives and the pressures they have emphasises the importance of listening well to the patient and of assessing whether the patient needs additional psychological care. An educational brochure may help some patients, whereas others will need additional professional help such as CBT or assistance and advice with managing the condition. When patients have a mild form of depressive mood, the motivation to pursue quality-of-life goals may be hampered. The rheumatologist should encourage the patient to pursue these quality-of-life goals and should, during subsequent consultations, check whether the patient was able to pursue them.

Even when the mood or behaviour does not appear to be pathologically disturbed, there may be a psychological impact on the disease process because the patient does not adhere to the prescribed medication or is reluctant to go to the rheumatologist when they have an exacerbation. The mood of the patient may affect pain, physical disability, and the number of tender joints. The physician should be aware that

psychological variables may impact the assessment of disease activity because of subjective judgments of health and tender joints or of commonly used disease activity indices.

Rheumatologists often ask in which way they could help patients with their psychosocial problems. They could help by broadening the consultation to assess more clearly the psychosocial impact of the condition, and by attempting to determine whether their patients need the professional help of a psychologist. It is important, however, to recognise that for all patients the rheumatic disease process is a threat to their psychosocial wellbeing, but that not all of these patients will need professional help. Descriptive, correlational and prospective research has shown the characteristics of patients who are doing relatively well. Moreover, clinical experimental research showed what kind of psychological changes brought about an improved outcome. Based on these sources, advice could be given to the patient, such as the encouragement to think positively.

Exercise is important and long-term adherence can be expected when exercise becomes a pleasurable activity. Second, put effort into achieving quality-of-life goals. Pain hampers quality of life. It is important to perform activities that bring back some joy in life. Third, pursue attainable goals. It is useless to ruminate about activities that are not possible because of the pain or disability. Accomplishing attainable goals may bring back a sense of control. Seize the hour when enjoying the whole day is difficult. Fourth, it is reasonable, and one should expect, to be sad occasionally. It is impossible to be happy all the time. Momentary sadness is understandable and acceptable, but the symptoms of the disease should not lead to chronic sadness and helplessness. Negative, dysfunctional beliefs that hamper the pursuit of these four recommendations should be managed first.

SUMMARY POINTS

- Clinicians should not only attend to the medical/physical dimension but also to the psychosocial and behavioural dimensions of rheumatic diseases for at least four reasons. First, the rheumatic disease process will have an impact on symptoms, well-being, and functioning. Second, physiological (e.g., hormones), psychological (e.g., strategies to cope with problems), and social (e.g., support) variables will also have an impact on symptoms, wellbeing, and function. Third, these physiological, psychological, and social variables may have an impact on the rheumatic disease process. Fourth, comprehensive care of patients necessitates looking beyond the treatment of the disease alone.
- People with rheumatic diseases report a lower quality of life. Physical quality of life is especially severely impaired. Although the impact on mental quality of life is less severe, the prevalence of anxiety and depression is higher than normal.
- Rheumatologists should screen for depression and anxiety in their regular clinical interview by asking whether the patient, during the previous month, has often been bothered by feeling down, depressed or hopeless and by having little interest or pleasure in doing things. What are their worries going forward?



- It is important to know how people feel about their condition and how they cope with it. Associating many symptoms with their condition (illness identity), beliefs in a long duration of illness and in more severe consequences of the disease, as well as a passive way of coping (exerting little control to manage the problem), are associated with worse disease-specific measures of functioning and general role and social functioning. Coping by seeking social support and beliefs in controllability and curability of the disease are related to better functioning.
- The interference of symptoms such as pain and fatigue with activities of daily living is important and in part accounted for by catastrophizing (excessively focusing on symptoms, thinking that something serious might happen, the helpless perception of not being able to cope with the situation), fear of pain, guarding, and control beliefs.
- Pain-related fear and avoidance of physical exercise are essential features of the development of physical disability for a substantial number of patients with musculoskeletal pain. An accumulating number of studies have shown that (graded) physical exercise is an effective means to improve physical function and mental wellbeing.
- Recognition of the role of social factors and social support is important. Social support—receiving emotional and instrumental help from others—is generally found to be beneficial to mental and physical health and it may blunt the harmful impact of stressors of the disease such as pain. Inappropriate and overprotective support is associated with reduced wellbeing and functioning.
- Many brief self-report questionnaires are available to screen patients for disturbances (depression, anxiety) as well as to gain a greater understanding of a patient's cognitions and behaviours. Examples of cognitions are fear avoidance beliefs, attributions about the supposed origin of the disease (somatic or behavioural), beliefs about the prognosis, perceived helplessness, acceptance and benefits and self-efficacy beliefs. Examples of coping behaviour are self-distraction, active coping, behavioural disengagement and expressing emotions.
- Several psychological interventions are available to help patients manage their illness. Patient education leads to improved knowledge and it generally leads to short term improvement of physical and psychological health, whereas long term changes in health status are not convincingly demonstrated. Self-management interventions have been shown to be effective in improving coping strategies and reducing the emotional challenges of the disease. Beneficial effects of self-management interventions on pain, disability, and psychological well-being have been reported over and above effects already obtained with medication. Cognitive-behavioural interventions have been shown to be effective in dealing with other adverse consequences of the disease such as pain and as a long-term treatment against depression. Aerobic and strength exercise is a means to improve physical function and mental well-being. To achieve long-term benefits of physical exercise training, adherence is important, which is better in the case of supervised treatment than in the case of home exercise programmes.
- In daily clinical practice, the patient should be encouraged to enjoy physical exercise, to pursue attainable quality-of-life goals, and to allow one to be sad occasionally. Negative, dysfunctional beliefs that hamper the pursuit of these four recommendations should be assessed and managed first—for example, in self-management interventions or cognitive-behavioural therapy.
- Information, exercise, and cognitive-behavioural treatments combined with appropriate medications may be the most effective treatment approach for patients with rheumatic diseases

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module

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IN-DEPTH DISCUSSION I

Provider-patient relations in rheumatology

The doctor-patient relationship is a cornerstone of medical practice. Communication skills are essential in the assessment of symptoms and determining diagnoses. Research over the past twenty years has documented that communication skills have a significant impact on patient satisfaction, adherence to treatment regimes, and health.

1. Lack of concordance between doctor and patient – The importance of the patient perspective

A number of studies have shown a lack of concordance between doctors and patients. In an American study of rheumatology patients, mostly with rheumatoid arthritis (RA), several differences were observed between patients' and physicians' ratings for pain and other health indicators. On average, physicians rated their patients' health status higher than the patients themselves [1].

There are also large variations in the concordance between the actual priorities of the patients and the health care providers' perceptions of what patients find to be important. One study found a relatively high concordance on the significance of pain, but much less concordance regarding the importance to patients of psychological factors [2]. Patients express strong needs to have some control over their disease and life situation. This was rated much more important by patients than most doctors had anticipated.

These findings highlight the importance of understanding the patient's perspective. Several studies have shown that it is important for patients to be considered as persons, not only as carriers of symptoms [3]. Clinicians should include questions on patients' own thoughts, worries, attributions, and priorities in clinical interviews. A number of studies have shown that such questions are often absent in medical consultations, which may be an explanation of the lack of concordance between doctors' and patients' views [e.g. 4].

The inherent invisibility of symptoms such as pain, fatigue, and stiffness challenges the clinician-patient relation and emphasizes the importance of attending to the patient perspective in the consultation, because the provider has to rely on patient self-report to make an appraisal of the severity of symptoms. The lack of objective evidence, uncertainty about symptoms, make it difficult to assess patient's health status in conditions such as, fibromyalgia.

2. Topics may be missed in the consultation

The differences between provider and patient on the understanding of priorities may have as a consequence that certain topics of importance for the patient may be missed in the consultation.

Sensitive topics such as emotional concerns are often only hinted to by patients [5]. In one study of RA patients, less than 20% of patients with moderately severe to severe symptoms of depression spontaneously raised their feelings of depression during their medical visits in a rheumatology clinic and was rarely initiated

by physicians themselves [6]. Similarly, in a study of how RA patients and providers communicated about fatigue the investigators found that while 72% of patients were worried about fatigue, patients more often used implicit cues instead of explicit mention when talking about fatigue. Fatigue was discussed in fewer than half of consultations with physicians, but in 4 of 5 consultations with nurses. In general patients were more satisfied with the nurse specialist's attention to fatigue than with the attention they received from their rheumatologist [7].

3. Premature reassurance

Communicating a positive and optimistic attitude may function well in a medical consultation. But a premature reassurance that all is well is not warranted. In an interview study of patients with rheumatic diseases patients reported that physicians often assured them that the disease was not so severe and that available treatments would be effective. When physicians told RA patients that they had a mild variety of the disease, patients tended to interpret the assurances of the doctor in light of their own understanding of their disease [7]. In general, the assurance from the doctor that the disease was benign lead to uncertainty or anxiety and did not have the intended consequence of providing confidence about the course of the disease. Those patients that had been given the opportunity to disclose their concerns and to be met empathically by the doctor felt the most relieved [8]. Empathic communication, characterized by sensitivity to patient concerns have in several studies been associated with increased patient satisfaction and reduced psychological distress.

4. Involvement of the patient in decisions

There is relatively little research on decision making in rheumatology. Generally, it appears that there is large variation in patients' preferences for taking part in medical decisions. In a study of Japanese RA patients there were significant relationships between active patient participation in the consultation, positive attitude to shared decision making, and a feeling of being understood by the physician [9]. Clinicians should take the opportunity to involve patients in the “negotiations” about treatment options to promote more active patient participation, acceptance, and adherence to recommendations. Patient verbal and nonverbal communications (i.e., pain behaviours, expressions of pain distress, and suffering) are significant sign for the impact of positive and negative reinforcement (i.e., operant learning) on pain. The rheumatologist can use strategies described in Box 1 to in efforts to decrease pain behaviours and increase healthy behaviours such as physical functioning and pacing of activities.

Box 1. Strategies to decrease pain behaviours and increase healthy, adaptive behaviours

- Explanation of pain behaviours, what they communicate, and how they can contribute to increased disability
- Explanation of the development of pain behaviours – the role of attention and responses by significant others to behaviour
- List of Pain Behaviours and Healthy Behaviours

The rheumatologists can explain what pain behaviours are, how they develop, and how they are maintained. He or she can raise the question of how the patients' significant other is aware of their pain, increase in pain, and their distress. Patients can be asked about how their significant others respond to them and how they feel about the responses they receive. Analogies can be used to illustrate the role of reinforcement in maintaining behaviours by using examples of how children or pets learn to engage in various behaviours. .

Box 2. Strategies to eliminate stress-increasing cognitions and to increase adaptive coping

- Explanation of the interaction between stress and pain as circular and vicious
- Explanation of the development of stress- and anxiety-evoking cognitions
- List of stress- and anxiety evoking cognitions in contrast to healthy, stress- and anxiety reducing cognitions
- Protocol of healthy cognitions, emotions and behaviour

Maladaptive cognitions (thoughts and processes) such as catastrophizing (e.g. "I will get more and more disabled and dependent on others", "I can't go on"), helplessness (e.g., "There is nothing I can do to reduce my pain and fatigue"), fear-related cognitions (e.g., "If I am active I may increase may cause damage to my joints and make my pain worse." provoke high levels of affective distress. The rheumatologist can use the cognitive-behavioural approach and explain the vicious cycle of "Stress-Tension-Pain" (see box 2) to help the patient become aware of how their own cognitions and feelings interact and can lead to greater inactivity and isolation. In collaboration with a psychological pain therapist, the rheumatologist can help the patient to create a list with stressful thoughts (e.g., Things I cannot do) and with thoughts for stress relief (e.g. When I breathe quietly, can reduce my feeling of helpless and distress.). Once practiced, the patient can apply that approach to thoughts of helplessness and catastrophizing to replace them by thoughts of active coping (e.g., "When I am relaxed then I can distract myself from pain.", "Despite my RA, there are many things I can still do to enjoy life.") The rheumatologist can make the patient aware to take responsibility of her/his own cognitions aiming on adaptive coping.

Both the operant and the cognitive-behavioural approaches can be used by the rheumatologist to improve communications with the patient, to reduce stress, to increase treatment effectiveness and patient adherence to recommendations by including the patient as a partner in the medical management and self-management of the patient's disease.

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IN-DEPTH DISCUSSION II

Psychological management of pain

Pain, a common consequence of most rheumatic diseases, the perception of the intensity and impact of pain is determined for each individual by their prior history, current emotional and cognitive state, contextual factors (financial resources, physical environment, and social support) in combination with physical pathology related to the disease itself. When pain persists, psychological processes evolve over the course of the disease and impact physiological processes as well as the adjustment to the disease over time (Figure 1). Thus, it is important to think of chronic diseases longitudinally and there will be changes throughout the course of the disease. The non-pharmacological management of chronic pain as an adjunct to standard pharmacological care is increasingly common. Its contents are listed in Table 1. The targets, outcomes and practice recommendations are discussed.

Figure 1. Factors that contribute to pain. Somatic and psychological inputs affect neural structures that lead to the perception of pain that will have behavioural consequences. The perception of pain involves sensory, affective, and cognitive components (after [19]).

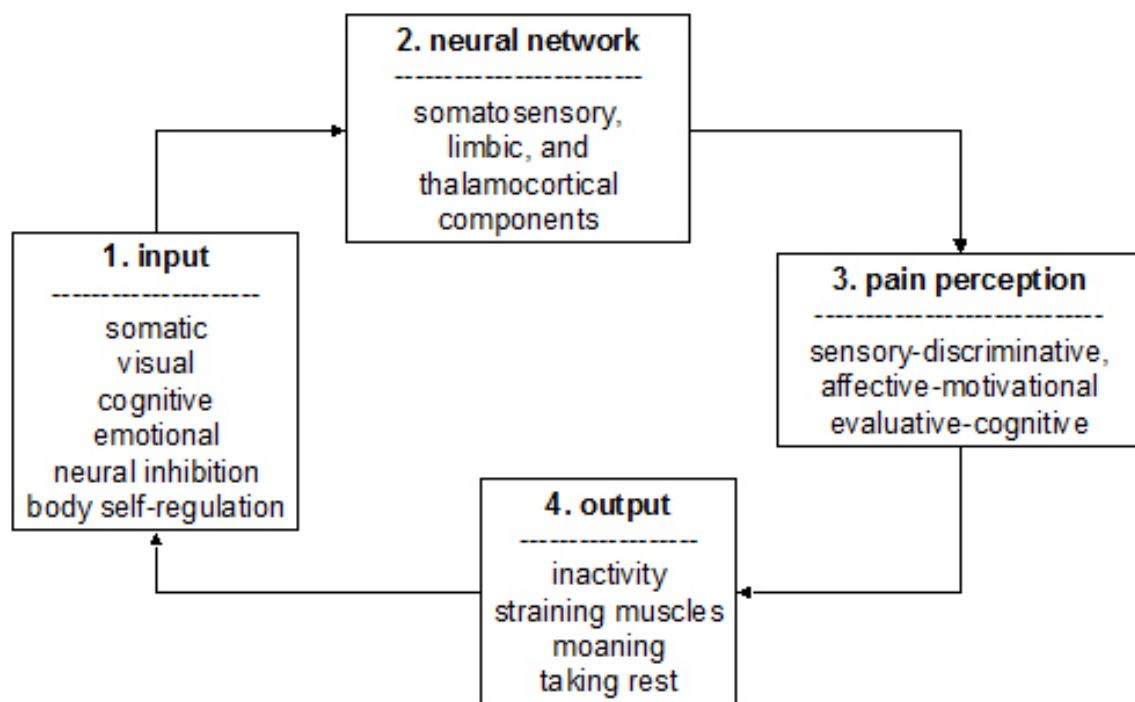


Table 1 Non pharmacological management of pain and its consequences

Patient education refers to any set of planned educational activities designed to reduce pain and its consequences. Education activities directed at the management of pain may involve such varied topics as information about the conditions, encouragement of physical exercise and feasible activities that promote the quality of life, relaxation techniques, physical exercise practices or schemes, the pacing of activities, coping advice, information directed at the importance of social support, decreasing negative, helpless thoughts, and a focus on symptoms, and increase of cognitive symptom management through distraction or guided imagery (e.g., [21]).

Physical exercise training is directed at a gradual build-up of endurance; examples are aerobic exercise training such as indoor or outdoor walking, cycling or aerobic dance, hydrotherapy such as aqua jogging, and strength training (e.g., [3]).

Cognitive behavioural therapy is directed at reduction of pain and physiological responses through the manipulation of maladaptive thoughts, feelings, and behaviour; examples are interventions with one specific aim, e.g., problem-solving, relaxation, stress reduction, or overcoming of fear-avoidance beliefs to support an exercise intervention and, more commonly, the incorporation of various methods, e.g., cognitive restructuring, pain coping skills training, activity pacing, stress management training, relaxation exercises [11, 20].

Education

Education provided to patients about the nature of their disease, treatment options, what to expect, and their responsibilities in self-management are essential to help patients with chronic diseases.

Meta-analyses suggest that on average, educational self-management programs result in a small improvement in pain and disability in rheumatoid arthritis (RA) [14-16]. Meta-analysis of a small number of studies suggests a moderate improvement in these variables in osteoarthritis (OA) [16]. Self-management programs have as yet not been systematically evaluated in fibromyalgia (FM) [3].

A rapidly advancing new feature of education and self-management programs is the use of the internet. This reduces the possibility to systematically evaluate interventions as determining access and outcomes is difficult but it is possible through the Internet to reach many people and for patients to obtain readily available relevant knowledge and in some cases support without much effort or cost.

Physical exercise training

Both inflammation and pain promote inactivity. In the short-term reduction in activity may be reasonable; however, over time reduction in physical activity may lead to physical deconditioning and greater disability. Only a few decades ago, the common recommendation given to patients with chronic inflammatory diseases was to rest. This recommendation has changed dramatically. Nowadays, mild or moderate exercise tailored to the abilities of the patient and severity of the disease is recommended because it leads to better well-being

and functioning. In RA, physical exercise training may improve functional ability without detrimental effects for disease activity, except possibly in patients with considerable joint damage [1].

In FM, mild physical exercise training is recommended as one of the primary interventions [2]. There is growing evidence for positive changes in global well-being, physical function and pain after supervised aerobic exercise training in FM [2-5]. Most sedentary patients with FM are able to manage low-to-moderate-intensity exercise, and positive effects for symptoms and overall functioning have been observed, although high-intensity exercise should be undertaken with care [4].

The increasing number of evaluations that report a positive outcome of such interventions may be due to the lower intensity of the more recent interventions. From a psychological point of view, stopping exercise after an increase in pain (the principle of 'no pain, no gain') results in the concept of 'stopping exercise permanently' being reinforced. It is only, when exercise becomes a pleasurable activity for the patient that long-term adherence can be expected.

High levels of noncompliance with recommendations and drop-out from treatment are common. Possible reasons for drop-out from exercise may include exercise of too high an intensity or too long a duration, too high muscle tension during exercises, an increase of pain on exercise, fear of injury or amplification of pain, and finding repetitive exercise boring. In clinical practice, it is particularly important to attend to the patient's mood and beliefs that may obstruct physical exercise, such as fear of joint or muscle damage or the belief that resting is the best therapy. It is important to listen to and address patients' concerns and make efforts to increase motivation (e.g., persisting with exercise will prevent greater disability; reduction in activity will increase isolation, exercising can actually reduce pain even if initially there may be some increase)

Cognitive-behavioural therapy (CBT)

More severe pain and poorer adjustment to pain have been associated with psychological factors such as catastrophising thoughts, pain-related fear, helplessness, and avoidant coping. In contrast, decreased pain and improved adjustment to pain have been associated with patients' perceived self-efficacy, perception of control, active coping, readiness to change, and acceptance of the chronic disease state [6, 7].

Studies have suggested that cognitive-behavioural interventions may be an adjunctive therapy in the management of rheumatic diseases, but the outcome appears to be dependent on the individual characteristics of the patients. The exact factors involved have not been fully clarified in research.

Meta-analysis of randomised controlled trials in RA showed, on average, a small but significant effect size on pain and functional ability over and above the effects of standard medical care [8-10]. In FM, CBT has not uniformly been shown to be effective [3, 11] but a meta-analysis [12] and a recent intervention [22] suggests that it is on average more effective in reducing symptoms than pharmacological treatment alone.

Individuals differ substantially in their adjustment strategy to pain as well as in their response to treatment. Better results for CBT alone or in combination with physical exercise training are to be expected when interventions are customized to the needs, interests, and abilities of individual patients [7, 11]. A better outcome was observed in patients who on baseline questionnaires were described as 'Dysfunctional', i.e. who had high levels of pain severity, pain interference, psychological distress and lower levels of activity as compared to patients who reported interpersonal problems and patients characterized by an adaptive coping style [13]. Apparently, the CBT that was offered hardly addressed interpersonal problems and provided little room for improving the already adjusted cognitions and behaviour of adaptive copers.

Discussion & the future of pain management

Special attention needs to be paid to the maintenance of what has been learned and to the longer-term integration of exercise and coping into everyday life to maintain improvements after from physical exercise programs and CBT.

In diseases associated with chronic pain, attention needs to be devoted to patients' crucial beliefs and coping strategies that have the capacity to explain the effect on pain of exercise training and cognitive-behavioural interventions. Attention also needs to be directed to the relative intensity of physical exercise that is required in order to reduce pain and improve functioning and well-being.

Prescription

Four simple recommendations for the psychological management of pain could be derived from correlational and clinical experimental research. *First* - Appreciate the importance of exercise. Exercise is important and long-term adherence can be expected when exercise becomes a pleasurable activity. *Second* - *invest time in maintaining and improving quality of life*. Pain hampers quality of life. It is important to perform activities that bring back some joy in life. *Third* - *pursue attainable goals*. It is useless to ruminate about activities that are not possible because of the pain. Accomplishing attainable goals may bring back a sense of control. *Fourth* - *it is allowed to be sad once in a while*. It is impossible to be happy all the time. Momentary sadness is understandable and acceptable but pain need not lead to chronic sadness and helplessness. Negative, dysfunctional beliefs that hamper the pursuit of these four recommendations should be managed first. *Fifth* – Communicate appropriately and openly with health care providers and significant others such as family members. These individuals can be tremendous source of support as you learn to live effectively despite your disease [23].

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LEARNING OUTCOMES

- ➔ **Select the most appropriate imaging investigation for assessing a patient with a particular musculoskeletal symptom or rheumatic disease**
- ➔ **Describe and explain the technical aspects of performing different imaging investigations**
- ➔ **Choose the best views, joints to scan and methods of assessment in order to achieve optimum image acquisition and maximal information for a particular purpose**
- ➔ **Compare and contrast the potential strengths and weaknesses of each imaging modality**
- ➔ **Critically evaluate the evidence base for each imaging technique in different musculoskeletal diseases**
- ➔ **Recognise the different pathological manifestations of rheumatic diseases and how these are visualised with the various imaging modalities**

Over the last 15 years, imaging techniques such as ultrasonography (US), magnetic resonance imaging (MRI) computed tomography (CT) but also conventional radiography (CR) have experienced considerable technical improvements. In rheumatology, in particular the advancements within US and MRI have permitted a better understanding of the pathogenesis of several pathologies such as psoriatic arthritis (PsA) and spondyloarthritis (SpA), and better management of rheumatoid arthritis (RA) thanks to their capability to visualize early signs of joint involvement, to objectively monitor the evolution and to predict patient outcome (Baraliakos and Maksymowych, 2016*; Maksymowych and Landewe, 2006; McQueen et al, 2006*; Ostergaard et al, 2008*; D'Agostino et al 2016a*; Ostergaard et al, 2010*; Poggendorf et al, 2011*, D'Agostino et al 2011*, Colebatch et al, 2013*, Mandl et al, 2015*), As compared to CR and CT, US and MRI are not associated with ionising radiation. However, US and MRI are time consuming techniques that require highly trained radiographers and/or radiologists/rheumatologists. To optimise the use of imaging in daily clinical practice it is not only important to consider advantages and disadvantages of the different imaging modalities, but also current evidence for the use of each technique. Furthermore, it is important to remember that prescription of radiologic procedures should always be based on medical history and objective examinations, and with a clear question to the examiner/radiologist, so that the answer can support the most appropriate treatment for the patient.

1 Conventional radiography

CR is a well-established technique and still the first imaging modality performed in patients with musculoskeletal symptoms. Changes in joint and cartilage surfaces, bone pathology, joint space narrowing, subluxation and dislocation can be evaluated with conventional radiography. This modality has a number of advantages. It is available to most physicians and readily accessible to most patients; it is relatively inexpensive; it is generally safe, although it does involve ionising radiation; it provides immediate information that can usually be readily interpreted by the requesting physician to aid diagnosis and management; data are reproducible and can be used for repeated serial evaluation and follow-up. However, this technique does have limitations. It provides a two dimensional picture of three dimensional structures so the plane of assessment is crucial to provide as much information as possible as there may be a danger of missing abnormalities if they are not caught in the plane of the X-ray beam. Thus radiography may be a less sensitive method compared to other tomographical imaging modalities such as CT and MRI. In addition, CR does not provide information on the synovium or other soft tissue structures, which can be critical for the management of patients with inflammatory arthritis.

Radiographic protocols have been established to provide optimal imaging of most joints. These include planes of assessment to maximise diagnostic sensitivity. Several planes are often utilised, typically for hands and feet, an anterior-posterior (figure 1) and lateral or oblique view. Specialist views may also be useful—for example, the 'skyline' view for patello-femoral joint assessment and the 'ball-catchers' view of the hand. Comparison of

bilateral joints can often be informative, and assessment of both hands and feet are useful in the assessment of inflammatory arthritis. Bilateral weight bearing films may be particularly valuable for assessment of joint space narrowing in osteoarthritis (OA) of the knee joint.

Figure 1 Normal posterior-anterior radiographs of the hands and feet. Images courtesy of WA Schmidt.



CR is routinely used in inflammatory as well as degenerative joint diseases. While rheumatoid arthritis (RA) is characterised by bone erosions and joint space narrowing, the radiographic features of the SpA spectrum differ from RA in a number of ways: the spine and sacroiliac joints are more commonly involved, the joint distribution is more likely to be asymmetric, and bone proliferation is frequently present. Degenerative joint diseases such as OA, are characterised by subchondral sclerosis, subchondral cysts and osteophytes. Much of the existing data on the assessment, diagnosis and management of patients with inflammatory arthritis, particularly RA, continue to be based on radiographic findings, and this will be reviewed in greater detail below as will radiographic data with regard to PsA, ankylosing spondylitis (AS) and OA.

1.1 Rheumatoid arthritis

1.1.1 Which joint involvement can be visualised by conventional radiography?

CR remains an important part of the evaluation of patients with peripheral arthritis and initial assessment often includes radiographs of the hands and feet as well as other affected joints. CR can provide important information which may help establish a diagnosis, in addition to determining disease extent, and have a value in prediction of structural progression (ie, progression in chronic bone changes) and long term prognosis. Various pathological abnormalities can be assessed using conventional radiography. These include peri-articular osteopenia (figure 2), joint space narrowing, joint erosions (figures 3 and 4), bone cysts, malalignment, subluxation, dislocation, sclerosis and ankylosis. Evaluation of the soft tissue structures with radiography is limited to describing shadows representing soft tissue swelling which may suggest effusion or

synovitis, but such pathological changes cannot be directly imaged using this technique. Therefore, radiographs are generally better utilised as serial assessments over time to determine any progression of joint damage rather than in the evaluation of initial inflammatory changes in early inflammatory arthritis. Studies have also demonstrated a correlation between joint damage seen on radiographs and disability in longstanding RA, although this link is less strong in patients with early disease (Poggenborg et al, 2011*). It has also been shown that the presence of radiographic erosions relates to disease outcome and confers a worse prognosis (Scott et al, 2000; Goronzy et al, 2004).

Figure 2 Posterior-anterior radiographs of the hands demonstrating widespread periarticular osteopenia in a patient with early inflammatory polyarthritis. Images courtesy of AK Brown.



A variety of joints can be affected by RA and exhibit characteristic features on radiography. These include the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints in the hand, the metatarsophalangeal (MTP) joints in the forefoot, as well as joints in the midfoot and hind foot, the wrist, knees, glenohumeral joint, the elbow and cervical spine.

Soft tissue swelling, periarticular osteopenia and joint space narrowing are often the first radiographic signs of RA (figure 1), although such changes are not specific to this condition. More characteristic changes include bone erosions (figures 3 and 4). Typically erosive changes are located at the bare areas at the margin of the joint (marginal erosions). Often the second and third MCP joints in the hand are affected, particularly on the radial aspect, the ulnar styloid at the wrist and the lateral aspect of the fifth metatarsal head. In chronic cases, erosions become more extensive and often develop more centrally within the joint, resulting in more severe joint space narrowing, which is usually concentric (figure 4), and ultimately subluxation, ankylosis and development of characteristic finger deformities such as ulnar deviation and boutonnière and swan neck deformities. Up to 80% of patients with RA may develop radiographic changes in the cervical spine with the

most important abnormality being atlanto-axial subluxation. This can occur in an anterior, lateral or vertical direction and may be progressive in the setting of uncontrolled inflammation with potentially serious consequences. Alignment can be assessed with anterior-posterior and lateral radiographs of the neck utilising flexion and extension views. Radiographs should usually be performed in a neutral position and forward flexion. If the atlas-dens distance exceeds 3 mm, MRI should be considered to exclude bony destruction, pannus and potential spinal cord or medulla oblongata compression.

Figure 3 Posterior-anterior radiograph of the hands and wrists in a patient with early rheumatoid arthritis demonstrating an erosion of the radial aspect of the right fifth metacarpophalangeal joint. Images courtesy of AK Brown.



Figure 4 Posterior-anterior radiograph of the hands and wrists in a patient with established rheumatoid arthritis demonstrating erosions and joint space narrowing in a symmetrical distribution in the proximal interphalangeal, metacarpophalangeal and wrist joints. Images courtesy of AK Brown.



1.1.2 Clinical utility

The importance of radiographic changes is supported by the American College of Rheumatology (ACR) which has recommended X-rays as part of the baseline assessment of RA patients (Arnett et al 1988^o). It is also important not to neglect the feet and perform a radiographic assessment of the hands, wrists and feet, as erosive changes may be present in the feet and not in the hands in early disease (McQueen et al, 2006^{*}). In the ACR/European League against Rheumatism (EULAR) 2010 classification criteria, patients who display bone erosions typical for RA plus at least one clinically swollen joint fulfil the criteria and can be classified as RA (Aletaha et al, 2010). Less than half of the patients with early RA have radiographic erosions (Machold et al, 2002), so caution should be applied when interpreting the significance of a normal radiographic assessment in this situation. Up to 30% of patients with RA may not develop radiographic erosions within the first 2 years of disease onset (Ostergaard et al, 2010^{*}). However the converse of this argument is that the majority of patients will have erosions within 2 years of a diagnosis of RA so there is arguably value in conducting radiography. Most experts suggest that radiographs of hands and feet should be performed every 6–12 months in early RA and every 1–2 years in more established disease.

Thus, identification of specific radiographic features, such as erosions, may be useful in the initial assessment of patients with suspected RA, and serial radiographic evaluation in established disease remains one standard by which disease progression, patient outcome and response to treatment may be measured. In addition, radiographs of the atlanto-axial region should be performed, particularly in longstanding and severe RA to exclude destruction and subluxation in this region.

1.1.3 Scoring systems

Several scoring systems have been developed for the evaluation of radiographic changes in RA. These scoring systems allow consistent assessment of joint damage and facilitate accurate measurement of disease severity and progression, and their validity and reliability have been documented. The most widely used systems are the Larsen method and its modifications, which assign to the joints an overall score based on mainly erosive damage by comparison with standard reference films; and the Sharp method and its modifications, which are based on detailed separate assessment of erosions and joint space narrowing in the hands and wrists and, according to the most recent modifications, the forefeet (van der Heijde, 2004). However, the use of such scoring systems is usually confined to research studies, particularly as an outcome measure for response to therapy studies. The complexity of such scoring systems tends to limit their use in routine clinical practice.

1.2 Ankylosing spondylitis and axial spondylarthritis

1.2.1 Which joint involvement can be visualised by conventional radiography?

1.2.1.1 The sacroiliac joints

In AS and axial-SpA, the first radiographic abnormalities are most often seen in the sacroiliac joints. Symmetrical sacroiliitis (figures 5 and 6) is a frequent presenting feature of this condition, and detection of this abnormality with conventional radiography remains part of the diagnostic evaluation of patients with inflammatory back pain and is a key criterion in the classification criteria for AS (see below).

Figure 5 Conventional radiography of sacroiliac joints with sacroiliitis grade 2 bilaterally.



Figure 6 Conventional radiography of sacroiliac joints with sacroiliitis grade 3 bilaterally.



The sacroiliac joints are challenging to image due to their position, anatomy and oblique orientation. An anterior-posterior view is the cornerstone in radiographic imaging of the sacroiliac joint and additional views may be added. The radiographs are often difficult to interpret, due to the irregular anatomy of the joint and projections of overlying structures such as the bowel. This is reflected by reports of significant intra-observer variability in the diagnosis of sacroiliitis on radiographs (Maksymowych and Landewe, 2006*).

The first radiographic finding is usually subchondral bone erosion of the iliac side of the synovial portion of the joint where the cartilage surface tends to be thinner. These erosive changes may progress to give the appearance of a widened joint space. Bone proliferative changes then occur with sclerosis and eventually ankylosis, which is not uncommonly seen early in the disease course. Appearances are typically bilateral and symmetrical in AS. The postero-superior aspect of the sacroiliac is formed by bony apposition and is held together by ligaments which commonly ossify as the disease progresses. These appear as sclerotic change on radiography and commonly obscure underlying structures including the posterior aspect of the joint.

An antero-posterior view of the pelvis may also be useful in the evaluation of patients with suspected spondyloarthropathy. This may reveal similar abnormalities such as erosion and bony proliferation of the cartilaginous pubic symphysis, and possibly changes of enthesopathy at tendon and ligament insertions around the pelvis.

1.2.1.2 The spine

The lumbar, thoracic and cervical spine can also be affected in patients with AS. Radiographs may demonstrate erosive change, ligamentous ossification, and squaring and fusion of the vertebrae (figures 7 and 8). The first changes are usually found at the corners of the vertebral bodies at the thoracolumbar junction in the form of small erosions with adjacent bony repair and proliferation. This produces a 'shiny corner' appearance which is called a Romanus lesion. Periosteal new bone formation along the anterior aspect of the vertebral body may result in 'squaring' of the vertebral body. This may be accompanied by ossification of the outer fibres of the annulus fibrosis of the intervertebral disc and longitudinal ligaments forming syndesmophytes (figure 9). Syndesmophytes are a hallmark of AS and represent vertical bony spurs which may form a bridge between vertebrae, ultimately giving a so-called 'bamboo spine' appearance. In contrast, bony proliferative lesions which tend to be more horizontally oriented are seen in PsA (parasyndesmophytes) and particularly degenerative spine disease (spondylophytes). Ossification of the adjacent paravertebral connective tissue fibres, and in particular the posterior interspinous ligament, may create a solid midline vertical dense line on antero-posterior radiographs in patients with AS. Calcification of the intervertebral discs may also occur. Ossification decreases the mobility of the spine. Low-energy fractures may occur through the ankylosed elements, creating pseudoarthroses typically at the cervico-thoracic and thoraco-lumbar junctions. Spondylodiscitis may also be present. In contrast to bacterial spondylodiscitis, the non-bacterial inflammatory

lesion is characterised by destruction of the vertebral endplate surrounded by well-defined sclerotic areas, reduced height of the disc, and no blurring of contours of the soft tissue.

Figure 7 Conventional radiograph (lateral projection) of the cervical spine. A syndesmophyte is seen at the lower aspect of the anterior vertebral corner of C5 (lower corner).



Figure 8 Conventional radiograph (lateral projection) of the lumbar spine. Syndesmophytes are seen at the anterior vertebral corners of L1 (lower aspect) and L4 (upper aspect).

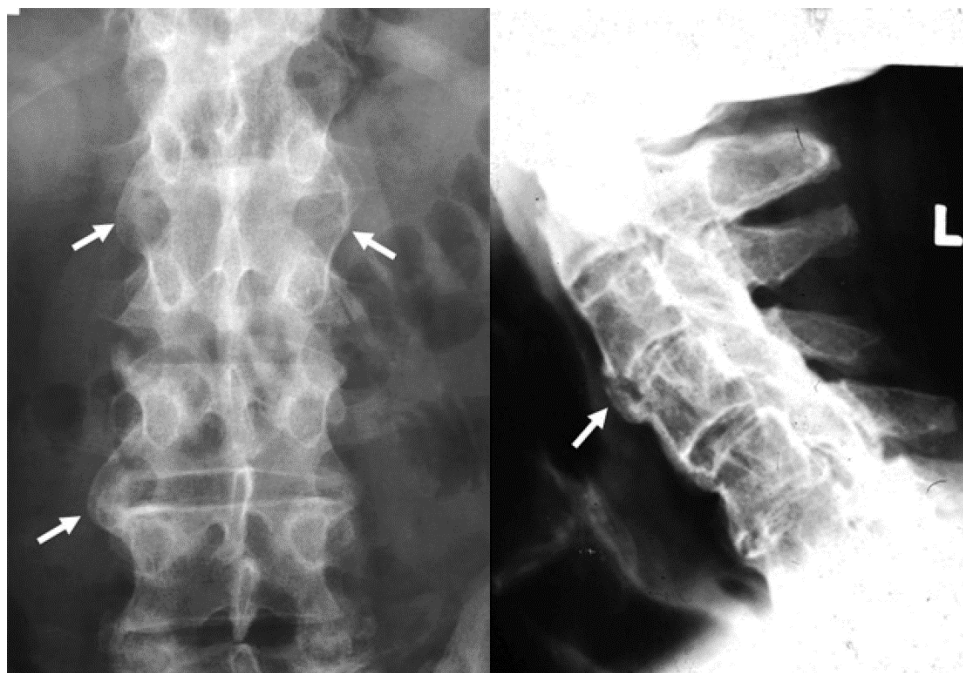


1.2.1.3 The peripheral joints

The peripheral skeleton may be affected in AS and radiographically detectable changes may occur in the hips, shoulders, knees and MTP joints, and at enthesal sites. Peripheral joint involvement in AS most commonly involves the hips and tends to be bilateral and symmetrical. The hip joint space may be uniformly narrowed, a collar of osteophytes may be seen at the femoral head–neck junction, and axial migration of the femoral head may occur. Up to a third of the patients may develop protrusio acetabuli. The shoulder may be involved in up to 30% of cases and, again, features tend to be bilateral and symmetrical. Typical features include joint space narrowing, erosions, bony proliferation of ligament attachments and the possibility of ultimately ankylosis. In

addition bony spurs may form at the attachment of the plantar fascia at the medial calcaneum and at the insertion of the Achilles tendon.

Figure 9 Cervical spine radiographs demonstrating massive syndesmophyte formation (arrows), almost ankylosis, in two patients with ankylosing spondylitis. (Reproduced with permission from Tan AL, McGonagle D. *Imaging of psoriatic arthritis*. In: Mease PJ, Helliwell PS, eds. *Atlas of psoriatic arthritis*. London: Current Medicine Group, 2005.)



1.2.2 Clinical utility

The New York criteria are, albeit classification criteria, the most commonly used criteria for the diagnosis of AS and are based on clinical features and radiographic sacroiliitis (van der Linden et al, 1984, Ostergaard M et al, 2008*). According to these criteria AS may be diagnosed if grade 2 sacroiliitis (minimal sacroiliitis: loss of definition of the joint margins, minimal sclerosis, joint space narrowing and erosions) or higher occurs bilaterally, or grade 3 (moderate sacroiliitis: definite sclerosis on both sides of the joint, erosions, and loss of joint space) or grade 4 (complete bony ankylosis) occurs unilaterally.

The definitions of radiographic changes according to the New York criteria are included in the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial SpA (Rudwaleit et al, 2009a), the European Spondyloarthritis Study Group (ESSG) criteria for SpA (Dougados et al, 1991), and the modified New York criteria (van der Linden et al, 1984).

Radiography of the spine is not included in the classification criteria, but may be useful to follow structural disease progression in patients with spinal involvement. The bone changes seen in patients with axial SpA develop slowly and are often not present in patients with early disease, and generally only minor changes can be observed in 1–2 years.

1.2.3 Scoring systems

Different scoring methods, all based on assessment of lateral views, have been developed to quantify changes in the spine of patients with AS: the Stoke AS Spine Score, Bath AS Radiology Index (BASRI), and the modified Stoke AS Spine Score (mSASSS). A study of the three methods concluded that all measures were reliable but mSASSS was more sensitive to change (van der Heijde, 2004). The spine scores are primarily used in clinical research.

1.3 Psoriatic arthritis

1.3.1 Which joint involvement can be visualised by conventional radiography?

The radiographic changes that may occur in patients with PsA are located at joint and soft tissue structures and comprise osteodestructive as well as osteoproliferative changes: erosions, osteolysis, periostitis, bony proliferation and ankylosis (figure 10), as well as soft tissue swelling and joint space narrowing.

Figure 10 Posterior-anterior radiograph of the hands and wrists in a patient with psoriatic arthritis. Note the 'pencil-in-cup' deformity in the distal interphalangeal joints of the right second and third fingers and the interphalangeal joints of the thumbs. There is also radial subluxation of the distal phalanx of the right thumb. (Reproduced with permission from Tan AL, McGonagle D. Imaging of psoriatic arthritis. In: Mease PJ, Helliwell PS, eds. Atlas of psoriatic arthritis. London: Current Medicine Group, 2005.)



The patterns of joint involvement in PsA are heterogeneous and may include the distal and PIP joints (alone or in combination) or diffuse soft tissue swelling of a digit indicating dactylitis. An RA-like distribution involving the symmetrical small joints of the hands, feet and wrists may occur and may be equally damaging to changes seen in RA (Helliwell et al, 2000). The feet are also commonly affected in PsA. An inflammatory oligoarthritis involving small and/or large joints, particularly ankles, knees and shoulders, may occur. Enthesopathy is often

seen at the acromion, elbow, ischial tuberosity, greater trochanter, patellae, lateral and medial malleolus, and at the attachment of the Achilles tendon and plantar fascia at the calcaneus. Sacroiliitis is also frequently seen (see above).

Radiographs of patients with early PsA may show asymmetric, well defined, marginal erosions. Such early erosions may be indistinguishable from those seen in patients with RA except they may also demonstrate bone proliferation, giving the erosion a slightly spiculated margin. In later progressive disease the characteristic irregular, indistinct erosions and ‘pencil-in-cup’ deformities (a blunt tapered surface of the proximal bone which may protrude into the expanded base of the distal bone of the interphalangeal joints) may be seen (figure 10). In addition, bony proliferation may be observed at entheses—for example, as spurs at the insertion of the plantar fascia and Achilles tendon.

1.3.2 Clinical utility

Several classification systems for PsA have been proposed which have generally been based on different patterns of disease manifestations and not on radiographic findings. However, the European Spondyloarthritis Study Group (ESSG) criteria, in which the presence of radiographic sacroiliitis is an important feature for the diagnosis of axial disease, include radiography of the sacroiliac joints (Dougados et al, 1991). The Classification criteria for Psoriatic Arthritis (CASPAR) criteria from 2006 include radiography of the hands and feet (Taylor et al, 2006). The presence of juxta-articular new bone formation appearing as ill-defined ossification (ie, not a well-defined ossification as in osteophytes) near joint margins is an important feature in the criteria. Up to half of patients with PsA may have evidence of joint damage on radiographs within 2 years of presentation (Kane et al, 2003a). Other changes in early PsA may include dactylitis, periostitis of the bone shaft, and spondylitis. The hand and wrist may be affected in up to three quarters of PsA patients, but the pattern of joint involvement varies from patient to patient and also over time in the individual patient. Spinal involvement may occur in PsA and sacroiliitis may be demonstrable in up to 75% of the patients (Watt 1996). The changes may be more extensive and are more likely to be asymmetrical in PsA and reactive arthritis than in AS.

1.3.3 Scoring systems

Structural joint damage on conventional radiography is an important outcome measure in PsA. Different radiographic scoring methods have been developed, for example, the Sharp/van der Heijde modified scoring method for PsA, which is a detailed scoring system for evaluating erosions and joint space narrowing, while osteolysis and pencil-in-cup phenomena are assessed separately (van der Heijde, 2004). The scoring systems are primarily used in clinical trials.

1.4 Osteoarthritis

1.4.1 Which joint involvement can be visualised by conventional radiography?

Conventional radiography remains the mainstay imaging investigation in the diagnosis and assessment of OA. However, before requesting radiographs, one should consider which joint or joints to image, the plane of assessment, and the questions to be asked of the imaging tool. This will help in selection of the most appropriate radiographic technique. Comparison with previous examinations is invariably useful.

The radiographic features of OA include osteophytes, joint space narrowing, subchondral sclerosis, subchondral cysts, bony remodelling (figure 11), and possibly joint effusions visualised as soft tissue swelling and fat pad displacement. Other arthropathies may co-exist such as calcium pyrophosphate crystal deposition evident as chondrocalcinosis (figure 12). Additional techniques can be employed to yield maximum information. These include weight-bearing films and particular views. For example, weight-bearing radiographs of the knee are essential in order to make the joint space width more representative of cartilage thickness. Other joints such as the hip and ankle maintain good articular contact in a supine position, so weight-bearing films may not be necessary although views of the hip joint may be improved by some internal rotation (eg, 15–20°) and using a standing position. A lateral oblique view of the hip may help to assess posterior-inferior OA. In addition movement and positioning of the joint may be useful. For example, a small amount of flexion of the knee facilitates increased contact of articular surfaces affected by OA. Other techniques such as image magnification, stress films, and systems for digital image analysis may provide additional useful information. Consistent standardised radiographic methodology is crucial for reproducibility of the technique and in particular to facilitate accurate comparison and assessment of severity and progression.

1.4.2 Clinical utility

Conventional radiography is the standard method for the diagnosis and follow-up of OA. However, newer imaging modalities, in particular MRI, are providing additional information which are used in clinical trials and for understanding the disease.

1.4.3 Scoring systems

Various scoring systems have been developed to grade the severity of OA. Among the most well known is the Kellgren and Lawrence five point scale which has been widely used in OA research studies (Plant et al, 1998). Further atlas based scoring systems have been developed which provide more accurate discrimination between individual radiographic features of OA. However, whichever system is used, there may be variable reliability. In addition, quantitative measurement of joint space width as a surrogate for cartilage thickness has been employed in research studies, particularly in cases of knee OA but also in the hip and hand.

Figure 11 Posterior-anterior radiograph of the hands of a patient with osteoarthritis demonstrating soft tissue swelling, joint space loss and osteophyte formation affecting particularly the distal interphalangeal and first carpo-metacarpal joints and particularly the proximal interphalangeal joints of the dominant right hand. Images courtesy of AL Tan.



Figure 12 Posterior-anterior radiograph demonstrating chondrocalcinosis of the triangular fibrocartilage in the ulna-carpal compartment of the wrist and meniscal calcification in the left knee, in a patient with calcium pyrophosphate crystal deposition. Images courtesy of AK Brown.



2 Magnetic resonance imaging

MRI allows assessment of all the structures involved in musculoskeletal pathologies, including arthritic diseases, and has been shown to be more sensitive than clinical examination and X-ray for detection of inflammation and damage in inflammatory and degenerative rheumatological disorders. The use of MRI in clinical practice requires considerations regarding safety, availability, cost and duration of examination. MRI is very safe. It involves no ionising radiation or increased risk of malignancies, and adverse effects of the contrast agents are very rare. Disadvantages of MRI include higher costs and lower availability than radiography, longer examination times, and restriction to a limited anatomical area per session..

Preceded by a section on key technical aspects, the characteristics of MRI with respect to diagnosis, monitoring, prognostication and clinical utility in RA, SpA, PsA and OA will be described below.

2.1 Technical aspects

2.1.1 *Peripheral disease*

Whereas MRI examination of axial joints require whole-body MR units, MRI of the peripheral joints can be performed with whole-body MR units or dedicated extremity MR units (E-MRI). Most studies have used whole-body MR units. Low-field E-MRI has been commercially available for some years, increasing the potential for widespread rheumatological use. The advantages of E-MRI compared with whole-body units include markedly lower costs, more comfortable patient positioning and elimination of claustrophobia, a considerable problem in the whole-body units. The disadvantages of E-MRI vary by type of unit, but may include a smaller field of view (ie, smaller anatomical areas are scanned), longer imaging times, and a reduced number of possible imaging techniques compared with the whole-body units. In particular, spectral fat saturation (FS) sequences cannot be acquired due to the low field strength. Some E-MRI units may provide information on synovitis and bone destructions not markedly inferior to what is obtained by standard sequences on high-field units (Taouli et al, 2004; Ejbjerg et al, 2005a), but it should be considered that the performance of different machines may be very different, stressing the need for careful testing before use (Duer-Jensen et al, 2009).

T1 weighted (T1w) imaging sequences are favoured by relatively short imaging times, good anatomical detail, and the ability to visualise the inflamed synovium after intravenous contrast (paramagnetic gadolinium compounds; Gd) injection. Accordingly, pre- and post-Gd T1w imaging has been included in the great majority of studies. Fat and Gd-enhanced tissues have a high signal intensity on T1w images, and as Gd-uptake depends on tissue vascularity and perfusion, the highly vascularised and perfused inflamed synovium is easily recognisable.

T2 weighted (T2w) images depict both fat and fluid/oedematous tissues with a high signal intensity. T2w images are particularly useful when FS techniques, in which the signal from fat is suppressed, are applied. Fat

suppression increases detection of oedematous tissue/fluid located in areas with fatty tissue, for example, bone marrow oedema. On T1w post-Gd images, the use of FS techniques increases the contrast between the inflamed synovium and adjacent structures, but whether it truly gives otherwise unachievable information is questionable. FS requires a homogenous field and a high magnetic field strength, which are not available in low field E-MRI units. The only fat-suppressed sequence possible on low-field E-MRI is the short tau inversion recovery (STIR) technique, which can provide information on bone marrow oedema (Aletaha et al, 2010).

Omitting injection of contrast would decrease imaging times and remove the only invasive element. Unenhanced T1w plus T2w FS/STIR MRI give comparable information on erosions and bone marrow oedema, but is less accurate on synovitis, when compared to Gd-enhanced MRI (Østergaard et al, 2009a). Thus, most authors recommend using Gd-enhanced MRI, if detailed assessment of synovitis is considered important. However, the clinical significance of the fewer details on synovitis presumably achieved with unenhanced imaging has not yet been definitively clarified.

2.1.2 Axial disease

The majority of MRI studies of the sacroiliac joint have used only one imaging plane (semi-coronal, ie, parallel with the axis of the sacral bone). To be maximally sensitive for changes in the ligamentous portion of the sacroiliac joints, imaging in two perpendicular planes is required (Machold et al, 2002). This may therefore be recommended when MRI is used for diagnostic purposes, while it is probably not essential when used as an outcome measure in clinical trials. The majority of MRI studies of the spine in SpA acquire only sagittal images, which are well-suited for assessment of vertebral body changes. However, standard imaging protocols often do not cover the facet, costo-vertebral and costo-transversal joints, due to an insufficient number of sagittal slices. This is crucial, as lesions in pedicles, facet joints, transverse and spinous processes and the posterior soft tissues have been detected in >80% of patients in a SpA cohort (Paulus et al, 1996). The importance of inflammation in the posterior elements in the monitoring and prognostication of SpA remains to be determined.

Bone marrow abnormalities in both sacroiliac joints and spine are detected almost equally well with the STIR and contrast-enhanced T1w FS sequences in patients with SpA (Baraliakos et al, 2005a; Madsen et al, 2010a); the STIR sequence may be better to detect bone marrow oedema in the periphery of fat infiltrations in the sacroiliac joints, whereas small sub-chondral lesions may not be visualised. However, the diagnostic confidence in early SpA may be better if contrast-enhanced MRI is used (Althoff et al, 2009).

For evaluation of structural changes, such as fat infiltrations, bone erosions, sclerosis, and syndesmophytes, T1w semi-coronal images are mandatory. A supplementary T1w FS sequence may improve the evaluation of erosions (Machold et al, 2002), and sequences designed for cartilage evaluation—for example, three dimensional gradient echo sequences—may also be added (Puhakka et al, 2004c).

Thus, recommendations for an adequate MRI of the sacroiliac joint or spine all include at least a T1w sequence without FS and a STIR sequence, in one plane. To which extent further sequences are needed is debated, and may depend on the goal of the examination.

2.2 Rheumatoid arthritis

The majority of MRI studies in RA have investigated knee, wrist and finger joints. While the knee joint is an excellent model joint for methodological studies, the clinical value of MRI is mainly dependent on its power to evaluate wrists, hands and feet, which is also the primary focus of this section. Reports on other peripheral joints are few and not essentially different.

2.2.1 Which joint involvement can be visualised by MRI?

MRI provides multiplanar tomographical imaging with unprecedented soft tissue contrast, without the use of ionising radiation, and allows assessment of all the structures involved in RA—that is, synovial membrane, intra- and extra-articular fluid collections, cartilage, bone, ligaments, tendons and tendon sheaths. MRI and histopathological signs of synovial inflammation are closely correlated (Spoorenberg et al, 2004). MRI can detect synovitis (figure 13), tenosynovitis, bone marrow oedema (figures 14 and 15) and erosions (figure 13) in patients with RA.

Figure 14 Coronal short tau inversion recovery MR image showing bone oedema in the distal part of the second and fourth metacarpal heads. Furthermore, synovitis is seen in the fourth metacarpophalangeal (MCP) joint. The joint to the right is the second MCP joint.



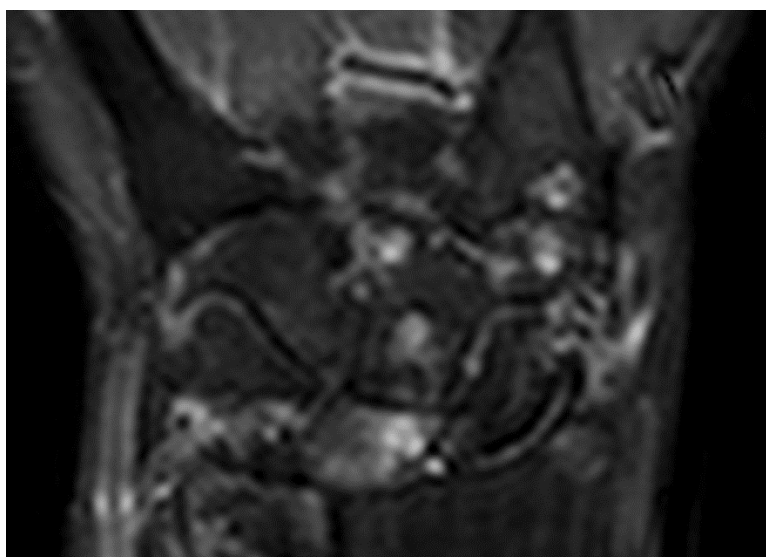
Figure 13 Coronal (A) and axial (B) T1 weighted (T1w) pre-contrast MR images of the second to fourth metacarpophalangeal (MCP) joints show bone erosion in the third and fourth MCP joints, visualised in two planes. (C) The corresponding coronal T1w fat saturated image after contrast injection shows enhancement in second to fourth MCP joints (synovitis) as well as in the third metacarpal head (corresponding to osteitis (bone oedema)).



In a study of MCP joints in patients with early and established RA, mini-arthroscopy confirmed the presence of bone pathology in all joints with MRI bone erosions and histologic and macroscopic synovitis in all joints with MRI synovitis (Ostendorf et al, 2001). MRI bone marrow oedema represents inflammatory infiltrates in the bone marrow—that is, osteitis—as demonstrated by comparison with histological samples obtained at surgery in RA patients (Jimenez-Boj et al, 2007; McQueen et al, 2007). Whereas erosions reflect bone damage that has already occurred, bone marrow oedema appears to represent the link between joint inflammation and bone destruction. A high level of agreement for detection of bone erosions in RA wrists and MCP joints

(concordance at 77–90% of sites) between MRI and CT, the gold standard reference for detection of bony destruction, documents that MRI erosions represent true bone damage (Døhn et al, 2006; Døhn et al, 2008).

Figure 15 Coronal short tau inversion recovery MR image of the wrist joint. Bone oedema is seen in the lunate. The intense bright areas in the capitate and trapezoid bones and the second metacarpal base are bone erosions. These are best visualised on T1 weighted images in two planes (not shown).



2.2.2 Diagnosis

A number of relatively small (≤ 50 patients per study) studies have investigated the differential diagnostic value of MRI, providing ambiguous results; however, recently two large follow-up studies of patients with undifferentiated arthritis have provided better knowledge of the diagnostic utility of MRI to diagnose RA (Tamai et al, 2009; Duer-Jensen et al, 2011). Tamai et al (2009) investigated 129 patients with non-classifiable arthritis despite routine examination, including conventional radiography and biochemical tests, and developed a prediction model containing anti-cyclic citrullinated peptide (anti-CCP) and/or immunoglobulin M rheumatoid factor (IgM-RF), MRI-proven symmetric synovitis, and MRI-proven bone marrow oedema and/or bone erosion. It was found that 71.3% of patients positive for >2 of these variables developed RA within 1 year (specificity 75.9%, sensitivity 68.0%). Presence of bone marrow oedema had a positive predictive value of 86.1% for subsequent development of RA (Tamai et al, 2009). In a study of 116 patients with early undifferentiated arthritis, Duer-Jensen et al (2011) documented that MRI bone marrow oedema in the MTP and wrist joints is an independent predictor of future RA in patients with early undifferentiated arthritis. A prediction model, including clinical hand arthritis, morning stiffness, positive IgM-RF and MRI bone marrow oedema score in MTP and wrist joints correctly identified the development of RA or non-RA in 82% of patients. Thus, two large studies document an independent predictive value of MRI for development of RA.

The ACR/EULAR 2010 criteria for RA (Aletaha et al, 2010) added a role of MRI in the diagnosis of RA. Classification as definite RA is based on the presence of definite clinical synovitis (swelling at clinical

examination) in ≥ 1 joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score ≥ 6 (of a possible 10) from the individual scores in four domains: number/site of involved joints (score range 0–5), serologic abnormality (range 0–3), elevated acute-phase reactants (range 0–1), and symptom-duration (range 0–1) (Aletaha et al, 2010). MRI and US may be used to determine the joint involvement—that is, joint involvement (ie, synovitis) by MRI or US counts in the scoring in the ‘joint involvement domain’ (Aletaha et al, 2010; Østergaard et al, 2010*; Aletaha et al, 2011).

2.2.3 Monitoring disease activity and structural damage

To be valuable for monitoring joint inflammation and destruction, a measure must be reproducible and sensitive to change. MRI allows quantitative (volume of various pathologies or early contrast uptake (‘enhancement’) rate after intravenous injection (only synovitis)) as well as less detailed (qualitative: presence/absence; semiquantitative: scoring) evaluation of synovitis and bone erosions. In observational and randomised clinical trials, semiquantitative scoring has been the most frequently used approach. The Outcome Measures in Rheumatology (OMERACT) Rheumatoid Arthritis MRI Scoring system (RAMRIS) involves semiquantitative assessment of synovitis, bone erosions and bone marrow oedema in RA hands and wrists. This method was developed and validated through iterative multicentre studies under OMERACT and EULAR banners. Consensus MRI definitions of important joint pathologies and a ‘core set’ of basic MRI sequences were also suggested (Rudwaleit et al, 2009b).

The OMERACT erosion scores are closely correlated with erosion volumes estimated by MRI and CT. Good intra- and inter-reader reliability and a high sensitivity to change has been reported, demonstrating that the OMERACT RAMRIS system, after proper training and calibration of readers, is suitable for monitoring joint inflammation and destruction in RA (Østergaard, et al 2003). A EULAR-OMERACT RA MRI reference image atlas has been developed, providing an easy-to-use tool for standardised RAMRIS scoring of MR images for RA activity and damage by comparison with standard reference images (Østergaard et al 2005).

Quantitative methods of synovitis (synovial membrane volumes and post-contrast enhancement rates) are rarely used, but is closely related to histopathological synovitis and sensitive to change (Spoorenberg et al, 2004). Recent software improvements, providing more automated methods, potentially increase assessment speed and reproducibility (Boesen et al, 2009). This encourages revisiting the usefulness of such quantitative methods.

Several studies have demonstrated that MRI is more sensitive than X-ray for monitoring erosive progression in the individual joint regions (McQueen et al, 1999; Østergaard, 1999; Klarlund et al, 2000). RAMRIS scoring of unilateral wrist and MCP joints is more sensitive to change than Sharp/van der Heijde X-ray scoring of bilateral hands, wrist and forefeet (Ejbjerg et al, 2005b).

The superior sensitivity to change and discriminatory ability of MRI compared to X-ray has been demonstrated in randomised controlled clinical trials (RCT) (Quinn et al, 2005; Østergaard et al, 2010*). Quinn et al (2005) demonstrated a significantly lower erosion progression rate by MRI, but not by the Sharp/van der Heijde X-ray method, in 12 methotrexate plus infliximab-treated early RA patients compared to 12 patients receiving methotrexate alone. Recently a large study of 318 methotrexate-naïve patients showed that inhibition of erosive progression of biological therapy compared to placebo can be demonstrated by MRI using half the number of patients and half the follow-up time as by X-ray (Østergaard et al, 2011). A recent review underlines the advantages of using MRI as endpoint in RCT (Peterfy et al 2016*).

2.2.4 Prognostication

Numerous studies have reported the ability of MRI pathology (synovitis, bone erosions or bone marrow oedema) of the wrist and MCP joints to predict radiographic erosive progression. All studies, except two early RA cohorts (Haavardsholm et al, 2008; Hetland et al, 2009), were imaging studies that did not include anti-CCP or take into account other potential prognostic markers such as smoking or shared epitope carriage. Haavardsholm et al (2008) reported bone marrow oedema and male gender (but not anti-CCP) to be independent predictors of radiographic progression after 1 year in a single-centre cohort of 84 patients treated according to standard clinical practice. A study by Hetland et al (2009) was the first clinical trial with a standardised treatment protocol that investigated the predictive value of a variety of potential prognostic markers including both imaging (MRI and conventional X-ray), immunologic (anti-CCP, IgM-RF and IgA-RF), environmental (smoking, educational level), genetic (shared epitope), and disease activity markers (Hetland et al, 2009). The main finding was that MRI bone marrow oedema at presentation was the strongest predictor of radiographic progression 2 years later in early RA patients. Three-year and 5-year follow-up, respectively, in the two retrospective cohorts have documented that MRI-bone marrow oedema is also a predictor of long term radiographic progression (Heltand et al, 2010; Bøyesen et al, 2011a).

A relation between baseline MRI findings and long term functional disability has only been documented in one study (Battistone et al, 1999). Furthermore, a high baseline MRI tendinopathy score was predictive of tendon rupture at 6 years (odds ratio 1.52) (McQueen et al, 2005).

Another issue of high clinical importance is whether MRI is useful in patients in clinical remission, to predict the disease course. Brown and co-workers reported that MRI and US synovitis is frequent in patients in clinical remission, and that baseline US synovial hypertrophy, US power Doppler (PD) signal and MRI synovitis scores in individual joints were significantly related with progressive radiographic damage at 1-year follow-up (Van Der Heijde et al, 2005). The study encourages further exploration of MRI and US for predicting the disease course and for evaluating disease status, including defining remission.

2.2.5 Summary/clinical utility

MRI can be used to visualise all structures involved in RA. Two large studies document an independent predictive value of MRI for the development of RA, implying a diagnostic utility when used in combination with clinical parameters. Furthermore, MRI and US have an important role in the ACR/EULAR 2010 criteria for RA, as it can be used to count involved joints. MRI can be used for sensitive monitoring of disease activity and damage and, as bone marrow oedema is a strong independent predictor of radiographic progression, for stratification into good- and poor-prognosis patients.

2.3 Ankylosing spondylitis/axial spondyloarthritis

MRI allows direct visualisation of the abnormalities in peripheral and axial joints and entheses that occur in AS, PsA and other forms of SpA. AS, which is thought to be the most common and most typical form of SpA, is dominated by axial disease manifestations in the spine and sacroiliac joints, and clinical assessment systems have focused on assessing axial disease. In accordance with this, this section will mainly focus on the axial manifestations, while the PsA section below will deal with peripheral manifestations.

2.3.1 Which joint involvement is visualised by MRI?

MRI, through its ability to detect inflammatory changes in bone and soft tissues, is the most sensitive imaging modality for recognising early spine and sacroiliac joint changes in AS/ axial SpA. MRI findings indicating active disease in the sacroiliac joints (sacroiliitis) include juxta-articular bone marrow oedema and enhancement of the bone marrow and the joint space after contrast agent administration (figure 16), while visible structural changes include bone erosions, sclerosis, periarticular fatty tissue accumulation, bone spurs (such as syndesmophytes), and ankylosis (figure 17). Typical lesions of the spine, which indicate active disease, are spondylitis, spondylodiscitis, and arthritis of the facet, costovertebral and costo-transverse joints (figure 18). Structural changes, such as bone erosions, focal fat infiltration, bone spurs and/or ankylosis, frequently occur. Enthesitis is also common, and may affect the interspinal and supraspinal ligaments and the interosseous ligaments in the retro-articular space of the sacroiliac joints. Some patients also have disease manifestations in peripheral joints and entheses, and these can be visualised by MRI as in other diseases (Hermann et al, 2004a; Maksymowych and Landewe, 2006*).

Figure 16 Semicoronal short tau inversion recovery (A) and T1 weighted (T1w) (B) MR images of a patient with axial spondyloarthritis, showing bone marrow oedema at both sacroiliac joints, being most pronounced in the right sacral and iliac bones, documenting active sacroiliitis. (B) Corresponding T1w MR image shows fat infiltration and bone erosion.

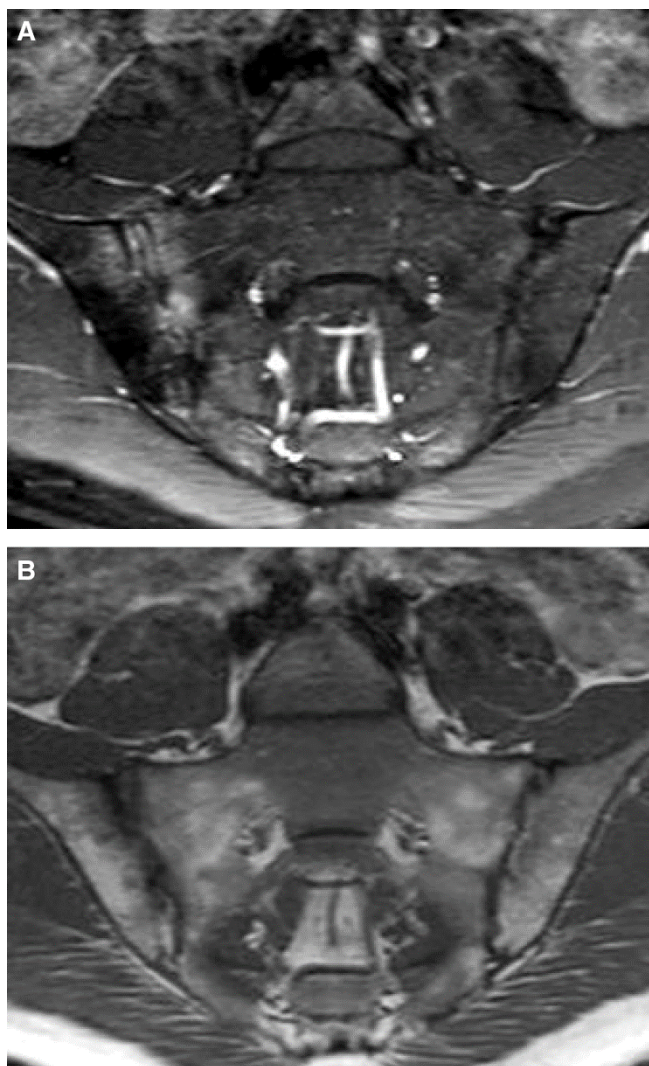
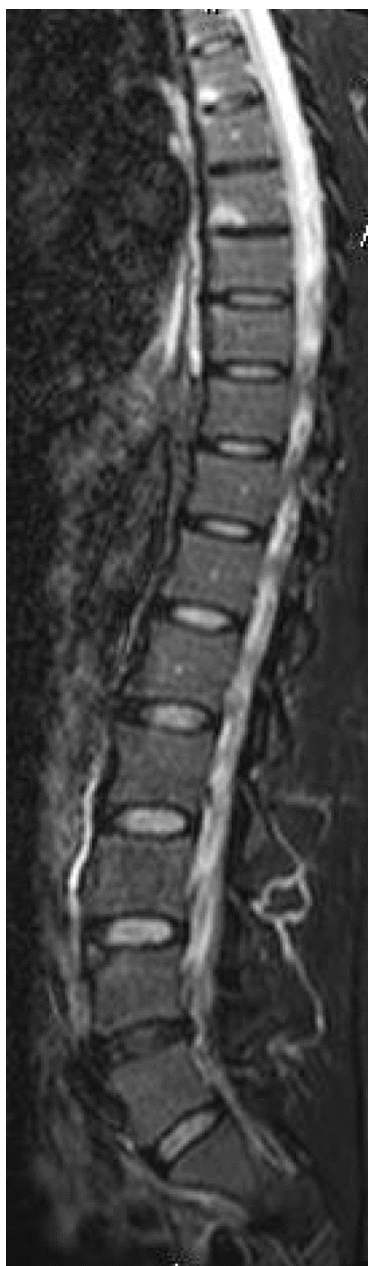


Figure 17 Semicoronal T1 weighted MR images of the sacroiliac joints of a patient with ankylosing spondylitis. (A) Sacral and iliac erosions primarily in the left sacroiliac joint. (B) Sacral fat infiltrations in the both sacroiliac joints located in the sacral bone.



Figure 18 Sagittal short tau inversion recovery image of the lumbar and lower thoracic spine showing bone marrow oedema at the anterior vertebral corners of Th4, Th5, Th6, Th7 and Th9.



2.3.2 Diagnosis

The introduction of MRI has resulted in a major improvement in the evaluation and management of patients with SpA. In particular, MRI makes it possible to diagnose patients earlier in the disease course (Rudwaleit et al, 2009a). Diagnosis was previously dependent on the presence of bilateral moderate or unilateral severe radiographic sacroiliitis, as part of the modified New York criteria for AS. This frequently delayed the diagnosis by 7–10 years (Taouli et al, 2004). Now, through the recent ASAS classification criteria for axial SpA, MRI forms an integral part, as patients with active sacroiliitis on MRI plus one clinical feature (eg, psoriasis, enthesitis or uveitis) should be classified as having axial SpA (Rudwaleit et al, 2009a). A consensus-based definition has been made of the requirements to constitute active sacroiliitis—that is, to fulfil the MRI criterion of the ASAS

criteria ('a positive MRI') (Rudwaleit et al, 2009b). Only bone marrow oedema, located in ≥ 2 sites and/or in ≥ 2 slices, counts.

Recent data demonstrate that incorporating structural damage lesions (erosions) into the criteria would improve the diagnostic utility of MRI (Weber et al, 2010a; Weber et al, 2010b). However, in January 2011 ASAS decided to await further data before revision of the definition of a positive MRI in the axial SpA criteria could be reconsidered.

2.3.3 Monitoring disease activity and damage

MRI can provide objective evidence of currently active inflammation in patients with SpA (Hermann et al, 2004a; Maksymowych and Landewe, 2006, Baraliakos and Maksymowych, 2016*). Until the introduction of MRI, disease activity assessment was restricted to patient-reported outcomes, such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Functional Index (BASFI), because disease activity could not be assessed in a sensitive manner by biochemical (mainly C-reactive protein (CRP) or erythrocyte sedimentation reaction) or physical evaluation.

Several scoring systems for assessment of disease activity in the sacroiliac joints and in the spine have been proposed (for details, see recent review by Ostergaard et al 2010*). Generally, MRI disease activity assessments have mostly focused on the spine.

Three main scoring approaches of activity in the sacroiliac joints have been proposed, based on either global scores per quadrant or individual scores in consecutive semi-coronal images through the joint (Hermann et al, 2004b; Puhakka et al, 2004a; Maksymowych et al, 2005b; Madsen et al, 2010a). The presence and extent of bone marrow oedema in the cartilaginous portion of the joint is the primary MRI feature that is scored. In an OMERACT-ASAS multi-reader exercise, agreement between readers and sensitivity to change were compared and found to be somewhat better for the most detailed scoring method (the Spondyloarthritis Research Consortium of Canada (SPARCC) method) (Lukas et al, 2007). A recent method also scores the ligamentous portion of the joint (Machold et al, 2002). Whether this system's ability to visualise inflammation in all aspects of the joint (comprehensiveness) outweighs the disadvantages of higher complexity and longer acquisition and reading time remains to be determined, as does the sensitivity to change.

Several scoring systems for assessment of disease activity in the spine have been proposed (Braun et al, 2003; Maksymowych et al, 2005a; Haibel et al, 2006; Lambert et al, 2009; Madsen et al, 2010b). While the two most recent scoring systems (Lambert et al, 2009; Madsen et al, 2010) have not yet been fully validated, the sensitivity to change and discriminatory ability of the three most used systems—the Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity (ASspiMRI-a) score, grading activity 0–6 per vertebral unit in 23 units; the Berlin modification of the ASspiMRI-a score, grading activity 0–3 per vertebral unit in 23 units; and

the SPARCC scoring system (Braun et al, 2003; Maksymowych et al, 2005a; Haibel et al, 2006)—have been demonstrated in clinical trials, and they have been tested against each other by the ASAS/OMERACT MRI in AS group (Lukas et al, 2007). All methods were feasible, reliable, sensitive to change and discriminative. The SPARCC method had the highest sensitivity to change, as judged by Guyatt's effect size, and the highest reliability as judged by the inter-reader intra-class correlation coefficient (ICC) (Lukas et al, 2007).

Other scoring systems include a combined score of sacroiliac joints and the lower part of the spine (Marzo-Ortega et al, 2001; Marzo-Ortega et al, 2005) and two recent systems (Lambert et al, 2009; Østergaard et al, 2009b); both have individual components for assessment of inflammatory and structural lesions. A Canada–Denmark system provides a detailed anatomy-based set of definitions plus an assessment system for active inflammatory lesions, which was particularly designed to study the temporal and spatial patterns of inflammation, and their relation to the development of structural damage on MRI and radiography (Lambert et al, 2009; Østergaard et al, 2009b).

MRI is much less established for the assessment of structural changes than inflammatory changes. Scoring methods assess erosions, sclerosis, fat deposition and/or bone bridges separately or as global score are under development (Maksymowych et al 2015a; Weber et al 2015).

Until recently, the only systematic evaluation method of structural changes proposed for evaluation of the AS spine was the Ankylosing Spondylitis spine Magnetic Resonance Imaging-chronicity (ASspiMRI-c) scoring system, in which each discovertebral unit is assigned a score from 0 to 6 based on an overall assessment of sclerosis, squaring of vertebrae, syndesmophytes and ankylosis (Braun et al, 2003).

Unfortunately, the reliability of the ASspiMRI-c score has been shown to be poor and in a comparative study this MRI system was not superior to radiography for detection of new bone formation (Braun et al, 2003; Braun et al, 2004). However, no specific definitions for syndesmophytes and ankylosis seen on MRI were proposed and it was not clear whether the poor reliability was due to unreliable detection of all or only some lesions, since data were only reported for the score as a whole. Two new systems (Østergaard et al, 2009b; Madsen et al, 2010b) score the individual features separately. Further studies are needed to elucidate the validity and clinical utility of these systems.

2.3.4 Prognostication

Three spine studies have documented an association between the presence of bone marrow oedema at anterior vertebral corners on MRI and subsequent development of syndesmophytes at the same vertebral corners on radiography after 2 years of follow-up. Presence as opposed to absence of MRI inflammation provides risks of a new anterior radiographic syndesmophyte at the level of 6.5% versus 2.1% (Baraliakos et al, 2008), 20% versus 6.3% (Maksymowych et al, 2009), and 15.6–16.7% versus 2.2–3.2% (Pedersen et al, 2009),

respectively. In two studies, the association was even more pronounced in those vertebral corners in which the inflammation had resolved following institution of anti-tumour necrosis factor (ant-TNF) therapy, possibly explained by TNF α in active inflammatory lesions inhibiting formation of new bone (through an upregulation of Dickkopf-1, a negative regulator of bone formation), whereas reduction of TNF by applying a TNF-antagonist therapy allows tissue repair to manifest as new bone (Maksymowych et al, 2009a; Pedersen et al, 2011).

One study suggests that inflammatory back pain in patients with early disease, severe sacroiliac MRI bone marrow oedema together with HLA-B27 positivity is a strong predictor of future AS, according to the modified New York criteria (likelihood ratio 8.0), whereas mild or no sacroiliitis, irrespective of HLA-B27 status, is a predictor of not developing AS (Bennett et al, 2008). Data on the value of MRI for predicting therapeutic response in SpA are very limited. A high spine MRI score (Berlin method) and short disease duration have been reported as statistically significant predictors of a BASDAI improvement of >50% (BASDAI50) in AS patients receiving a TNF-antagonist (Rudwaleit et al, 2008). Further and larger studies are needed to clarify the role of MRI in the prediction of therapeutic response.

2.3.5 Summary/clinical utility

MRI has a very important clinical role in the diagnosis of early SpA, and it is a part of the recent ASAS classification criteria for axial SpA. MRI allows sensitive and reproducible monitoring of axial inflammation and is frequently used for this purpose in clinical trials. Certain MRI findings have predictive value for subsequent development of syndesmophytes. However, further studies are needed to determine the optimal use of MRI for monitoring and prognosticating SpA in clinical practice.

2.4 Psoriatic arthritis

The clinical appearance of PsA is very diverse, involving the spine, sacroiliac joints, peripheral joints and/or entheses; accordingly MRI findings vary. PsA shares clinical manifestations with RA and SpA and this also applies to its MRI features (McQueen et al, 2006*). Peripheral PsA synovitis appears similar to RA synovitis on MRI. Similarly, PsA bone erosions do not have disease-specific MRI features, and MRI bone marrow oedema can involve any bone. As in other spondyloarthritides, enthesitis, dactylitis and spondylitis can be seen. Enthesitis may occur adjacent to peripheral and axial joints, and is often associated with synovitis and sometimes with bone marrow oedema (McQueen et al, 2006*). Dactylitis has been shown on MRI to be due to tenosynovitis with effusion, and is sometimes associated with diffuse soft tissue oedema and/or synovitis in nearby finger or toe joints (Olivieri et al, 1997; Olivieri et al, 2002). There are few MRI studies in axial PsA, but findings are similar to AS findings, although more frequently asymmetric (Bollow et al, 2000; Williamson et al, 2004).

2.4.1 Which joint involvement can be visualised by MRI?

MRI can visualise both peripheral and axial musculoskeletal anatomy and PsA disease manifestations. Findings include synovitis (figure 19), tenosynovitis (figure 20), periarticular inflammation (figure 20), enthesitis, bone marrow oedema, bone erosion (figure 21), and bone proliferation (figure 21) (Totterman, 2004; Eshed et al, 2007; Østergaard et al, 2009c).

Figure 19 T1w fat suppressed MR images of the metacarpophalangeal (MCP) joints of a patient with psoriatic arthritis before (A) and after (B–C) injection of gadolinium. Contrast enhancement after contrast injection (synovitis) is particularly seen in the fourth MCP joint, but also in the second MCP joint. The orange line on the coronal slice (C) illustrates the localisation of the axial slices (A–B). Images courtesy of C Wiell.

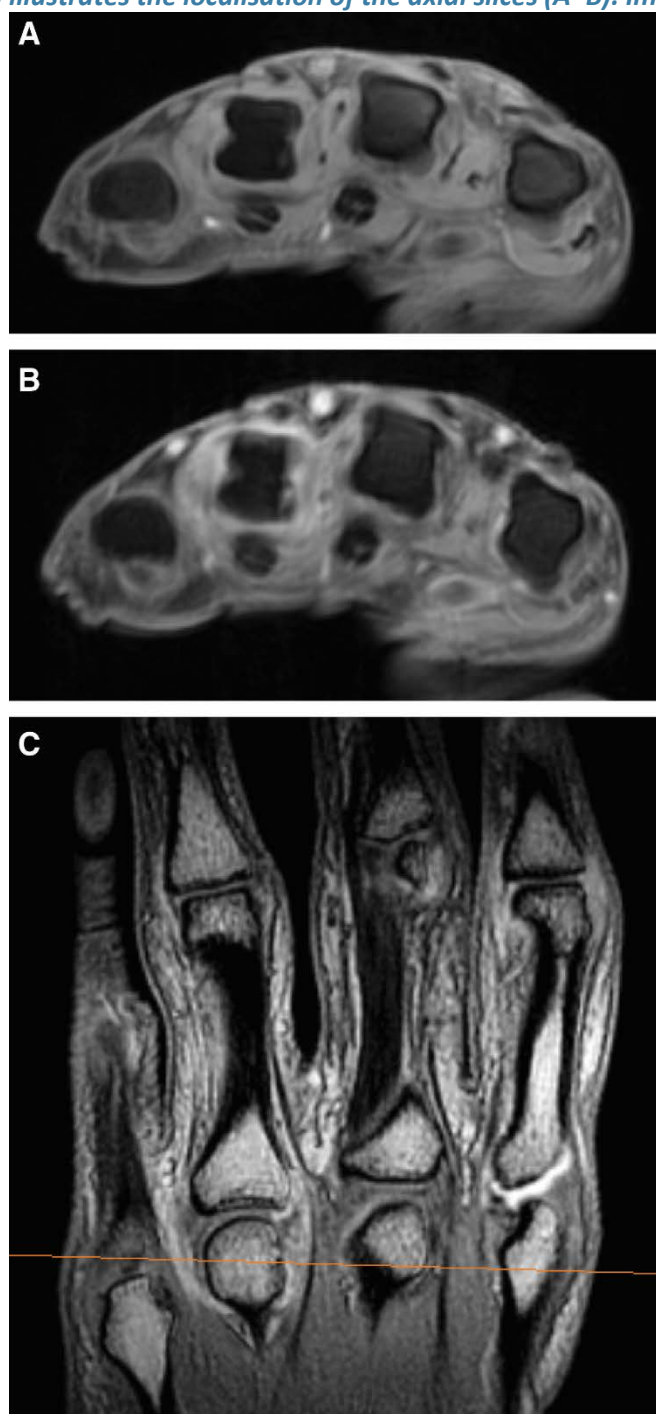


Figure 20 T1 weighted MR images of the fingers of a patient with psoriatic arthritis before (A) and after (B) injection of gadolinium. Axial (A, B) and coronal images show flexor tenosynovitis in the second, fourth and fifth finger and subcutaneous oedema (periarticular inflammation) of the second finger. Images courtesy of C Wiell.

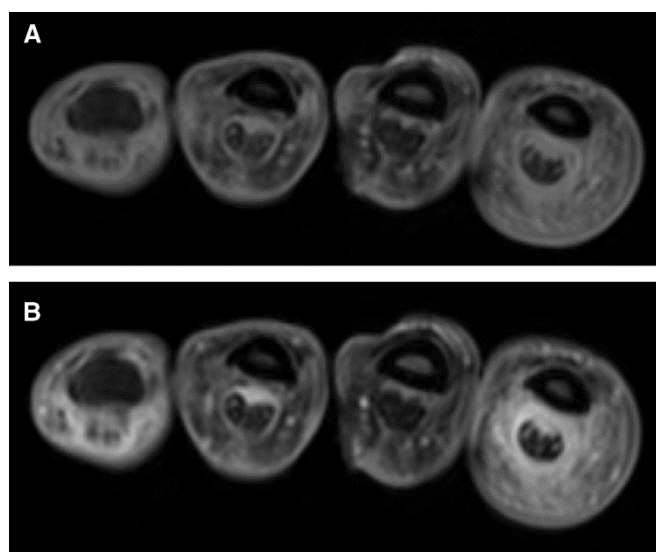
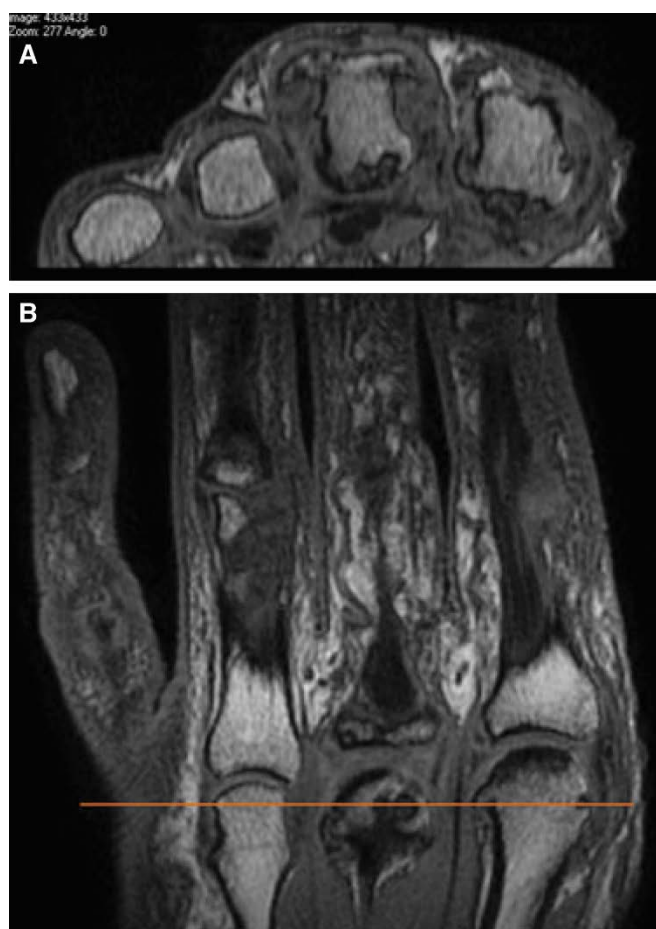


Figure 21 Axial and coronal T1 weighted MR images of the fingers in a patient with psoriatic arthritis. Bone erosion and new bone formation are found in the second and third metacarpophalangeal joint. Image courtesy of C Wiell.



The entheses have attracted attention as a possible primary location of disease in patients with PsA (Maksymowych et al, 2010). Nail disease is common in PsA, and distal interphalangeal joint (DIP) joint inflammation on MRI has been described to extend to the nail bed (Tan et al, 2007). It has been suggested that onychopathy precedes DIP joint damage in PsA, and that MRI of nails is of diagnostic value in undifferentiated SpA (Soscia et al, 2005).

PsA can be clinically silent. In patients with psoriasis without arthritic signs or symptoms, pathological findings on MRI (including periarticular oedema, tendon sheath effusion, intra-articular effusion, synovial pannus, bone erosion, bone cysts, subchondral changes, and joint (sub)luxation) have been reported in >2/3 (68–92%) versus none to ≤1/12 of healthy controls (Offidani et al, 1998; Erdem et al, 2008; Emad et al, 2010).

A general agreement on which joints to image to assess PsA disease activity and damage is not established, and possibly needs to be individualised, based on the disease pattern. It is generally suggested that T1w sequences are in two planes, supplemented by a T2w fat-suppressed or STIR sequence, preferably also in two planes. Intravenous contrast injection is optimal for assessment of synovitis and tenosynovitis, but can be omitted if the aim is purely to detect bone marrow oedema, bone erosion and/or bone proliferation (Madsen et al, 2010c).

2.4.2 Diagnosis

As described above, MRI can detect the different pathologies involved in PsA. However, no studies have documented that MRI in an early undifferentiated arthritis cohort can be used to differentiate PsA from other arthritides.

2.4.3 Monitoring

Most studies only report qualitative MRI assessments of the different pathologies of PsA (see McQueen et al (2006)* for summary up to 2005). Quantitative assessment of contrast enhancement has been reported (Antoni et al, 2002; Cimmino et al, 2005), but is insufficiently validated for clinical use.

Different scoring systems for bone marrow oedema, erosions and/or synovitis in patients with PsA have been developed (Tehranzadeh et al, 2008; Anandarajah et al, 2010), but these have only been used in a few patients and not by centres other than the ones that developed them. To be able to compare the results of different MRI studies of PsA, it is of major importance to have a standardised system for scoring the pathologies. The international OMERACT MRI in inflammatory arthritis group has developed the OMERACT Psoriatic Arthritis Magnetic Resonance Image Scoring System (PsAMRIS) for evaluation of inflammatory and destructive changes in PsA hands (McQueen et al, 2009; Østergaard et al, 2009c; Bøyesen et al, 2011b). This method has shown good intra- and inter-reader reliability and, for inflammatory features (synovitis, tenosynovitis, periarticular inflammation), also good sensitivity to change. In a randomised controlled trial the reductions in synovitis and

oedema were larger in patients treated with abatacept than placebo (Althoff et al, 2009, Glinatsi et al 2015). The usefulness of the OMERACT PsAMRIS in clinical trials and practice needs further testing in clinical trials.

2.4.4 Prognostication

In contrast to RA, no longitudinal studies of the prognostic value of MRI findings in PsA are available. In a cross-sectional MRI study of 11 patients with the aggressive arthritis mutilans form of PsA, and 17 patients with non-mutilating PsA (erosive PsA without bony lysis), there was a close relation between presence of erosion and bone marrow oedema. Based on this, the authors suggest that MRI bone marrow oedema in PsA is also a 'forerunner' of structural joint damage (Tan et al, 2009). Further longitudinal studies are needed to clarify this.

2.4.5 Summary/clinical utility

MRI can be used to visualise all structures involved in PsA, and a system for monitoring of disease activity and damage has been developed. The value of MRI for diagnosis, monitoring of disease activity, and prognostication needs to be established.

2.5 Osteoarthritis

Based on the tomographic nature and ability to visualise cartilage, bone and various soft tissues, MRI is very well-suited for assessment of inflammatory changes, and structural and compositional changes in the cartilage and other structural lesions in OA. The majority of studies have been undertaken in knee joints, or less frequently hip joints, but recent findings in small joints in the hand in generalised OA have also attracted attention.

2.5.1 Which joint involvement can be visualised by MRI?

MRI allows direct assessment of the thickness, surface contour, and internal architecture of articular cartilage in OA (Gray et al, 2004; Eckstein et al, 2007; Guermazi et al, 2008), making staging and monitoring of OA development possible. Osteophytes at the joint margins or beneath the articular cartilage may be seen. Subchondral changes include bone marrow oedema, sclerosis, and bone cysts. MRI 'bone marrow lesions' (or bone oedema lesions), which are areas with inhomogeneous, intermediate-low signal on T1w and high signal on water sensitive techniques (STIR/T2FS), have, by comparison with histological samples obtained by surgery in advanced OA, shown trabecular micro-fracture and bone marrow fibrosis and/or necrosis, but limited interstitial oedema (Bergman et al, 1994; Zanetti et al, 2000; Saadat et al, 2008; Taljanovic et al, 2008). Cystic changes may occur within the areas of subchondral sclerosis and produce well-defined lesions, with high signal on STIR/T2FS. Synovitis is seen frequently by MRI in OA, albeit to a lesser degree than in RA (Østergaard et al,

1997). Synovitis scores obtained by contrast-enhanced MRI have demonstrated a good correlation with arthroscopic and microscopic synovitis scores (Loeuille et al, 2009).

2.5.2 Diagnosis

The use of MRI in the diagnosis of OA offers the advantages described above—that is, that MRI can sensitively depict all the involved pathological changes.

2.5.3 Monitoring

Various quantitative and semi-quantitative techniques have been used to measure structural abnormalities and changes on MRI in OA (Guermazi et al, 2008). Quantitative measurements apply computer-aided image processing to quantify various aspects—for example, volumes of cartilage, bone volume, bone marrow lesion volume, menisci or synovium. Measures of cartilage composition are also available—for example, quantification of glycosaminoglycan content (Gray et al, 2004; Eckstein et al, 2007). Semi-quantitative methods have been used to provide semi-quantitative ‘multiple feature’ (‘whole-organ’) assessments in the knee, based on conventional MRI acquisitions (Biswal et al, 2002; Peterfy et al, 2004; Kornaat et al, 2005; Hunter et al, 2008). These features include articular cartilage morphology, sub-articular bone marrow abnormality, bone cysts, sub-articular bone attrition, marginal and central osteophytes, medial and lateral meniscal integrity, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, synovitis/effusion, intra-articular loose bodies, and periarticular cysts/bursitis (Hunter et al, 2011).

Available data, as reported in a recent systematic literature review, indicate that quantitative measures of joint structure have excellent reliability (ICCs >0.80), and the agreement for semi-quantitative measures was also good-excellent (kappa 0.52–0.88) (Hunter et al, 2011). Furthermore the responsiveness data showed a potential benefit of MRI compared to conventional radiography that generally has standardised response means (SRMs) in the 0.3–0.4 range (Emrani et al, 2008), while certain MRI measures had SRMs >0.80. Multi-feature assessment of the knee by semi-quantitative scoring methods showed a responsiveness of cartilage assessment comparable with quantitative methods (Biswal et al, 2002; Peterfy et al, 2004; Kornaat et al, 2005; Hunter et al, 2008). SRMs for semi-quantitative assessments of medial tibiofemoral cartilage morphology, synovium and bone marrow lesions of 0.55, 0.52 and 0.43, respectively, have been reported (Hunter et al, 2011).

2.5.4 Prognostication

In a recent systematic literature review, the value of MRI to predict certain outcomes in OA was explored, focusing on the ability to predict total knee replacement surgery, change in symptoms, radiographic progression as well as MRI progression (Hunter et al, 2011). It was reported that quantitative cartilage volume change and presence of cartilage defects or bone marrow lesions in all studies was significantly related to

subsequent total knee replacement—that is, a predictive value was demonstrated (Cicuttini et al, 2004; Wluka et al, 2005; Scher et al, 2008).

Furthermore, bone marrow lesions have been moderately related to symptom onset and increased pain in a 15-month follow-up study (Felson et al, 2007). An increase in bone marrow lesion volume was observed in 49.1% of patients with painful knee OA as opposed to only 26.8% of OA patients without knee pain. Among patients with no bone marrow lesions at baseline, the development of new bone marrow lesions were more common in painful knees than in control knees (32.4% vs 10.8%) (Felson et al, 2007). A recent knee OA case–control study showed that changes in bone marrow lesion extent was associated with fluctuations in knee pain, and improvement of bone marrow lesions, but not of synovitis or effusion, was associated with a decreased risk of knee pain (Østergaard, 1999). In contrast, the systematic literature review showed an inconsistent and generally weak relation between cartilage loss and symptom change, and a weak relation between change in synovitis and change in pain. Finally, the review indicated that the presence of meniscal damage, cartilage defects and/or bone marrow lesions predicts subsequent MRI progression.

2.5.5 Summary/clinical utility

MRI can be used to visualise all structures involved in OA, and several reproducible and responsive quantitative and semiquantitative methods for monitoring of disease progression have been established. These include both systems for pure cartilage assessment and ‘whole-organ’ assessment systems, incorporating aspects of synovitis, bone marrow lesions, etc. A prognostic value of certain MRI features, particularly bone marrow oedema, for disease progression has been established. Availability of effective therapies, and the ensuing increased need for sensitive diagnosis, monitoring and prognostication, would increase the clinical benefit of using MRI in OA clinical practice.

3 Computed tomography

CT enables high resolution imaging in multiple planes, although it requires exposure to ionising radiation. Multislice CT offers advantages over conventional CT with improved scan resolution, shorter imaging time and a lower radiation exposure (Ostendorf et al, 2001). CT is especially useful for visualising bone and cartilage, so it has been applied to the study of pathologic changes in these structures including subtle cortical or intraosseous lesions. However, unlike US and MRI, it is unable to visualise other joint and soft tissue structures with discernible clarity so it is not able to clearly demonstrate changes such as inflammation or infection.

In the evaluation of bone erosions in RA, the first comparison study between imaging modalities suggested that CT may be more sensitive than radiography but inferior to US and MRI in the detection of erosions of the humeral head, although it was commented that MRI may overestimate erosion size (McQueen et al, 2007).

Some authors regard CT as the gold standard for the assessment of destruction of calcified tissue, such as bone erosions in RA (Dohn et al, 2007; Dohn et al, 2008).

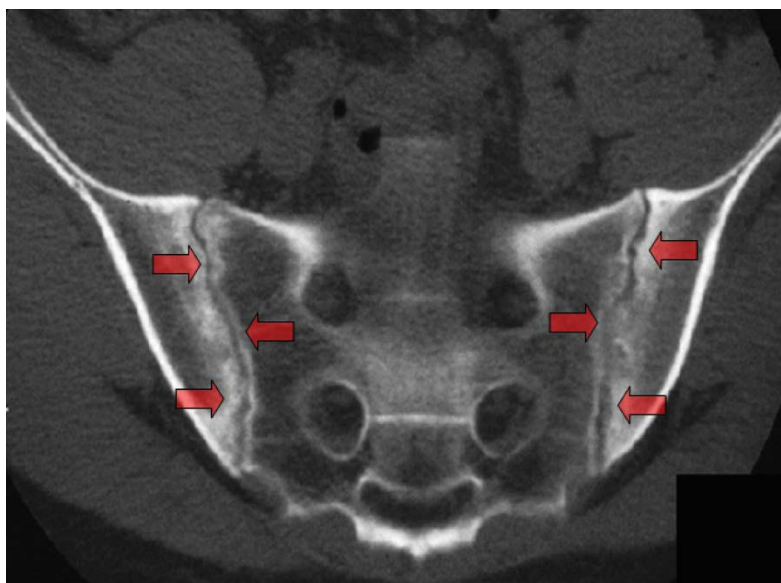
3.1 Rheumatoid arthritis

Using CT as the reference method, Døhn et al demonstrated high specificities for MRI (96%) and US detected erosions (91%) in RA MCP joints. Radiography exhibited high specificity (100%) but low sensitivity (19%). CT detected more erosions than the other imaging modalities (Døhn et al, 2006). A study comparing CT and MRI, to determine erosion volumes in the MCP joints of RA patients, demonstrated very high intra-modality and inter-modality agreements (Dohn et al, 2007). The use of micro CT in RA and PsA patients seems to permit a better visualization of erosive changes and proliferation with possible implication in term of diagnosis, follow up or prognosis (Barnabe et al, 2015; Albrecht et al 2013; Finzel et al 2011; Simon et al 2016). However this technique is actually used predominantly for research and not for clinical management. There may also be a role for CT in the imaging of patients with crystal arthropathies such as gout with evidence to suggest that CT may provide more specific detection of tophi than US or MRI (Jimenez-Boj et al, 2007, Araujo et al 2015; Bayat et al. 2016). In general, the use of CT in the evaluation of patients with early inflammatory arthritis is limited, as better validated, more sensitive tools not requiring radiation or contrast exposure are currently available, such as US and MRI.

3.2 Axial spondyloarthritis

The demonstration of sacroiliitis is important in the diagnosis of AS, but this can be difficult to detect clinically and radiographs may be normal especially in early disease. CT may be useful to assess such patients as this technique is often able to depict sacroiliitis before it is apparent on radiography (figure 22). CT has also been compared to MRI in imaging sacroiliitis. While some studies have found the two techniques to be comparable, MRI has the advantage of being able to image subchondral bone oedema, an early marker of active sacroiliitis (Yu et al, 1998; Puhakka et al, 2003), and is therefore the imaging modality of choice in such cases. However, CT is well suited for exact delineation of structural bone changes, including fractures, and is of value for resolving particular clinical problems, or for diagnosing early the presence of a definite radiographic sacroiliitis in patients with suspected SpA (Devauchelle et al, 2009). Another potential use of CT is the detection of insufficiency fractures of the pelvis and sacrum. Such patients may exhibit indeterminate clinical symptoms and signs and radiography may be normal. Isotope bone scanning and MRI can be used in such circumstances but CT may be able to provide more accurate visualisation of a fracture.

Figure 22 CT scan demonstrating erosions, sclerosis (mainly iliac) and joint space narrowing consistent with sacroiliitis in a patient with spondyloarthropathy. (Reproduced with permission from Tan AL, McGonagle D. Imaging of psoriatic arthritis. In: Mease PJ, Helliwell PS, eds. Atlas of psoriatic arthritis. London, Current Medicine Group, 2005.)



4 Ultrasonography

US is an imaging technique based on the emission and reception of mechanical sound waves by piezoelectric crystals located inside the transducer or probe. The frequency is greater than the hearing frequency range of the human ear (ie, 20 kilohertz (kHz)). Ultrasound wave frequencies of diagnostic US systems range from 3 to 25 megahertz (MHz). Ultrasound waves transmit differently through different media depending on their composition and are reflected at the interfaces between materials of different acoustic impedance. The reflection of ultrasound through the body tissues generates US images that consist of varying degrees of black-and-white images. The US technique includes grey scale (GS) imaging of anatomic structures and blood flow detection by Doppler technique. Doppler US is based on the alteration of the frequency of a sound beam reflected back to the source when it encounters a moving object.

For the last 50 years, the medical applications of Doppler US have included diagnosis of abdominal, pelvic, obstetric, breast and cardiac pathologies. More recently, musculoskeletal ultrasonography (MSUS) has progressively become an established imaging technique for evaluating periarticular and intra-articular structures involved in musculoskeletal conditions, including rheumatic diseases. The use of high-resolution transducers improves the visualisation of different anatomic structures (figure 23) and permits the assessment of a wide range of inflammatory and structural abnormalities (figures 24–27). The use of appropriate probe frequencies is mandatory for the correct imaging of musculoskeletal structures and optimises the US detection of local pathology. At higher frequencies, the image resolution is greater but the tissue penetration is lower. Therefore, higher frequency linear transducers (eg, 10–18 MHz) should be used for superficial anatomic

structures, such as the small joints of the hand and feet, whereas lower frequency transducers (eg, 5–10 MHz) are appropriate for deeper joints, such as the hip, ankle and shoulder. In addition, a correct machine setting markedly increases the sensitivity of the equipment in assessing a number of abnormalities, both by using GS and Doppler modalities.

Figure 23 *Ultrasonography of the third metacarpophalangeal joint of a normal subject demonstrating joint and soft tissue structures.*

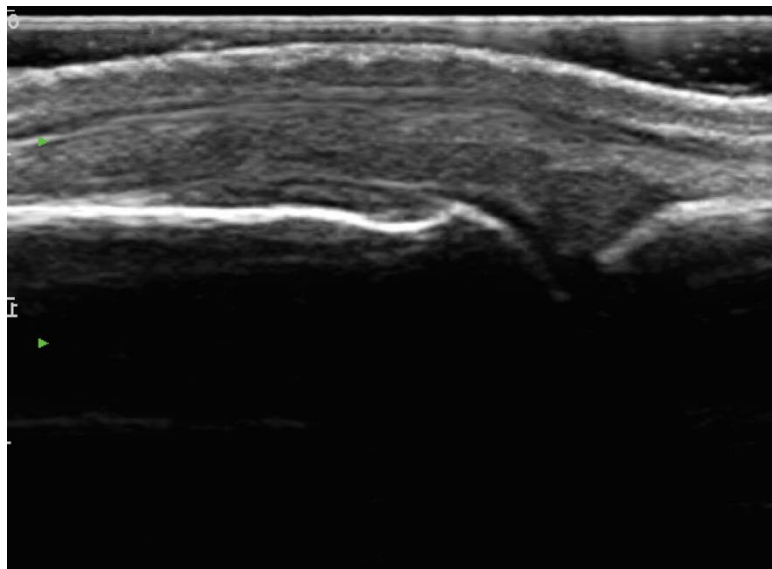
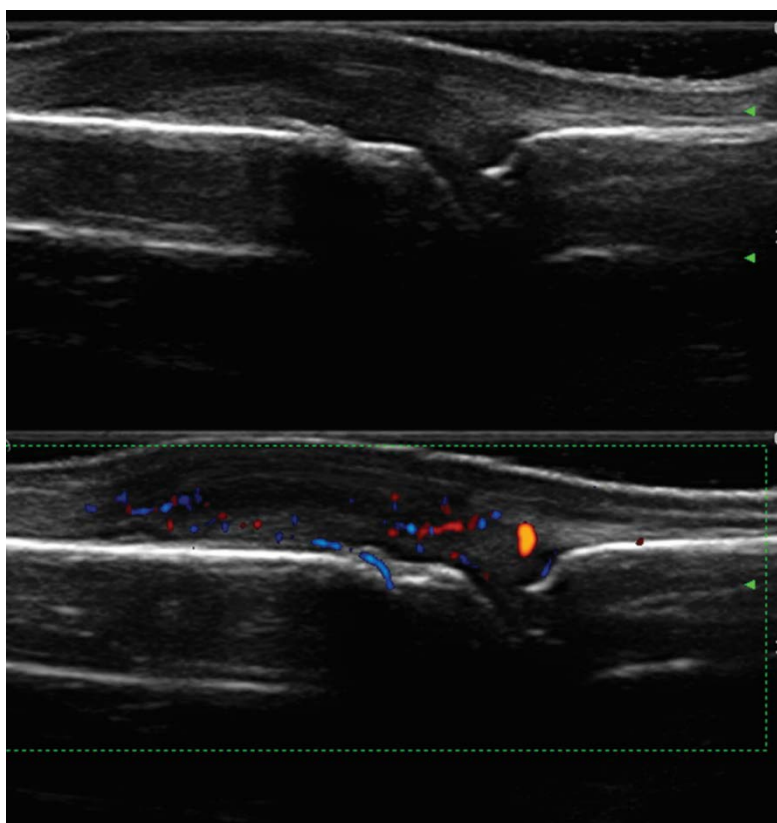


Figure 24 *Ultrasonography (grey scale and power Doppler) demonstrating synovial hypertrophy of the third metacarpophalangeal joint in a patient with early rheumatoid arthritis. Images courtesy of G Sakellariou.*



US is a routinely available, dynamic, non-invasive and relatively inexpensive bedside imaging method that allows for a multiplanar assessment of the musculoskeletal system, with high patient acceptability. In addition, a multi-joint assessment can be performed during the same scanning session.

Recent advances in technology have led to an extraordinary improvement in the quality and level of US equipment, with production of machines that offer good visualisation of most superficial and deep musculoskeletal structures. In particular, the great resolution of anatomic details at the level of superficial musculoskeletal structures imaged by high frequency transducers has promoted an increasing use of MSUS both in rheumatologic routine clinical practice and in research settings. In addition, the enhanced sensitivity for detecting low velocity flow in small synovium, tendon and enthesis vessels achieved by recent colour Doppler and PD techniques has led to the incorporation of Doppler US in rheumatology. The difficulties in detecting abnormalities within deep joints by physical examination facilitate the applications and use of US also in the assessment of pathology at the level of large joints.

MSUS allows an immediate correlation between imaging findings and clinical data, which improves diagnosis and management of patients with a range of rheumatic diseases from inflammatory arthritis, vasculitis or OA to soft tissue diseases.

4.1 Rheumatoid arthritis

In patients with RA, US demonstrates a wide range of elementary lesions. It provides detailed information on the quantity and characteristics of the fluid collection, the presence of synovial hypertrophy, and the integrity of articular cartilage and bony surface. US is also useful in supporting differential diagnosis, in monitoring the disease course, and in stratifying disease severity once the diagnosis is made.

4.1.1 Elementary lesions

US allows direct visualisation of most features of inflammatory arthritis, including effusion, synovial hypertrophy, tenosynovitis and bony erosions (figures 24–27).

Effusion is defined as ‘abnormal hypoechoic or anechoic intra-articular material that that can be displaced and compressed, but does not exhibit a Doppler signal’, while synovial hypertrophy/proliferation (figure 24) is defined as ‘abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible and which may exhibit a Doppler signal’ (Wakefield et al, 2005).

Tenosynovitis (figure 25) is defined as ‘hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath with possible signs of Doppler signals, which is seen in two perpendicular planes’ (Wakefield et al, 2005).

Figure 25 Ultrasonography (grey scale and power Doppler) demonstrating tenosynovitis of the extensor digitorum tendon in a patient with early rheumatoid arthritis, in transverse and longitudinal planes. Images courtesy of G Sakellariou.

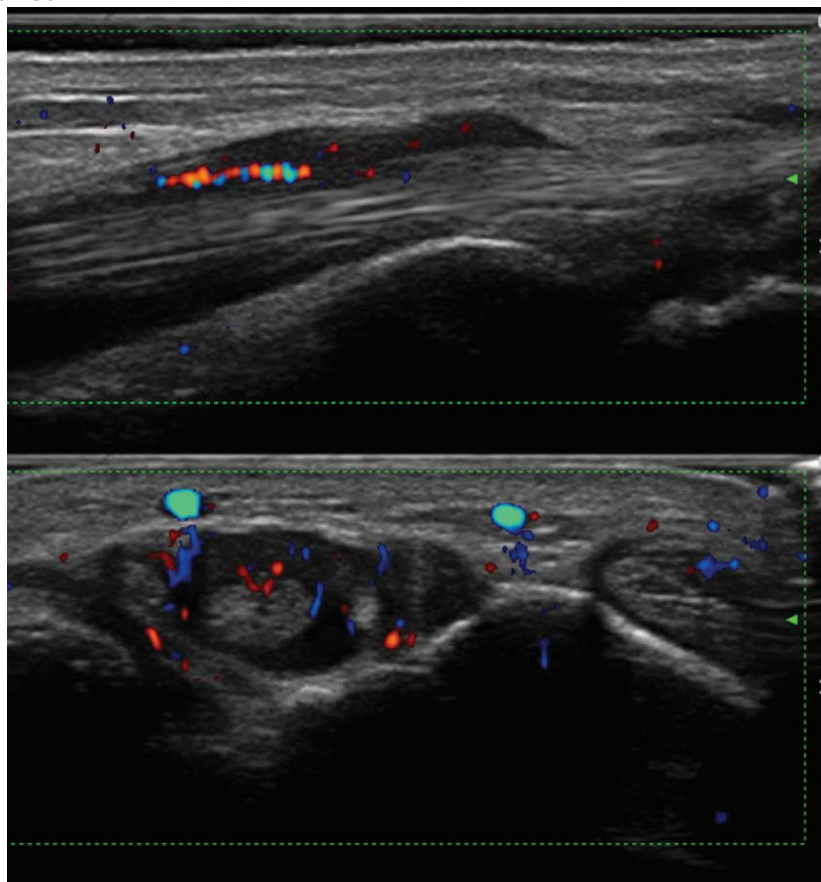
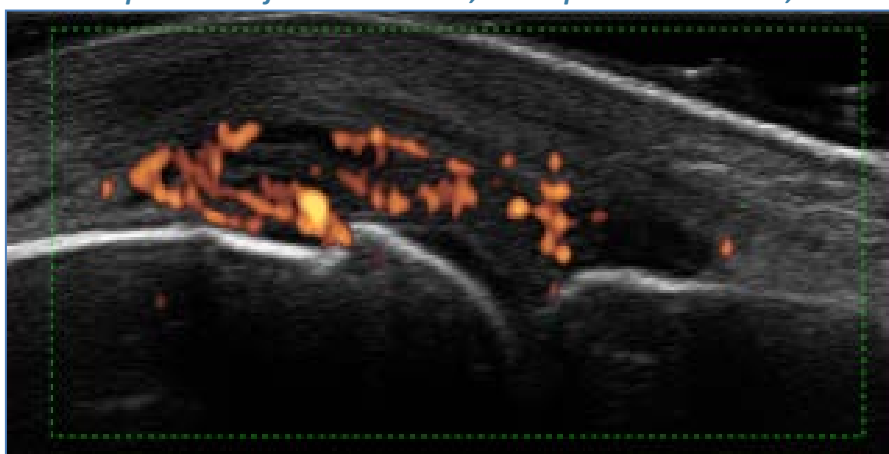
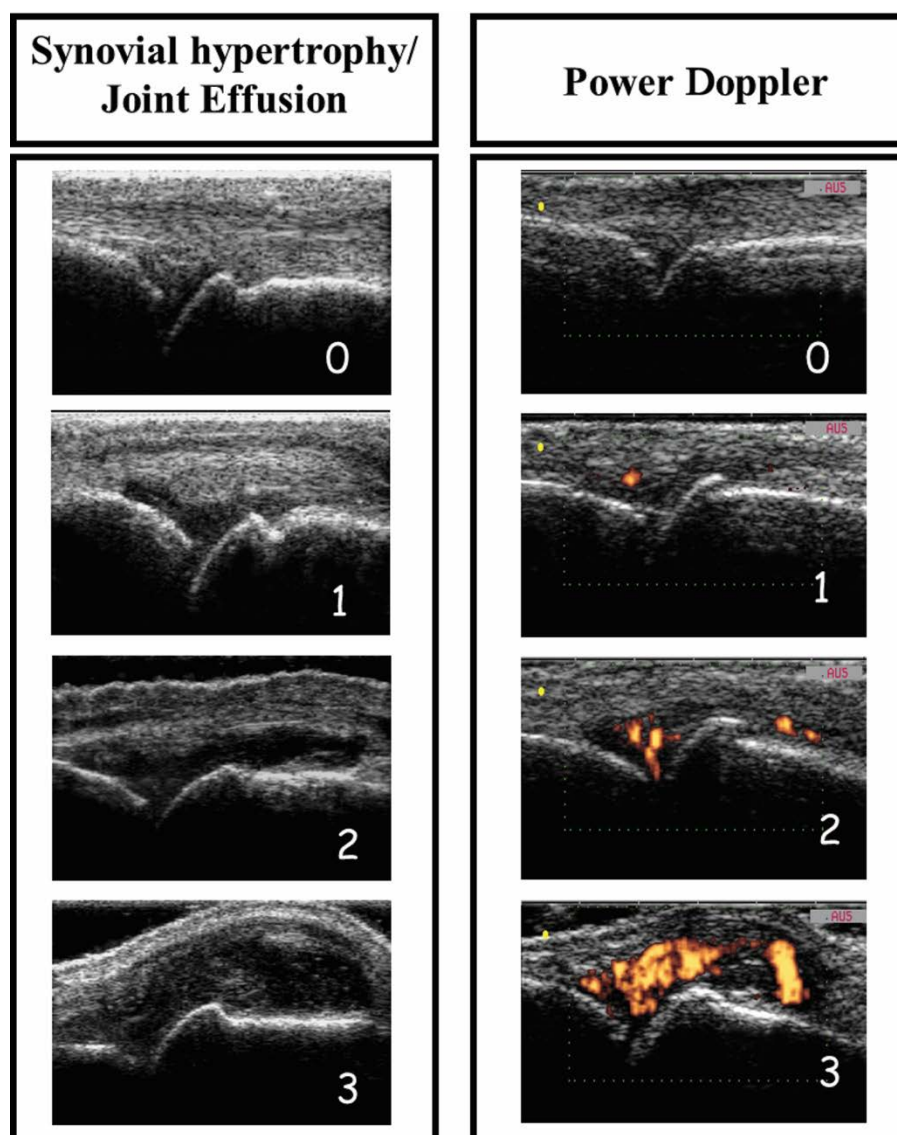


Figure 26 Ultrasonography (grey scale and power Doppler) demonstrating synovial hypertrophy (SH) and erosive change (Er) in the fourth metacarpophalangeal joint in a patient with established rheumatoid arthritis. (Reproduced with permission from Brown et al, Clin Exp Rheumatol 2004;22:S18–25.)



The most typical RA lesion detectable by MSUS is RA bone erosion (figure 26), which is defined as an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes.

Figure 27 Ultrasonography (grey scale and power Doppler) scoring system for metacarpophalangeal joints.



4.1.2 Diagnosis

The potential utility of US in the diagnostic work-up of early onset inflammatory polyarthritis relies on the detection of bony erosions and on the accurate assessment of joint inflammation. However, a recent study demonstrated the high prevalence of isolated effusion, as compared to synovial hypertrophy, in small joints of healthy subjects, suggesting that effusion should not be considered as a sign of joint inflammation in the absence of synovial hypertrophy (Padovano et al, 2016*)

Several studies have evaluated the performance of US in detecting bony erosions in comparison with conventional radiography, MRI and CT scan.

MSUS has consistently been demonstrated to be more sensitive than conventional radiography at detecting bone erosions in the hands, wrists, feet and shoulder in RA (Alasaarela et al, 1998; Backhaus et al, 1999; Wakefield et al, 2000; Schmidt, 2001; Backhaus et al, 2002; Hermann et al, 2003; Weidekamm et al, 2003;

Lopez-Ben et al, 2004; Magnani et al, 2004; Scheel et al, 2006; Szkudlarek et al, 2006; Grassi and Filippucci, 2007*). This is largely explained by the multiplanar nature of an MSUS assessment and its ability to detect small lesions. Wakefield et al (2000) detected 6.5 times more erosions in the MCP joints of patients with early RA using MSUS than were visible on X-ray compared to 3.4 times in established disease. MRI was used to successfully corroborate the accuracy of the MSUS results and the same study also reported a high level of intra- and inter-observer reliability of the MSUS findings. MSUS is particularly valuable for detecting erosions at the second and fifth MCP and fifth MTP joints, but sensitivity is reduced where probe access is more difficult, particularly the third and fourth MCP and intercarpal joints.

However, the clinical relevance of US joint erosions in terms of diagnostic properties is highly variable and depends on the site and dimension of erosive changes. Erosions in the fifth MTP are the best candidate to increase the probability of RA diagnosis in patients with arthritis.

The longitudinal progression of erosions on MSUS has not been extensively evaluated, but in a single study, erosive progression was seen more often on MSUS and MRI over a 2-year period than on radiographs, implying that these imaging techniques may be more sensitive measures of change in bone damage than conventional radiography (Backhaus et al, 2002). Another study has demonstrated the ability of MSUS to follow erosion progression over a 6-month period, although in this particular paper, MSUS identified a lower number of erosions than either MRI or radiography (Klarlund et al, 2000).

Rather than a direct application of US as a diagnostic test of RA, the combination of clinical and US findings may help in improving diagnosis in the earliest phases of the disease, in which classification may not be made by standard clinical, laboratory and radiographic data. Two different algorithms combining clinical and US findings have shown a satisfactory accuracy in the identification of early-onset undifferentiated arthritis evolving towards RA over time (Freeston et al, 2010; Salaffi et al, 2010).

As for MRI, the ACR/EULAR 2010 criteria for RA (Aletaha et al, 2010) have added a role of US in the diagnosis of RA, allowing MRI and US to be used to determine the joint involvement (Aletaha et al, 2010; Ostergaard et al, 2010*; Aletaha et al, 2011).

4.1.3 Monitoring and scoring

Accurate assessment of disease activity and joint damage in RA is important for monitoring treatment response. Several MSUS scores have been used for assessing and monitoring RA disease activity, and only recently a consensus on a reliable and sensitive to change instrument has been reached (Ohrndorf et al, 2013). Different semiquantitative (0–3) systems and quantitative measurements are used at joint level to quantify elementary lesions: joint effusion, synovial hypertrophy, tenosynovitis, PD synovitis and bony erosions (table 1)

Table 1 Different scoring systems proposed at joint level

		Elementary lesions	Grading	Joints
Szkudlarek	2003	Effusion, synovial hypertrophy, PD synovitis, erosion	0–3	Unilateral MCP II, III, PIP II, MTP I, II
Scheel	2005	Synovitis	0–3	Unilateral MCP II–V, PIP II–V
Naredo	2005	Effusion, synovial hypertrophy, PD	0–3	Sum of bilateral 60-, 18-, 16-, 12-, 10-, 6-joint score
Backhaus	2009	Synovitis, tenosynovitis/paratenonitis, PD synovitis, bone erosions	0–3 0/1	Unilateral wrist, MCP II, III, PIP II, III, MTP II, V
Ellegaard	2009	PD synovitis	0–3	Unilateral wrist
Dougados	2010	Synovitis	0–3	Bilateral 28 joints vs 38 joints (28+MTPs) vs 20 joints (20 MCPs+20 MTPs)
Hammer	2011	Synovitis; tenosynovitis, PD, bursitis	0–3	Bilateral 78 joints vs 44 joints 28 joints 12 joints 7 joints
Perricone	2012	Effusion, synovial hypertrophy, PD synovitis	0–3	Wrists, II MCPs, knees
Naredo	2013	Tenosynovitis, PD	0–3	Wrist extensor compartments, two finger flexor tendons and two ankle tendons
D'Agostino	2016	Synovitis, GS and PD combined score (GLOESS)	0–3	Bilateral 22 joints

MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PD, power Doppler; PIP, proximal interphalangeal joint.

Szkudlarek et al (2003a) developed a four-step semiquantitative US grading system separately for joint effusion, synovial thickening, bone erosion, and PD activity of five preselected small joints (unilateral MCP II, III, PIP II and MTP I, II joints examined from a dorsal aspect). Joint effusion was defined as a compressible anechoic intracapsular area and the amount of fluid semi-quantitatively scored as follows: grade 0: no effusion; grade 1: minimal amount; grade 2: moderate (without distension of the joint capsule); grade 3: extensive (with distension of the joint capsule). Synovial thickening was defined as a non-compressible hypoechoic intracapsular area scored as follows: grade 0: none; grade 1: minimal synovial thickening; grade 2: synovial thickening bulging over the line linking tops of the periarticular bones without extension along the bone diaphysis; grade 3: synovial thickening bulging over the line linking tops of the periarticular bones with extension to at least one of the bone diaphyses. Bone erosions were defined as follows: grade 0: normal bone surface; grade 1: bone surface irregularity without the defect being seen in two planes; grade 2: defect of the surface in two planes; grade 3: bone defect creating extensive bone destruction. Semiquantitative grading of the PD evaluation was as follows: grade 0: no flow; grade 1: single vessel signals; grade 2: less than half of the area of the synovium filled with vessels; grade 3: more than half of the area of the synovium filled with vessels.

The overall disease activity or damage can be quantified by accumulating findings from different sites into scores at the patient level, which can be monitored over time.

In the development of US multi-joint cumulative scores, several studies have analysed different numbers of joint scores, and all studies reached the conclusion that reduced summated scores provide a good reflection of overall inflammatory activity in RA (Szkudlarek et al, 2003a; Scheel et al, 2005; Naredo et al, 2005b; Backhaus et al, 2009; Ellegaard et al, 2009; Dougados et al 2010; Hammer et al, 2011; Perricone et al, 2012; Naredo et al, 2013).

All the scoring systems presented assessed the most frequently affected joints in RA and included the components of synovitis such as synovial hypertrophy, effusion and PD activity (table 1). Moreover, in some of them periarticular involvement is also assessed. In addition, a new scoring system—Global OMERACT-EULAR Sonography Scoring (GLOESS)—has been recently developed and represents a promising novel tool to measure synovitis in RA (Iagnocco et al, 2014, D’Agostino et al, 2016b*).

4.1.4 Prognostication

US is a tool that can help clinicians to predict disease progression and the development of joint damage in early RA patients. Initial evidence came from Taylor et al (2004), who investigated US-detected synovial thickness (using grey scale US (GSUS)) and vascularity (using power Doppler US (PDUS)) as predictors of radiographic joint damage of the hands and feet after 1 year. They found that a high baseline PDUS signal at the MCP joints correlated with radiographic joint damage over the following year in patients receiving methotrexate. Naredo et al (2007) confirmed this result by studying 42 early RA patients, who were followed up using PD after the initiation of disease modifying antirheumatic drug (DMARD) therapy. US imaging was carried out at 3, 6 and 12 months and radiographic progression monitored over a 12-month period. GSUS and PDUS were performed at 28 joints including shoulders, elbows, wrists, hands and knees. Time-integrated PDUS values were strongly correlated with DAS28 (Disease Activity Score 28) after 1 year and with radiographic damage progression measured by the SvdH (Sharp/van der Heijde) score. The implication from these studies is that highly vascular and inflamed rheumatoid synovium may contribute to the development of bone erosion and is therefore an important imaging biomarker in early RA.

A recent study examined this question prospectively over 2 years in patients with established RA and found that evidence of baseline US synovitis (PDUS scores) did increase the risk of structural damage progression (on X-ray) with an OR of 1.75, but clinically detected synovitis also predicted damage with an OR of 2.01, implying equivalence (Dougados et al, 2010). The authors concluded that the assessment of synovitis was important for predicting subsequent structural deterioration, irrespective of whether the joints were examined clinically or using US.

However, in a setting in which clinical assessment is not sensitive enough to identify inflammation and define clinical remission, a considerable body of evidence now exists in support of the use of US in the assessment of residual disease activity. It is well recognised that some patients with RA in clinical remission still have radiographic progression. Brown et al (2008) have investigated the predictive value of subclinical inflammation in terms of radiographic progression. This study clearly indicated that the patients with PD signal in clinical remission had the highest risk of progressive joint damage. This result has been confirmed in other studies. Analysing RA patients in clinical remission, it has also been shown that the presence of subclinical inflammation detected by US may help in discriminating patients with short-lived or unstable clinical remission. In particular, several reports support that patients with PD positive synovitis showed a significantly increased risk of early relapse compared with PD negative synovitis (Scirè et al, 2009; Foltz et al, 2012; Saleem et al, 2012).

A recent publication summarizes the evidence of the clinical utility of US for the management of RA in clinical practice by addressing the evidence of the literature and the experts' experience (D'Agostino et al, 2016a*).

4.1.5 Summary/clinical utility

US can be used to visualise all structures involved in RA except subchondral bone, at multiple joint sites at the same time. Diagnostic utility is specially enhanced by the combination of clinical and imaging findings, and also in the application of classification criteria for RA. US is a promising tool to monitor disease activity over time and to readily assess persistence of subclinical inflammation, and to drive decision-making in clinical practice.

4.2 Spondyloarthritis

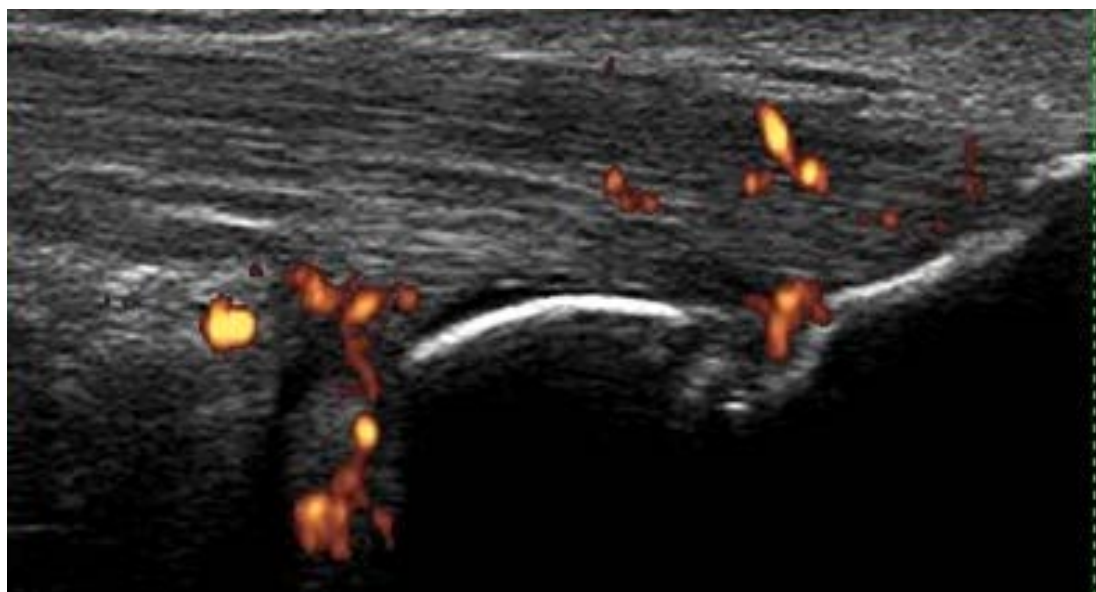
Studies on the application of US in SpA are less systematic than in RA. However, most of the results achieved in research on RA can be extended to SpA. US allows the visualisation of most of the relevant joint pathologies associated with SpA, including enthesitis, bone erosions, synovitis, dactylitis, bursitis and tenosynovitis.

4.2.1 Elementary lesions

Though synovial inflammation and bony erosions do not show distinctive features compared to RA, in SpA US can also demonstrate some peculiar characteristics such as enthesitis, dactylitis and sacroiliitis.

A clear consensus US definition of enthesitis has been recently proposed by the OMERACT US working group (Terslev et al, 2013), even if the following broader definition of enthesopathy, proposed by the same group is still applied: “abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification) seen in two perpendicular planes which may exhibit Doppler signal and/ or bony changes including enthesophytes, erosions or irregularity” (Figure 28) (Wakefield et al, 2005).

Figure 28. Ultrasonography (grey scale and power Doppler) pattern of a SpA related enthesitis demonstrating thickening of the enthesis insertion, erosions of cortical bone, Doppler signal at enthesis insertion but also in the body of tendon and in the bursa, in a patient with an enthesitis of the Achilles tendon insertion.



Dactylitis may be readily demonstrated by US as subcutaneous soft tissue enlargement, flexor tenosynovitis and adjacent synovitis. However, a valuable heterogeneity in frequency of soft tissue involvement and synovitis has been found, while flexor tenosynovitis findings are consistently reported (Bakewell et al, 2013).

Sacroiliitis may be demonstrated using colour and duplex Doppler US, or microbubble contrast-enhanced colour Doppler US. In AS, US has in one study been reported to show good sensitivity and specificity for the diagnosis of active sacroiliitis, using MRI as reference standard (Klauser et al, 2005). However, US can only visualise the most posterior part of the joint limiting its ability to assess the joint, including its sensitivity in detecting anatomical changes compared to other techniques such as MRI and CT.

4.2.2 Diagnosis

US has a greater sensitivity than clinical examination and other imaging techniques for the detection of peripheral involvement of SpA (Balint et al, 2002b).

Several studies have tried to use imaging techniques, including US, to demonstrate different patterns of joint involvement between SpA and other rheumatic diseases (Gutierrez et al, 2011). However, US synovitis, erosion and tenosynovitis in SpA do not substantially differ from those observed in other inflammatory arthritides (D'Agostino et al, 2010*).

US is able to clearly depict enthesal pathology and would appear to be the best candidate tool for the discrimination between spondyloarthropathies and RA.

Several studies have highlighted the diagnostic value of US in assessing the inflammation of enthesitis in SpA (D'Agostino et al 2016c*). A significant proportion of SpA patients (including PsA) have been found to have subclinical enthesitis using US. Balint et al (2002b) showed that 22% of entheses assessed were abnormal on clinical examination and 56% were abnormal on GSUS. D'Agostino et al (2003) used PDUS to assess multiple enthesal sites (greater trochanter, pubis, patella, Achilles tendon, plantar fascia, medial and lateral epicondyles) and showed that GS enthesal involvement on US of at least one of these sites is seen in 98% of patients with SpA including PsA, but is far less common in controls with mechanical back pain (44%) or RA (60%) (D'Agostino et al, 2003). The authors also demonstrated that the clear difference in the US enthesal involvement between SpA and the other diseases was made by the presence of enthesal vascularization in SpA patients which was never detected in RA and in mechanical back pain patients. Falsetti et al (2003) looked specifically at the calcaneal enthesitis using GS US and plain radiography comparing patients with PsA, RA and OA. There was no significant difference found between the PsA and RA groups, but there was a trend towards more Achilles enthesitis and plantar fasciitis in PsA and more erosive disease in patients with RA. Freeston et al (2012) assessed 42 patients with new-onset PsA (median disease duration 11.1 months) and 10 control subjects with clinical examination and GS/PD US of a standard set of entheses and found the prevalence of subclinical enthesitis in this early PsA cohort was low. It should be noted that the US equipment is of outmost importance when studying enthesitis, as the Doppler modality, which makes the difference in defining an SpA/PsA related enthesitis can be different according to the quality of the machine (Torp-Pedersen et al, 2015*).

4.2.3 Monitoring and scoring

The use of US as an objective outcome measure has also been expanding in SpA. The majority of US studies on synovitis have used definitions and scoring systems developed in the setting of RA.

One of the main issues in SpA, compared to RA, is related to the set of joints to be assessed. Given the wide diversity of joint involvement between specific diagnoses and individuals, a restricted joint evaluation is less valid to evaluate the overall disease activity or damage in these patients (Ficjan et al, 2014)

Several US enthesitis assessment tools have been developed in SpA cohorts. The Glasgow Ultrasound Enthesitis Scoring System (GUESS) tool examines five lower limb sites (Achilles, quadriceps, superior and inferior patellar tendons and plantar fascia) (Balint et al, 2002b), while the Madrid Sonographic Enthesis Index (MASEI) assesses six sites (five as before plus the triceps tendon) (De Miguel et al, 2009). Using these tools, US has been shown to be more sensitive than clinical examination for detecting enthesitis in established SpA cohorts (De Miguel et al, 2009; Naredo et al, 2011). However, it should be noted that these scoring systems have been developed for diagnostic purposes and are not suitable for evaluating therapeutic response as

mainly based on GS structural abnormalities. The OMERACT US group is working on a scoring system suitable for evaluating responsiveness.

4.2.4 Prognostication

In contrast to RA, no longitudinal studies of the prognostic severity value of US findings in SpA are available. One study evaluated the prognostic value in term of early diagnosis in a cohort of patient with suspected SpA (D'Agostino et al, 2011*)

4.2.5 Summary/clinical utility

US can be used to visualise articular and peri-articular structures involved in SpA, particularly enthesitis. A valid and reliable definition of elementary lesions and a system for monitoring of disease activity and damage is required to develop prospective studies which can elucidate the impact of US abnormalities on differential diagnosis, prognostic stratification and evaluation of treatments in SpA.

4.3 Osteoarthritis

Plain radiography is considered the gold standard for assessing OA bony abnormalities and indirectly evaluates articular cartilage damage. However, this technique is limited by its inability to directly visualise articular cartilage, synovial recesses, the peripheral aspect of the menisci and other soft tissues involved in the pathophysiology of OA. High resolution MSUS offers an overall assessment and follow-up of the joints in OA. It provides valuable information that fills the gap between clinical and radiological evaluation. MSUS of the peripheral joints can be easily carried out at the time of consultation, allowing an immediate correlation between clinical and imaging findings, which may improve the diagnosis and management of patients with OA.

The articular cartilage, bone contour, synovial recesses, tendons, ligaments, bursae and peripheral aspect of the menisci can be evaluated by US.

In addition, MSUS can be routinely used to guide accurate and safe diagnostic or therapeutic injections in the OA joints. Some technical limitations of MSUS can reduce its diagnostic capability in OA, including limited acoustic windows for cartilage and bony cortex assessment in some joints (eg, hip, glenohumeral), lack of visualisation of bone marrow abnormalities, low sensitivity of current Doppler modalities in deep/large joints (eg, hip, glenohumeral), and operator dependence.

4.3.1 Which pathologies are visualised by US?

In OA, US is appropriate for the assessment of joint inflammatory changes such as effusion and synovial hypertrophy. In addition, due to their sensitivity in demonstrating pathological vascularisation within the synovial tissue, Doppler modalities can show synovitis and differentiate between active and inactive

inflammation (Maksymowych and Landewe, 2006*; Ostergaard et al, 2008*). OMERACT definitions for effusion and synovial hypertrophy developed in RA can also be applied in OA.

US is also able to demonstrate the signs of structural damage involving the hyaline cartilage and the bony cortex at joint margins.

The correct use of appropriate acoustic windows at different joint sites is fundamental for imaging articular cartilage by US: maximal flexion for hand and knee, extension for elbow, wrist, ankle and foot, and in intra-rotation/extra-rotation for hip and shoulder. With a correct, perpendicular insonation of the structure by the US beam, in healthy joints the cartilage typically has a well-defined anechoic echotexture with sharp, regular and continuous margins.

The anterior interface, localised between cartilage and soft tissues, is thinner than the posterior edge, visualised between cartilage and bony cortex. According to the size of the joint, the thickness of the cartilage varies between 0.1 and 0.5 mm (hand and foot) and 3 mm (knee) and is accurately measured with current high tech equipment that allows even sub-millimetre measurements. Assessment of the contralateral site to perform complete comparisons is always recommended.

US is able to demonstrate a wide set of cartilage abnormalities in OA. In early disease, loss of sharpness and irregularities of surfaces are imaged and initially involve the superficial edge. These abnormalities, which correspond to tissue degeneration and cleft formation, are followed by echotexture changes with inhomogeneous hypoechogenicity, and, later on, by focal and asymmetric thinning up to the complete absence of the cartilaginous layer that is related to cartilage breakdown and bony denudation.

Bony cortex is imaged by US as a hyperechoic, regular and continuous surface. It has a linear shape that becomes curvilinear at the joint margins. Osteophytes are characteristic findings in OA and are imaged by US as a step-up of the bony prominence at the end of the normal bone contour, or at the margins of the joint seen in two perpendicular planes, with or without acoustic shadow.

The high sensitivity of US in showing bony cortex changes has been widely reported and, in erosive hand OA, erosions are imaged as intra-articular discontinuities of the bone surface visible in two perpendicular planes. Even in this case, OMERACT definitions for erosions in RA can also be applied in OA. They can be detected with varying degrees of clarity related to the interposition of osteophytes, which may determine narrowing of the acoustic window (Plant et al, 1998).

The involvement of joint structures such as ligaments and menisci or periarticular bursae can be evaluated by MSUS.

Meniscal degeneration, degenerative meniscal tears and parameniscal cysts are common findings in knee OA. Protrusion of the medial meniscus of the knee with displacement or distension of the medial collateral ligament and the medial joint capsule are frequently detected by MSUS in patients with medial femorotibial OA.

Baker's cyst is commonly found in knee OA. It results from pathological fluid distension of the gastrocnemius-semimembranous bursa that communicates with the knee joint in adults. Baker's cyst can be symptomatic by itself, independently of the degree of accompanying knee synovitis, and has been associated with knee pain in OA (Machold et al, 2002; Spoorenberg et al, 2004). Baker's cysts are easily identified and their aspiration and injection can be safely guided with MSUS.

4.3.2 *Diagnosis*

As recently reported in a systematic literature review, US studies compared patients with hand OA with healthy controls and reported significant differences in joint space narrowing (JSN), osteophytes, synovitis, PD signal and joint effusion, while no significant differences were found for tendon effusion (Saltzherr et al, 2014). In studies comparing structural US changes with conventional radiography, US generally detected more osteophytes, erosions and JSN. Only one study detected fewer erosions with US (sensitivity = 0.73, specificity = 1.0). Joint pain, tender joints and swollen joints agreed poorly with grey scale US measurements of synovitis, effusion, PD measurements, JSN, and osteophytes.

The diagnostic performance of knee US for the detection of degenerative changes of articular cartilage has been tested using arthroscopy as the reference standard. Positive US findings were specifically associated with cartilage degeneration, but with limited sensitivity.

4.3.3 *Monitoring and prognostication*

A few studies found significant association between US-detected inflammatory features and knee pain and function.

Chao et al (2010) evaluated US as a predictor of clinical response to intra-articular glucocorticoid injections in patients with knee OA, and found a significantly higher improvement in pain among non-inflammatory patients than among inflammatory patients 12 weeks after injection.

A cross-sectional European study performed under EULAR umbrella analysed 600 patients with painful knee OA and found that US-detected synovitis and or effusion were present in 53% of the examined patients (D'Agostino et al, 2005) and correlated with advanced radiographic OA and clinical signs and symptoms suggesting an inflammatory flare. In addition the follow-up of the same cohort demonstrated that the presence of an US detected effusion at baseline was predictive of a joint prosthesis replacement at 2 and 5

years of follow-up. (Conaghan et al, 2010). However, US-detected synovitis was not a predictor of subsequent joint replacement.

One US study reported a significant decrease in PD and effusion in patients treated with intra-articular hyaluronic acid injections. These decreases correlated with a significant reduction of pain ($r = 0.7$ and $r = 0.8$) (Klauser et al, 2012). The other US study reported a small non-significant decrease in synovitis in patients treated with intramuscular methylprednisolone injections, while there was a significant decrease in pain.

A preliminary US scoring system for features of hand OA includes semiquantitative evaluation of synovitis in 15 joints of the hand, with a moderately good intra-reader and inter-reader reliability (Keen et al, 2008).

Metric properties of this and other scores are still to be systematically evaluated.

4.3.4 Summary/clinical utility

US allows accurate assessment of the periarticular and intra-articular structures involved in the osteoarthritic joint in clinical practice. Technological development will probably enhance the role of US in the assessment of cartilage, bony cortex and inflammation in both clinical practice and research.

5 Nuclear imaging

Nuclear medicine imaging is based on the detection of gamma rays emitted from unstable isotopes as they decay. For each isotope of ^{99m}Tc , a single gamma ray is directly emitted during decay, while for ^{18}F , which emits positrons, two gamma rays are emitted indirectly.

Before the scan, the patient is injected with the radioisotope and a certain time interval elapses.

During the scanning procedure, gamma rays are emitted from the patient and registered by an external detector (gamma camera) producing the scintigraphic image. When the gamma camera is orbited around the patient, three dimensional tomographic images can be made of the gamma rays emitted and hence the technique is called single photon emission CT, or SPECT. A combination of biologically active molecules and an unstable isotope are called radiopharmaceuticals. These include fluorine-18 labelled fluoro-2-deoxy-D-glucose (^{18}F FDG), autologous white blood cells, labelled with ^{99m}Tc or ^{111}In , ^{99m}Tc -labelled bisphosphonates, such as methylene diphosphonate or hydroxymethylene diphosphonate, ^{67}Ga -citrate, ^{99m}Tc -labelled nanocolloids, and ^{99m}Tc - or ^{111}In -labelled proteins, such as IgG or albumin. None is specific for inflammation, and none offers the possibility of directly distinguishing the aetiology of the underlying inflammatory process.

The accumulation of these agents in inflamed tissues is based on different mechanisms: uptake into inflamed tissue as a result of increased metabolism, either of inflammatory cells or of tissue-specific cells with increased

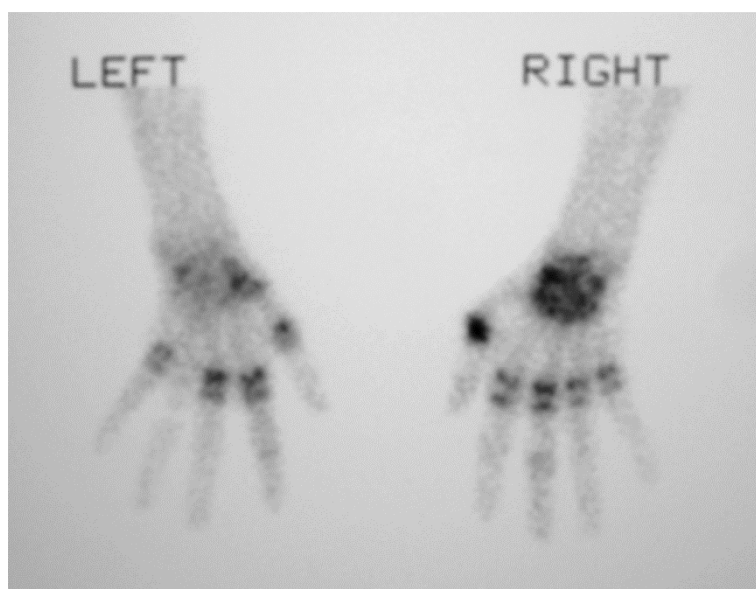
activity as a reaction to inflammation; unspecific accumulation in the site of inflammation as a result of increased blood flow and enhanced vascular permeability.

5.1 Scintigraphy

The first nuclear medicine imaging technique applied to detect joint inflammation in RA was 99mTc-immunoglobulin G (99mTc-IgG) scintigraphy (de Bois et al, 1995).

Localisation of 99mTc-diphosphonate to periarticular bone is related to both osteoblastic activity and skeletal vascularity (figures 28 and 29). Thus, it is interesting that joint uptake of this tracer in early RA has been shown by several groups to predict later bone erosion. A 2-year multimodality observational study by Palosaari et al (2006) showed that 99mTc-nanocolloid (99mTc-NC) scintigraphic uptake predicted MRI erosion score progression from baseline to 2 years ($r = 0.45$) but was closely correlated with other baseline predictors. On multivariate analysis, only MRI bone oedema maintained significance (OR 4.2, 95% CI 1.3 to 13.8) (Olivieri et al, 2002). MRI bone oedema has been shown to be a vascular lesion by Hodgson et al (2008). Hence, this could be at least part of the explanation why scintigraphic joint activity so closely parallels MRI bone oedema/osteitis.

Figure 29 Nuclear medicine isotope bone scan demonstrating symmetrical uptake in the metacarpophalangeal and wrist joints in a patient with rheumatoid arthritis. Images courtesy of AK Brown.



Scintigraphy has recently been extended as an imaging modality by the development of radiopharmaceuticals, formed by conjugating the isotope with molecules that have biological activity relevant to the inflammatory process. In one proof-of-concept study, [99mTc]–infliximab scintigraphy of inflamed joints predicted the response to anti-TNF treatment in a group of RA and AS patients. Responders demonstrated a much greater increase in pre-therapy tracer uptake within affected joints than non-responders ($p = 0.00001$) (Williamson et al, 2004). Another group used anti-human TNF α labelled with 99mTc to evaluate joint inflammation in eight RA

patients. The sensitivity and specificity for the nuclear imaging technique versus MRI were 89.8% and 97.3%, respectively (Roimicher et al, 2011).

Figure 30 Nuclear medicine isotope bone scan demonstrating widespread increased isotope uptake in wrists, spine, ribs, hips, knees, and ankles. This patient has metastatic bone disease. Images courtesy of AK Brown.



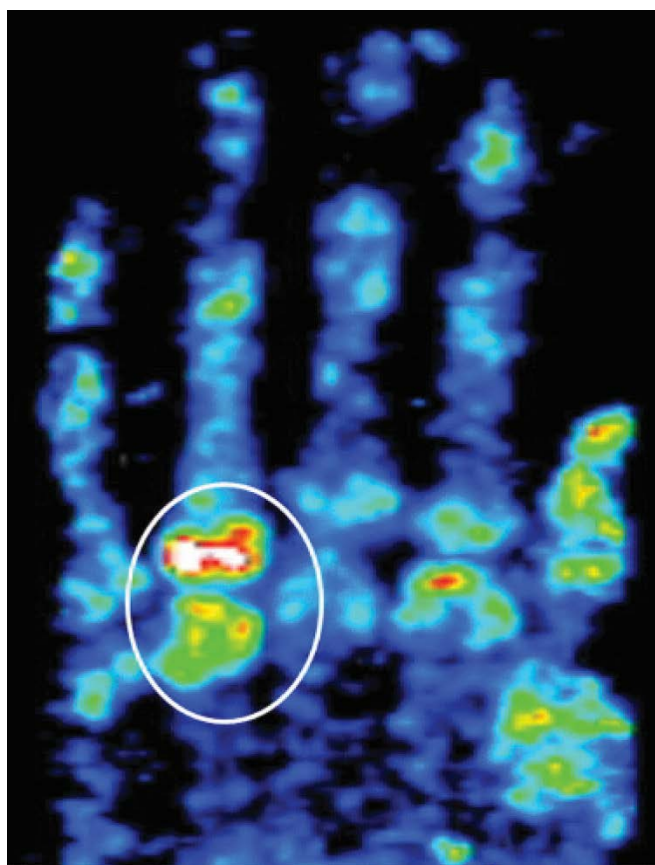
5.2 Single photon emission CT

SPECT bone scintigraphy has improved the accuracy of isotope bone scanning. This technique is now available in most nuclear medicine departments and provides additional information enabling more precise interpretation as well as functional data to complement other cross-sectional imaging techniques, such as MRI and CT. The basic methodology of standard scintigraphy applies, but in addition it involves rotating the gamma camera around the patient and using computer software to reconstruct tomographic images in any plane. Additionally, camera sensitivity is improved by using modern cameras with two heads. Image acquisition typically takes 30 min. The result is increased contrast resolution and greater sensitivity but also improved anatomical localisation and more precise definition of an area of interest, which also improves specificity (Haavardsholm et al, 2008).

SPECT has been applied in a number of clinical settings (figure 30). The most common situation is evaluation of spinal pathology in vertebral bodies, posterior vertebral elements, facet joints, pars inter-articularis defects, neoplastic disease and evaluation of post-surgical cases, with most studies reporting increased sensitivity

compared with standard three-phase scintigraphy and conventional radiography. Other indications include suspected avascular necrosis of hips, the diagnosis of meniscal tears in the knees, temporomandibular joint dysfunction and evaluation of lesions at the base of the skull. Again there is evidence to support increased diagnostic utility compared with standard three-phase scintigraphy and conventional radiography (Haavardsholm et al, 2008).

Figure 31 Single photon emission CT image of the hand from a patient with early rheumatoid arthritis showing increased uptake of tracer at several joints, most marked at the fourth metacarpophalangeal joint (proximal and distal regions, circle). (Reproduced with permission from McQueen, *Best Pract Res Clin Rheumatol* 2013;27:499–522.)



SPECT has also been used to assess functional brain abnormalities in neurological disease. This technique has been applied to the investigation of patients with systemic lupus erythematosus (SLE) exhibiting neuropsychiatric manifestations, with some studies demonstrating regional hypoperfusion (Appenzeller et al, 2007), although other studies have shown similar results in SLE patients without neurological disease (Hetland et al, 2010). SPECT has also been used to detect abnormal regional cerebral blood flow in patients with fibromyalgia (Benton et al, 2004).

Recent advances include correlation of the anatomical and functional information presented by SPECT and CT which can aid in the clinical decision-making process by enabling better localisation and definition of organs and lesions.

Ostendorf et al (2010) investigated multi-pinhole SPECT (MPH-SPECT) in early RA (<6 months' disease duration) and OA patients and compared results with bone scintigraphy and MRI. MPH-SPECT detected more positive joints than bone scintigraphy (80 vs 26 joints in 21 and 13 patients, respectively). The mean tracer uptake in affected joints was threefold higher than in unaffected joints but this did not differ between OA and RA patients. However, investigators noted that the pattern of tracer uptake on MPH-SPECT images allowed differentiation between RA and OA joints in the majority of patients whereas this was not possible on review of bone scintigraphy images. In 11/13 RA joints, pathological tracer accumulation on MPH-SPECT images matched MRI bone marrow oedema and erosions. In two patients there was increased MPH-SPECT uptake without evidence of bone oedema on MRI (synovitis alone). These findings suggest that radionuclide SPECT imaging could be more sensitive to very early disease than 1.5 T MRI scanning and suggest a potential role in RA diagnosis.

5.3 Positron emission tomography

Positron emission tomography (PET) is a nuclear imaging technique based on positron-emitting radioisotopes. A positron loses energy during collisions with atoms and finally becomes annihilated after collision with an electron, resulting in the formation of two perpendicular gamma rays. PET detectors register these two photons along with their orientation. Circular PET detectors simultaneously register photons from multiple projections. Concomitant CT scanning enhances anatomic definition and spatial localisation.

Usually, PET studies have been performed with [18F] fluorodeoxyglucose ([18F]FDG), which is a radiolabelled glucose analogue that accumulates in metabolically active tissue, as actively inflamed tissues. Increased uptake of [18F]FDG is mediated through glucose transporters type 1 (GLUT1) and type 3 (GLUT3) on the cell surface. [18F]FDG is rapidly phosphorylated to [18F] FDG-6-phosphate by hexokinase, but cannot undergo further metabolism, effectively trapping this molecule intracellularly.

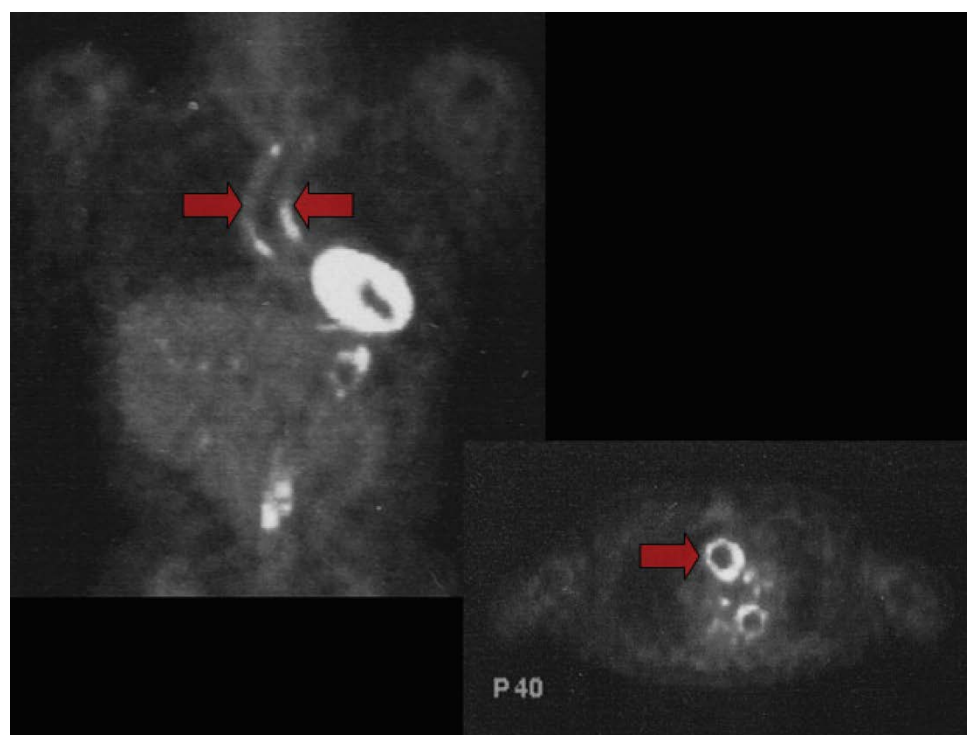
This technique has been used to assess disease activity (Beckers et al, 2004; Goerres et al, 2006) and metabolic changes in response to treatment (Palmer et al, 1995; Beckers et al, 2006). It may have a role in the assessment of early inflammatory arthritis as, like a traditional isotope bone scan, it can provide a high degree of sensitivity in detecting early signs of inflammation in multiple joints, but in addition quantification of 18F FDG uptake may be used to assess disease activity which can be directly compared to follow-up imaging. Using extrapolations from oncology data, it has been speculated that the degree of intensity of 18F FDG uptake may correlate with more aggressive inflammation which may relate to prognosis (Brown et al, 2008). With regard to monitoring response to therapy, Palmer et al (1995) reported that quantitative 18F FDG PET helped to detect metabolic changes as measures of response to therapy that were not apparent with conventional measures of disease activity. In addition, a recent pilot study by Beckers et al (2006) in RA patients treated with TNF α blocking therapy demonstrated close correlations between the PET findings and MRI and US

assessments of the synovitis, and biochemical markers of disease activity such as CRP and matrix metalloproteinase-3.

Gent et al (2012) used macrophage targeting with [11C] PK11195 PET to detect subclinical joint inflammation in a group of 29 anti-citrullinated protein autoantibody (ACPA)-positive patients with arthralgia (pre-RA). Small joints of the hands and wrists were assessed for tracer uptake and scored 0–3 for each joint. Patients were then observed for 24 months, looking for the development of clinical arthritis. PET-positive joints were found in four patients at baseline, and within 2 years of follow-up all had developed RA. There were another five patients who were scan-negative at baseline but who also developed clinical RA. Three of these developed joint involvement outside the PET field of view used in this study. Inter-observer reader reliability data were presented with kappa values of 0.91 (95% CI 0.74 to 1) at the patient level and 0.81 (95% CI 0.65 to 0.96) at the joint level.

Other promising indications for 18F FDG PET include assessment of disease activity and the extent of inflammation in large vessel vasculitides such as giant cell arteritis and Takayasu's arteritis (Walter et al, 2005; Dasgupta et al, 2007) (figure 31). Furthermore, this technique may demonstrate inflamed soft tissues in the shoulder and hip region as well as along the processi spinosi in active polymyalgia rheumatica (Blockmans et al, 2007).

Figure 32 Positron emission tomography scan in a patient with large-vessel vasculitis (aortitis) demonstrates characteristic fluorine-18 labelled fluoro-2-deoxy-D-glucose (18F FDG) uptake in the wall of the aorta visualised in coronal and axial sections. Image courtesy of WA Schmidt.



However, PET scanning is expensive and it is unlikely to become a routine imaging tool for the detection of musculoskeletal inflammation.

6 Conclusion

There are increasing data to support the validity of imaging tools such as conventional radiography, US, MRI, CT and nuclear medicine modalities in the evaluation of rheumatic diseases. Evidence supports their potential utility in facilitating prompt recognition of pathology, precise measurement of disease activity, sensitive monitoring of response to therapy, and effective assessment of disease outcome as well as challenging our understanding and providing valuable insights into disease pathogenesis. Therefore, musculoskeletal imaging is becoming an indispensable tool in the diagnosis and management of patients with rheumatic disease and an integral part of clinical rheumatology practice. This situation is likely to continue to evolve as a result of ongoing advances in research and technological development and application of these techniques to other disease areas.

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SUMMARY POINTS

- Different imaging techniques should be used in a complementary way to investigate joint diseases; each technique has their own advantages and limitations.
- X-ray remains an important method of investigating structural damage; however, it is relatively insensitive in early disease.
- Ultrasound is a promising and feasible tool for the assessment of both soft tissue inflammation and structural damage in peripheral joints. It may be available in a clinical setting and can assess multiple joints in a relatively short period of time. Through the development of guidelines, reproducibility is now acceptable among trained examiners. Its main limitation is that a trained user needs to be present to examine the patient and that some areas are not accessible (an acoustic window is needed).
- MRI is the overall most sensitive tool for assessing inflammation in peripheral and axial soft tissue and bone, and (except for CT) for bone damage. In particular, MRI is the only modality which offers information on inflammation at the subcortical level, for example, bone marrow oedema. It is expensive and time consuming, however.
- CT is the gold standard for the assessment of structural damage but is limited by radiation exposure, especially for repeated examinations.
- Joint diseases are characterised by different pathological lesions which will influence the choice of imaging.
- Different scoring systems for different techniques and diseases have been proposed and validated; it is generally accepted to separate inflammatory parameters (eg, synovitis) from structural ones (eg, bone damage). EULAR/OMERACT scoring systems are widely recognised methods of assessment for inflammatory joint diseases using MRI and US.
- The potential role of imaging may be divided into (1) early diagnosis, (2) prognostication, (3) monitoring, and (4) treatment endpoint. Further work, however, is still required in some of these aspects, particularly with regard to their cost-effectiveness and added-value over standard clinical parameters.

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EULAR on-line course on Rheumatic Diseases

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IN-DEPTH DISCUSSION I

**The Utility of Ultrasonography in the management of
Psoriatic Arthritis**

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease which can present with a spectrum of clinical phenotypes, including axial disease, a rheumatoid arthritis-like form, peripheral oligoarthritis, predominant involvement of the DIPs or enthesitis. The enthesis is considered the primary site of pathology, however patients may also present with significant synovial abnormalities and bone erosions at the joints occur in up to 62% of subjects (Veale, 2000). PsA may result in significant disability, reduced quality of life and life expectancy (Muhammad et al., 2015). Early diagnosis has shown to lead to better outcomes (Kane et al., 2003) and this has become a central issue since effective treatments have been introduced (Ash et al., 2012).

Conventional radiography at peripheral joints may show bone apposition and bone erosions in patients with PsA, however, these may not be present in early disease and radiography is not particularly useful in detecting soft tissue involvement related to active disease. Over the past decade, ultrasonography (US) and MRI have been identified as useful techniques in inflammatory arthritis patients. Although MRI can produce simultaneous and multiplanar images of bone and soft tissues, its widespread use is limited by cost, availability and by the need to select a restricted number of joints to scan. MRI remains the reference technique for management of the axial disease, however in the assessment of peripheral joints US has also emerged as an imaging technique of value. This overview will therefore focus on the use of US for the peripheral joint and enthesal disease.

In the field of PsA, the potential role of US includes diagnosis, prognostication, monitoring and guiding intra and periarticular procedures. The use of US as a treatment endpoint has yet to be extensively investigated. US has several advantages: it is well tolerated by the patient, with the possibility of an interactive examination allowing rapid decision making, also it does not involve exposure to ionizing radiation. In PsA, US examination includes both a morphologic examination using grey scale and a functional examination in order to detect vascularised tissues using Doppler techniques.

Ultrasound and diagnosis

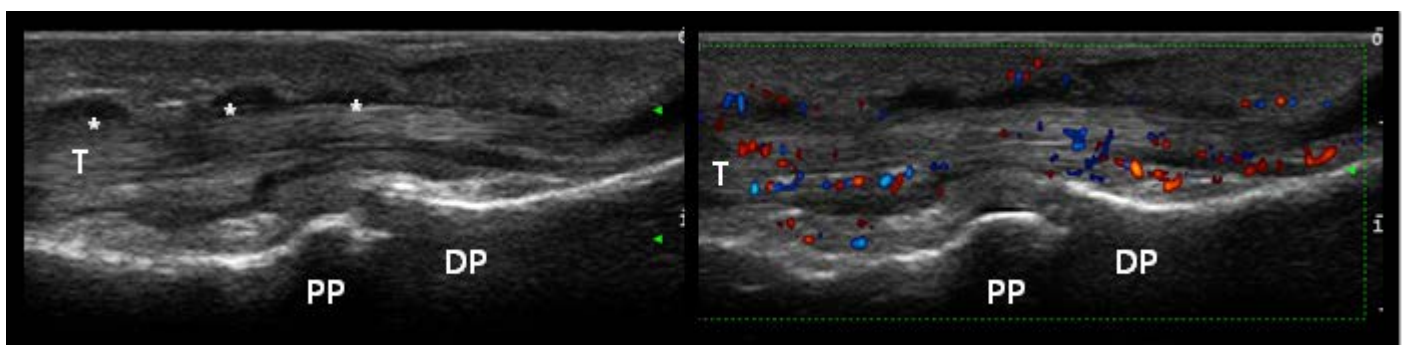
US has shown to be more sensitive than clinical examination in detecting joint inflammation (Backhaus et al., 2009) and more sensitive than conventional radiography in the detection of bone erosions in selected areas (Wakefield R et al, 2000) in patients with RA. Similar findings emerge in early PsA, in which subclinical synovitis, detected by GS and PD, was found in more than 75% of patients, in particular at the wrist (Freeston et al, 2014). Although there are no typical US patterns characterizing PsA synovitis, with the exception of a possible more intense intra-articular vascularization, US demonstrated a good accuracy in assessing synovitis in PsA (Coates et al 2012, Gutierrez et al. 2010; De Simone C et al 2011, Wiell C et al 2007; Sankvoski AJ et al 2013), as compared to other imaging modalities. In addition the presence of an US-detected synovitis has been shown

to be associated with long-term erosive radiological progression and poor outcome (Soriano et al, 2015). Also at the knee US more frequently detected synovial abnormalities compared to clinical examination (Delle Sedie et al., 2010). US has the ability to identify enthesitis, whose US definition has been recently renewed (Terslev et al., 2014). However, in this context a poor correlation between physical examination and US findings has been shown, with enthesitis being diagnosed more frequently by clinical examination than by US (Freeston et al., 2012). Thus US might emerge as a tool to reduce over-diagnosis of clinical enthesal involvement and potentially PsA over diagnosis.

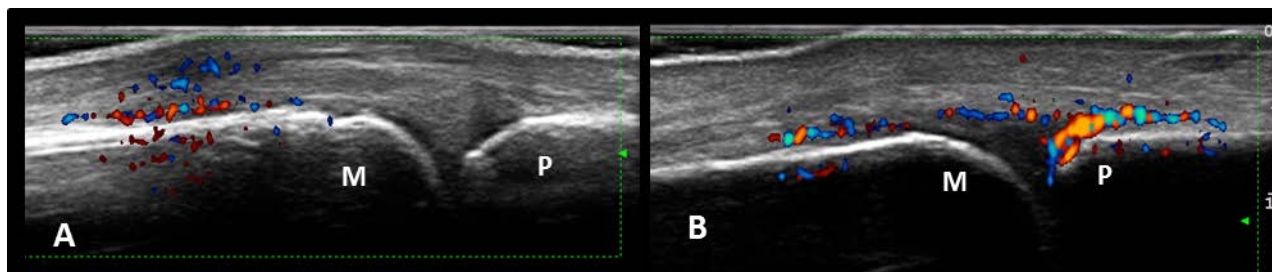
When considering US for diagnostic purposes, it should be underlined that the technologic improvement in US equipment has led to the possibility of detecting mild abnormalities, especially with GS examination, in the joints of healthy subjects. PD at joint level can also be seen in healthy individuals, though less frequently (Witt et al., 2013, Padovano et al 2016).

Most diagnostic studies in PsA evaluated US to detect elementary lesions, however the role of comprehensive US evaluation in addition to clinical findings to increase the certainty of diagnosis has not been investigated. The use of US can be considered to confirm the presence of dactylitis, which is considered typical of the disease (Bakewell et al., 2013). Populations of patients with PsA and RA have been compared to identify features that might help differentiate these conditions. US at MCPs can demonstrate a pattern of peritendinous inflammation surrounding the extensor tendon, which was found frequently (65.8%) in patients with PsA but not in patients with RA (Gutierrez et al., 2011). At the finger joints enthesitis, tendon involvement and inflammation of periarticular tissues were seen exclusively in patients with PsA and never in RA patients (Lin et al., 2015).

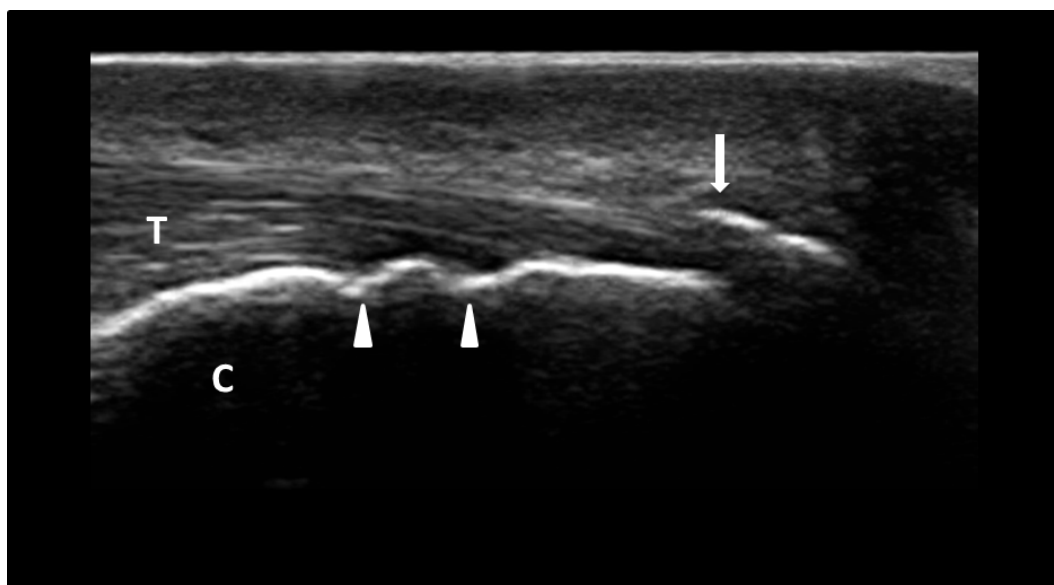
US may also help distinguish between patients with fibromyalgia and those with multiple enthesal inflammation. Inflammatory changes, detected by PD, were more prevalent in patients with PsA, with the Achilles tendon and plantar fascia sites providing higher specificity for differentiating the two conditions (Marchesoni et al., 2012). An additional advantage of US is to show features of different or concurrent conditions, such as crystal-related arthritis or osteoarthritis.



Longitudinal scan of the 3rd finger in a patient with recent onset PsA, showing the region over the proximal interphalangeal joints. The superficial and deep flexor tendons (T) are surrounded by fluid (asterisks), the use of power Doppler (on the right) demonstrates hypervascularisation within the tendon sheath and in peritendinous tissues. These aspects are consistent with dactylitis. PP: proximal phalanx; DP: distal phalanx.



Longitudinal scan of the metacarpophalangeal (MCP): comparison of different power Doppler patterns in early PsA and early rheumatoid arthritis. A) Early PsA: power Doppler signal is located in the area surrounding the extensor tendon. B) Early RA: power Doppler is mainly located into the MCP and in contact with the bony surface. M: metacarpal bone; P: phalanx.



Longitudinal scan of the insertion of the Achilles tendon (T) at the calcaneus (C) in a patient with PsA. Arrowheads: presence of irregularity of the bony cortex at the tendon insertion. Arrow: enthesophyte.

Prognosis

US features as prognostic markers have been investigated more extensively in patients with psoriasis without arthritis. In this population, enthesal thickness was higher and the number of enthesophytes greater compared to healthy controls (Gisondi et al., 2008), although patients with PsA had still more severe enthesal involvement (17). No correlations were found between the extent of skin involvement and US alterations (Gutierrez et al, 2011). Also patients with isolated nail disease show higher enthesopathy and inflammation

scores than healthy controls (Ash et al., 2012). Preliminary evidence on 30 patients followed for up to 7 years supports the hypothesis that US enthesal abnormalities might predict the onset of arthritis, with the thickness of the quadriceps tendon independently predicting PsA onset (Tinazzi et al., 2011). A subsequent study evaluated the lower limb entheses of patients with psoriasis, PsA and healthy controls. Patients with psoriasis had higher scores for inflammation compared to healthy controls, while patients with PsA showed higher scores for both inflammatory and chronic components than patients with psoriasis and healthy controls. This supports the hypothesis of subclinical involvement in patients with skin psoriasis (Aydin et al., 2013).

In patients with a defined diagnosis of PsA, US abnormalities have been cross-sectionally correlated with measures of disease activity. A comprehensive US assessment, including joints and entheses, was significantly related to clinical disease activity ; in the same population, up to 66% of patients in clinical remission had still US joint and enthesal inflammatory involvement (Husic et al., 2014). The presence of synovitis and erosive changes has also been related to pain at the MTP joints (Turner et al., 2014).

Prognostic information from prospective studies is limited in PsA. The value of US to predict radiographic progression has been tested and higher scores of synovial hypertrophy and PD were shown to be predictive of radiographic progression, as well as higher GUESS scores (see below) (El Miedany et al, 2015).

Therefore, the prognostic application of US might play a role in patients with psoriasis, and might identify patients with a more severe disease course.

Disease monitoring

The use of US to monitor disease relies on the expertise of the operator and on the quality of the equipment, requiring also validated tools. In the context of PsA this assessment is made more complex by the presence of different structures of interest.

For enthesal assessment, two scores have been developed. The Glasgow Ultrasound Enthesis Scoring System (GUESS) (Balint et al., 2002) has been validated in a population of spondyloarthritides. This includes five enthesal sites at the lower limbs, evaluating bursitis, thickness, erosions and enthesophytes (each abnormality scored as present/absent). The GUESS correlates with radiographic progression (El Miedany et al., 2015), but it is not useful for sensitivity to change. The Madrid Sonographic Enthesis Index (MASEI) has been presented, including six enthesal sites at limbs. Calcifications, bursae, erosions, PD signal in bursa or enthesis, tendon thickness and structure are scored separately (de Miguel et al, 2009). The MASEI has demonstrated discriminative capacity between patients with spondyloarthropathy and healthy controls (de Miguel et al, 2011) and between patients with PsA, psoriasis and healthy controls (Eder et al., 2014).

Recently, in a prospective and longitudinal study an US composite score for the assessment of inflammatory (synovial and enthesal) and structural lesions in PsA was developed, which has shown to have good metric properties including a good sensitivity to change (Ficjan et al, 2014).

Ultrasound-guided procedures

Specific studies applying US to drive injections in PsA are not available, however, some information can be extrapolated from studies on arthritis populations. There are only two studies comparing US guided and blind injection techniques, supporting a greater accuracy of guided injections, possibly driving a better response (Sibbitt et al., 2012; Cunnington et al., 2010). Imaging could be of particular interest in injecting small and anatomically variable sites, to increase the accuracy and safety of the procedure, such as tendons (Di Gesso et al., 2012).

Conclusion

US has a potential role in several phases of the management of PsA. The technique can detect the main elementary lesions in the joints and in the entheses and this can be informative also in pre-clinical phases. In patients with psoriasis, US may help predict the development of PsA, and in patients with confirmed disease US findings may be helpful to characterise subsets with a more severe prognosis. Validated tools to monitor the disease are available and might be routinely applied in the future. US can also be useful in the clinical setting when intra-articular and peri-articular treatments are required.

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EULAR on-line course on Rheumatic Diseases

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IN-DEPTH DISCUSSION II

Imaging of Gout

Gout is characterised by the deposition of monosodium urate (MSU) crystals in joints, periarticular and soft tissue. The crystal deposition takes place when urate concentration raises above 6.8 mg/dl under physiological conditions, which is the uric acid saturation threshold (Loeb, 1972). This condition can lead to flares of acute arthritis and, in long standing disease, to a chronic arthropathy with intra-articular or extra-articular tophus formation, joint damage and associated complications.

Imaging techniques are useful in measuring inflammation, MSU deposits and damage, and they assist clinicians in the diagnosis and monitoring of gout and provide useful information on gout pathology.

Conventional radiography

Conventional radiography (CR) is the oldest most used imaging technique in gout. It is feasible, readily available and reliable, though it is not enough sensitive to evaluate soft tissues.

In early disease CR is usually normal or eventually may show non-specific soft tissue swelling around the acutely inflamed joint. Typical findings appear in long-standing disease and include: soft tissue opacifications (tophi), articular and peri-articular erosions with overhanging and sclerotic margins and new bone formation. (Watt, 1975)

Despite CR detected asymmetric swelling and sub-cortical cysts being included in the preliminary 1977 American Rheumatology Association criteria for gout (Wallace et al, 1977), their clinical usefulness in discriminating between different arthritis is limited. More specific signs of gout, such as soft-tissue opacifications with densities between soft tissue and bone, articular and peri-articular bone erosions and osteophytes at margins of opacifications or erosions showed sensitivity ranging from 5 to 26% and specificity from 95 to 100% (Rettenbacher et al., 2008). Given the low expected prevalence of specific CR signs in early disease, the relevance in diagnosis is limited.

However, CR can be successfully used in monitoring damage over time. A modified Sharp/van der Heijde scoring method has shown to be reliable and valid in gout (Dalbeth et al., 2007), supporting its use in practice and clinical trials.

In summary, CR may assist the diagnosis and monitoring damage of gout, but its low sensitivity limits its application in assessing inflammation, urate deposits and early signs of intra- and extra-articular damage.

Ultrasonography

Ultrasound (US) is an emerging imaging modality for gout. It is relatively inexpensive, readily available and ionising radiation-free. Reliability and validity are limited by the operator- and machine dependency, the availability of acoustic windows, and the inability to see beyond the bony surface.

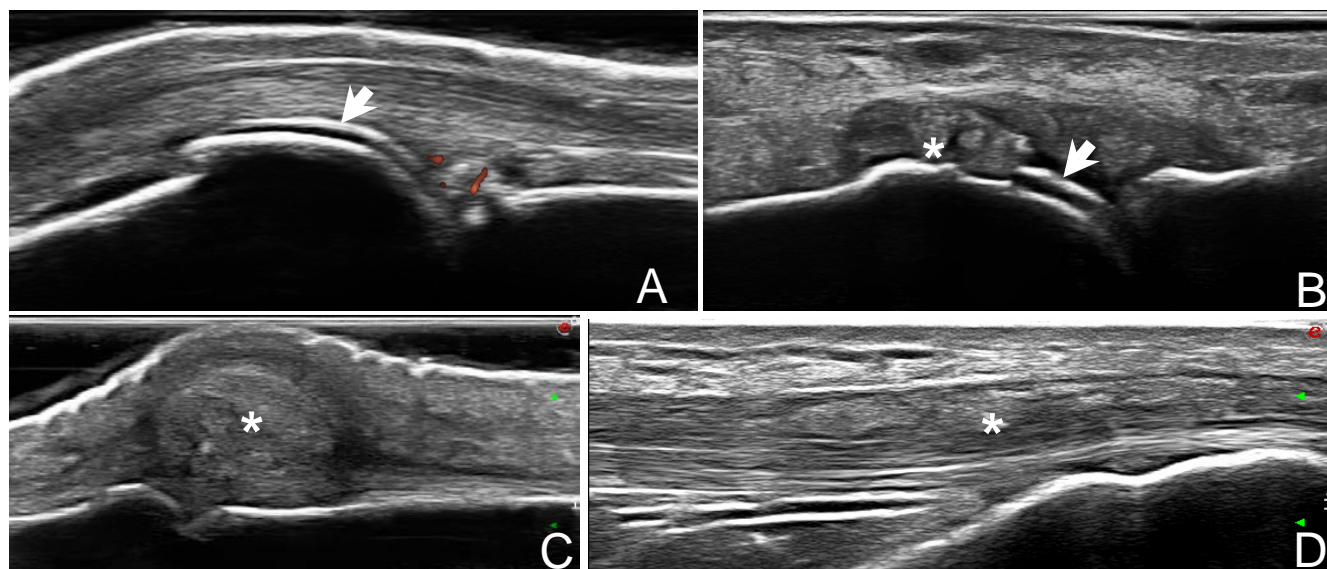
An important diagnostic usefulness of US in gout is its use as a guide for synovial fluid aspiration (Gonçalves et al., 2011). Furthermore US seems to be able to detect deposits of MSU crystal over the cartilage, an US sign named ‘double contour’ sign, which is defined as “hyperechoic band over anechoic cartilage” (Grassi et al., 2006). (Figure 1)

The US appearance of tophi previously described as “hypoechoic to hyperechoic, inhomogeneous material often surrounded by a small anechoic rim” (Howard et al., 2011) has been recently reformulated and tested, along with other gouty lesions, in a series of Delphi and images and patients based reliability exercise performed within the OMERACT US group (Terslev et al, 2015a and b, Gutierrez et al. 2015)

Synovial membrane may show non-specific signs of hypertrophy and presence of power Doppler signal, but intra-synovial tophi or hyperechoic spots in synovial membrane are also detectable in patients with gout (Naredo et al., 2013). Hyperechoic spots in synovial fluid, called ‘snowstorm’ sign, can also be present in gout.

Finally, US can detect bony erosions (“breaks in hyperechoic cortical bone detectable in two perpendicular planes”) more sensitively than CR. (Wright et al., 2007).

Figure 1. Ultrasonographic features of gout. A. 2nd MCP with double contour sign (arrow) and power Doppler synovitis; B. 1st MTP with double contour sign (arrow) and intra-articular tophus (asterisk); C. MCP with extra-articular tophus (asterisk); D. Patellar tendon with extra-articular tophus (asterisk). (Image courtesy of Dr Georgios Filippou).



Several case control diagnostic studies have evaluated the accuracy of US for gout diagnosis compared with clinical diagnosis (crystal-proven or not). The sensitivity of the ‘double contour’ sign ranged from 21 to 92%, and specificity from 98 to 100%; while detection of tophi showed a sensitivity ranging from 0.23 to 100% and a specificity from 91 to 100% (Thiele et al., 2007, Ottaviani et al., 2012; Naredo et al., 2013; Gruber et al., 2014).

It is likely that the combination of clinical and US findings might optimise the diagnostic process of acute monoarthritis. (Lamers-Karnebeek et al., 2014)

Small studies have reported that US features of gout such as the double contour sign, hyperechoic spots in synovial fluid, hyperechoic cloudy areas, tophus diameter and volume improve in patients who reach the target of serum uric acid $\leq 6\text{mg/dL}$. (Villaverde et al., 2013)

Though US is able to detect simultaneously and at different sites different aspects of the disease, clinical application of US might be limited by the experience of the operator. However, in one study, after 1 week of disease-oriented training program, rheumatologists with limited experience in US were satisfactorily able to detect and interpret the main US signs indicative of MSU crystal deposits at different tissues in patients with gout. (Gutierrez et al., 2013)

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has a very high resolution in imaging soft tissue and bone. Although it does not involve ionizing radiation, it is expensive, time consuming and not readily available within the office setting.

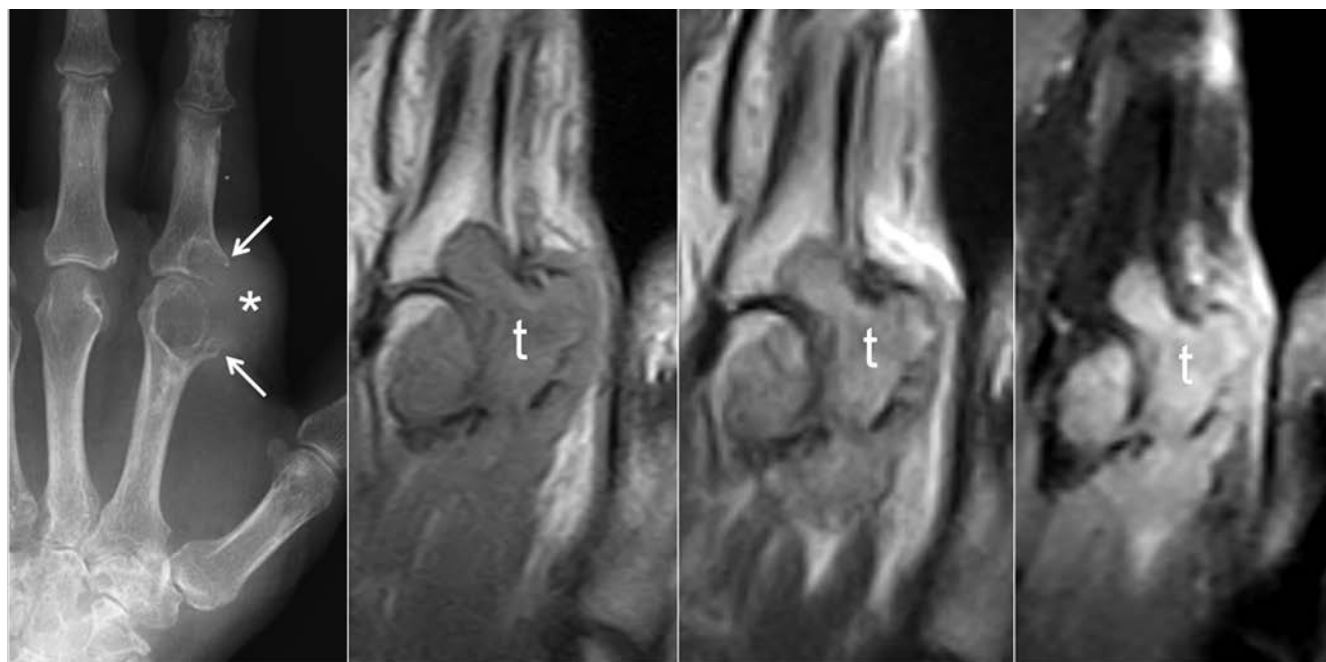
Although MRI is not able to directly image MSU crystals, tophi are observed as amorphous/nodular areas of low-intensity signal on T1-weighted images, variable intensity on T2-weighted images and variable, patchy enhancement after intravenous contrast (Yu et al., 1997). Tophi may appear as discrete nodules, expanding along defined anatomic planes, or depositing in a contiguous manner (Popp et al., 1996).

MRI can also observe intra-articular features, such as synovitis, synovial hypertrophy, joint effusions and soft-tissue oedema (Cimmino et al., 2011). Of interest, even in patients without clinically apparent gouty inflammation, synovial pannus (Carter et al., 2009). Moreover, MRI is more sensitive than both CR and US in detecting bone erosions (Carter et al., 2009), and it is able to detect erosions in gout even at its first presentation (Cimmino et al., 2011).

Though MRI has the specific capability of detecting bone marrow oedema (BME), this feature is less frequently observed in gout compared with other erosive arthropathies. In patients with gout, BME is more likely to be associated with infectious complications (osteomyelitis). (Poh et al., 2011)

The ability of MRI to visualise soft-tissue including bursae, tendons and ligaments allows for detailed assessment of these structures in patients with gout, increasing the sensitivity in detecting tendinopathy, dactylitis and intratendinous tophi (Andracco et al., 2010; Poh et al., 2011).

Figure 2. Magnetic resonance imaging features of gout. (Image courtesy of Prof Marco A Cimmino).



Data on the diagnostic accuracy and responsiveness to treatment are still lacking for MRI. (Villaverde et al., 2013) Nevertheless, MRI is a good candidate imaging modality to measure tophi burden and damage over time. Moreover, MRI is clinically useful when spine involvement or complications, such as osteomyelitis, are suspected. (Poh et al., 2011)

Conventional and Dual-energy Computed Tomography

Modern multi-detector computed tomography (CT) scanners are able to quickly provide high resolution images of the peripheral areas. Despite ionising radiation are administered, the application to the extremities does not limit the application of CT in gout.

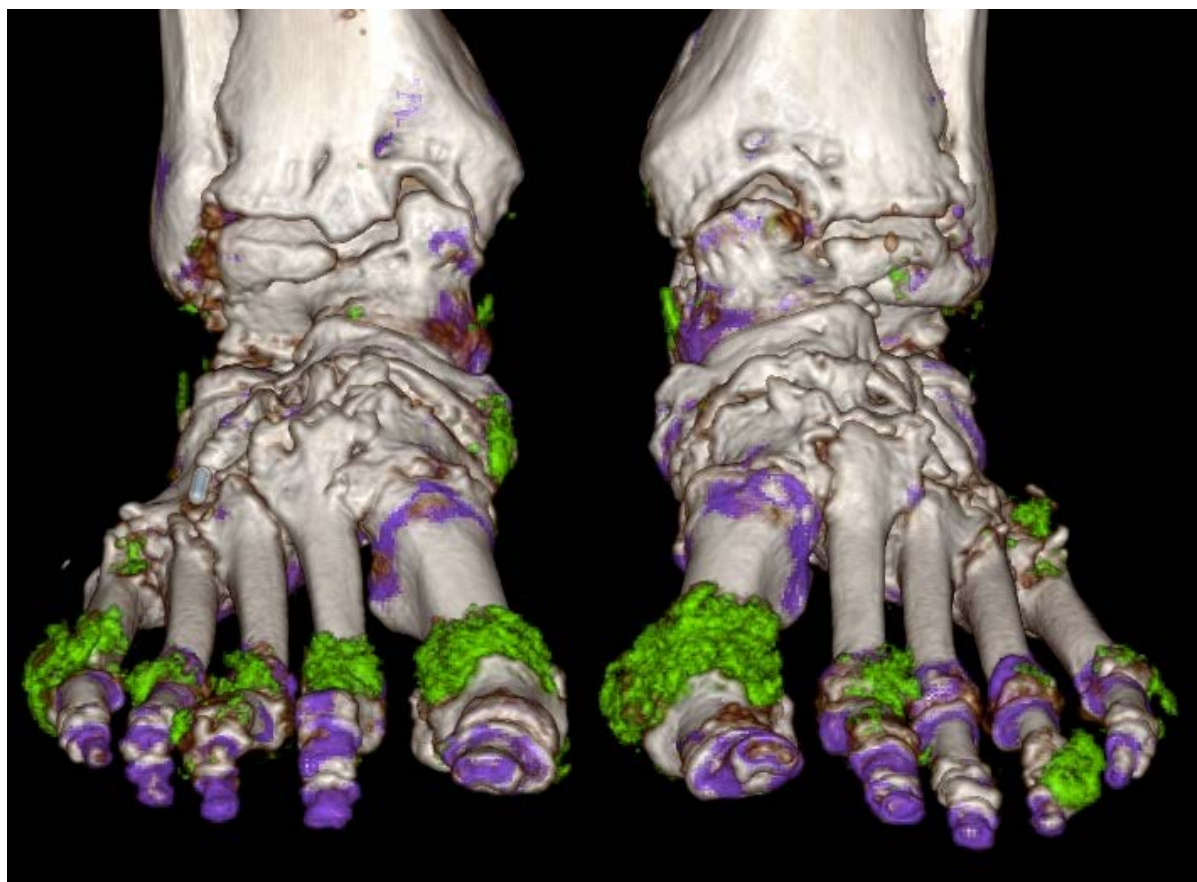
CT scan is very accurate in detecting bone disease and tophi (Gerster et al., 1996). Because of its multi-planar visualisation and resolution, CT is the gold standard technique to image bone erosion in inflammatory joint diseases (Not sure what ref 24 is: could use Døhn et al, 2006)

Conventional CT scan is not able to detect MSU crystal deposition, synovitis and BME.

The diagnostic accuracy of conventional CT for gout has not been reported to date, and its use is now limited to research or to evaluation of complications of disease, such as spinal involvement.

There is increasing interest in on dual source CT (DECT) in gout. DECT uses a specific algorithm that assigns different colours to materials of different chemical composition and has been well validated as a non-invasive method to determine the chemical composition of kidney stones. Due to its characteristics it can readily visualize MSU crystal deposition and is a good candidate to diagnose and monitor the disease.

Figure 3. Dual Energy Computed Tomography in a patient with tophaceous gout. MSU crystals are colour-coded green. (Image courtesy of Dr Nicola Dalbeth).



Several studies have evaluated the diagnostic performance of DECT in case-control diagnostic studies with sensitivity ranging from 78 to 100% and specificity from 79 to 100%. (Glazebrook et al., 2011; Choi et al., 2012, Gruber et al., 2014)

A recent study compared US and DECT showing high diagnostic performance for both imaging modalities with higher concordance of US with MSU crystal detection (Gruber et al., 2014)

As with conventional CT, DECT can also depict bone disease in gout including bone erosion, and features of new bone formation (Dalbeth et al., 2014). Its capability of detecting MSU crystal deposition may be useful in monitoring disease and in the evaluation of the response to treatments. As for conventional CT, DECT use is limited by its cost, availability and using of ionising radiation.

Conclusions

Imaging is useful to evaluate many aspects of disease in gout: inflammation, MSU deposits and damage. Different imaging modalities assist in different phases and aspects of the disease. US and DECT are the principal candidates to be applied in the diagnostic process and in monitoring long term consequences of the disease.

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Connective tissue diseases: Concepts and pathogenesis, overlap syndromes, mixed CTD and undifferentiated CTD

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A previous version was co-authored by Gemma Lepri, Silvia Bellando Randone, Christian Beyer, Oliver Distler, Jorge H.W. Distler

LEARNING OBJECTIVES

- Acknowledge that patients with symptoms suggestive of one or more inflammatory rheumatic diseases who do not fulfil classification criteria for a specific entity often present in daily clinical practice
- Describe and explain the prospects and limitations of classification criteria in the diagnosis of connective tissue diseases
- Apply knowledge of clinical symptoms and diagnostic findings suggestive of undifferentiated connective tissue disease, overlap syndromes and mixed connective tissue disease
- Describe and explain the course and prognosis of undifferentiated connective tissue disease, overlap syndromes and mixed connective tissue disease and their clinical warning signs for major organ involvement
- Use diagnostic screening algorithms for the individual patient depending on her/his risks for major organ involvement, such as pulmonary arterial hypertension in a patient with mixed connective tissue disease
- Apply treatment strategies for patients with undifferentiated connective tissue disease, overlap syndromes and mixed connective tissue disease depending on their disease activity and individual organ involvement
- Evaluate the limited scientific evidence for the treatment of undifferentiated connective tissue disease, overlap syndromes and mixed connective tissue disease

1 Introduction

Diagnosis of rheumatic diseases can be challenging. Many clinical signs and symptoms as well as laboratory markers are not specific for a certain rheumatic disease but may occur in different diseases. This includes Raynaud's phenomenon, arthritis, interstitial lung disease and small vessel vasculitis, as well as antinuclear antibodies (ANAs), rheumatoid factor (RF), anti-Ro/SSA and anti-La/SSB antibodies. Only a few clinical findings like scleroderma and some biomarkers, including anti-cyclic citrullinated antibodies in rheumatoid arthritis (RA), anti-Sm and anti-double-stranded DNA antibodies in systemic lupus erythematosus (SLE) and anti-topoisomerase and anticentromere antibodies in diffuse and limited systemic sclerosis (SSc), have a relatively high specificity for the corresponding disease.

Thus, 25–50% of patients referred to tertiary rheumatology centres do not carry a diagnosis of a clearly defined rheumatic disease or present with features of two or more rheumatic diseases (LeRoy et al, 1980*; Cervera et al, 1990*). These patients are classified as having either undifferentiated connective tissue disease or overlap syndrome. Mixed connective tissue disease, however, should not be confused with undifferentiated connective tissue disease or overlap syndrome. This, in fact, is a distinct clinical entity that manifests as a mixture of certain clinical features also seen in other rheumatic diseases. The following article will shed light on the subtle differences among these three rheumatic entities; it will explain the different organ manifestations and risks for severe complications; it will further demonstrate the consequences for organ screening, follow-ups and treatment of these diseases; this article will finally show why it is important to differentiate between each of these entities and separate them from other rheumatic diseases.

2 Undifferentiated connective tissue diseases

2.1 Introduction and definition

Patients who present with features of a connective tissue disease but who do not fulfil current criteria for a specific connective tissue disease are diagnosed as having 'undifferentiated connective tissue disease' (UCTD) (LeRoy et al, 1980; Mosca et al, 2014). Classification criteria for UCTD have not been defined, but there is a general consensus that the term UCTD refers to unclassifiable systemic autoimmune diseases which share clinical and serological manifestations with definite connective tissue diseases but not fulfilling any of the existing classification criteria. Some authors even add undifferentiated arthritis to the group of UCTDs. Since UCTD in significant numbers of these patients will evolve into RA, spondyloarthritis or other rheumatic diseases that do not belong to the group of connective tissue diseases, we believe that these patients should not be grouped as UCTDs. This is particularly true for patients with undifferentiated arthritis positive for anti-CCP antibodies. As many as 83% of these patients will fulfil the American College of Rheumatology (ACR) criteria for RA after 1 year and up to 93% after 3 years of follow-up (van Gaalen et al, 2004). Undifferentiated

arthritis might evolve into a defined connective tissue disease in only a minority of patients (<10%) (Wolfe et al, 1993).

2.2 Clinical features of UCTD

The definition of UCTD includes a wide spectrum of diseases that can be referred to the following scenarios with variable disease course and prognosis:

- Patients with recent onset of symptoms and unclassifiable clinical picture; in this group of patients, the undifferentiated condition better refers to a “incomplete”, “atypical” or “mild” disease presentation which is very likely to progress into a definite CTD in the short time or, sometimes, even years after symptoms onset. This group of undifferentiated conditions represents the “early phase” of a CTD and their effective recognition has a crucial clinical importance in term of treatment decision making and disease monitoring.
- Patients with “stable UCTD”, a distinct clinical entity with peculiar clinical findings; the proposed preliminary classification criteria for UCTD include at least one clinical manifestation of CTDs, positive ANA results, and disease duration of at least three years (**Mosca M, 1999**). In these patients severe organ involvements (such as renal or neurological manifestations) are only occasionally reported, the clinical picture is usually stable over time and necessitates mild therapeutic intervention (**Bodolay E, 2003 ; Mosca M, 2013, Danieli MG, 1999**)
- Patients with ‘organ-dominant’ conditions (e.g., idiopathic non-specific interstitial pneumonia) and antinuclear antibodies or other serological features or mild clinical symptoms suggesting an autoimmune process.

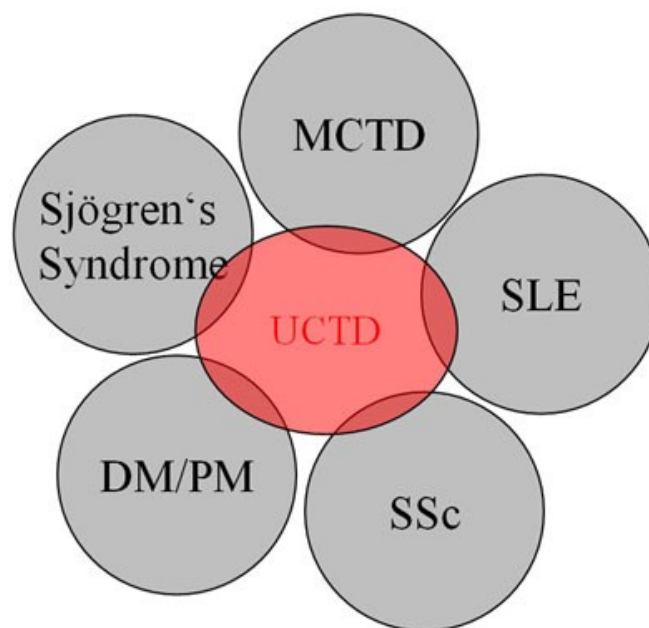
Typical presenting symptoms of patients with UCTD are Raynaud’s phenomenon (80%), arthralgias (60–70%), arthritis (30–40%), sicca symptoms (25%), alopecia (20%), photosensitivity (15–25%), malar rash (3–10%), sclerodactyly (10%), leucopenia (10–25%), thrombocytopenia (5–15%) and anaemia (5%) (Danieli et al, 1999; Mosca et al, 2002).

When suspecting an early form of a specific rheumatic disease that does not fulfil classification criteria, the suffixes ‘pre-’ or ‘early’ might help to distinguish this condition from a “true” (stable) UCTD. For example, patients with new-onset Raynaud’s phenomenon, typical changes detected at nailfold capillaroscopy, telangiectasias and specific antibodies for SSc, might be classified as pre- or early SSc, also according to the new ACR/EULAR classification criteria (Van den Hoogen et al, 2013). It is necessary to emphasise the importance of one of the earliest signs of many connective tissue diseases: Raynaud’s phenomenon. This may precede by several years the onset of a connective tissue disease, such as SSc, where it is considered a pivotal sign. For

this reason, a careful history and physical examination of these patients is mandatory to identify potential organ manifestations suggestive of rheumatic disease (Koenig et al, 2008).

When we encounter patients with Raynaud's phenomenon (RP) it is important to distinguish between the primary and the secondary form, and also to exclude patients with other causes of Raynaud's syndrome, such as vibration injury, drugs (eg, β blockers, ergotamines or cocaine), chemicals (eg, vinyl chloride), occlusive arterial disease and hyper viscosity syndrome. Studies have shown that after an extended screening programme during a mean follow-up of 11.2 years, the prevalence of transition from primary to secondary RP, was 14.9% of all patients (Hirschl et al, 2006). This result suggests that patients initially identified as having a primary RP should be followed up with a nailfold capillaroscopy examination in order to identify alterations of the capillary network as soon as possible. Screening of patients with SSc for ANAs and—in certain cases—for cryoglobulins will complete the basic investigation. In addition to the patient's clinical history, clinical findings (eg, severe digital ischaemia, asymmetrical attacks, later age at onset), suspicious findings on capillaroscopy and the presence of ANAs at high titres increase the probability of a rheumatic disease and reject the diagnosis of primary RP (fig. 1)

Figure 1 The concept of undifferentiated connective tissue disease. DM, dermatomyositis; MCTD, mixed connective tissue disease; PM, polymyositis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.



2.3 Prognosis of UCTDs

Several large, prospective studies have examined the outcome of patients with UCTD. These studies show consistently that most patients with UCTD will have the same diagnosis even after several years of follow-up. In the remaining patients, the development of a defined rheumatological disease is more common than complete resolution of the symptoms.

In a prospective study of 143 patients with a mean follow-up of 10 years, the diagnosis of UCTD persisted in 65% (Williams et al, 1999). At the end of the follow-up, a total of 29% fulfilled the criteria for a defined rheumatic disease, most commonly SSc (15%) and SLE (13%), but also RA and mixed connective tissue disease (MCTD) (3% each). Remission of symptoms was found in only 6% of the patients. In 165 Italian patients, 82% were still classified as having UCTD after 5 years and only 6% developed defined connective tissue diseases, with SLE being most common. Twelve per cent of the patients were asymptomatic after 5 years (Danieli et al, 1999). In a Hungarian prospective study, 53% of 665 patients still carried the diagnosis of an UCTD after 5 years. A defined rheumatological disease developed in 35% of cases with 13% of patients being diagnosed with RA, 7% with Sjögren's syndrome, 4% with SLE, 4% with MCTD, 3% with SSc and <1% with polymyositis (PM) or dermatomyositis (DM). In addition, 3% of patients developed systemic vasculitis. Complete remission of clinical findings occurred in 12% of patients with UCTD (Bodolay et al, 2003).

Based on available data, several factors may be predictive for the development of SLE. These predictors include serological findings such as anti-dsDNA antibodies, anti-Sm antibodies, anticardiolipin antibodies, false-positive test for syphilis, positive Coombs test, a homogeneous ANA pattern and multiple antibody specificities. The following clinical findings are also predictive for the development of SLE: alopecia, acute or subacute skin rash, discoid lesions, serositis and cardiac complications (Alarcon et al, 1996; Mosca et al, 2002; Bodolay et al, 2003; Bortoluzzi A, 2016). Of note, anti-Sm antibodies, anticardiolipin antibodies, a homogeneous ANA pattern, discoid lesions and serositis may be the strongest predictors.

Furthermore, oesophageal dysfunction might predispose for the development of a connective tissue disease. In a study on 145 patients with UCTD, 46% were found to have oesophageal dysfunction by radionuclide oesophageal transit scintigraphy (Gaal et al, 2005). Of note, 71% of the patients with oesophageal dysfunction were asymptomatic. Pathological findings from radionuclide oesophageal transit scintigraphy predicted the development of a defined connective tissue disease.

In addition to studies investigating the outcome of patients with UCTD, in general, several studies have analysed the outcome of patients with UCTD with particular manifestations. A meta-analysis of 10 articles with a total of 639 patients concluded that a secondary connective tissue disease develops in about 13% of those patients presenting with isolated RP by an average of 10 years from its onset (Spencer-Green, 1998). The best predictor for the transition to a connective tissue disease was an abnormal nailfold capillary study demonstrating avascular areas and giant capillaries with an overall reduced capillary density. The positive predictive value for developing a connective tissue disease in a patient presenting with RP was 47%.

Isolated positive ANA testing is a poor predictor for the development of a specific connective tissue disease, with a positive predictive value of 30% (Spencer-Green, 1998). In contrast, positive ANAs together with anticentromeric staining patterns are good predictors for the development of SSc. In a small series of 46

patients with RP and one other symptom, the disease evolved into SSc in 24%. The best predictor for the development of SSc was the presence of autoantibodies with a sensitivity of 60% and a specificity of 98% in this population (Kallenberg et al, 1988; Kallenberg, 1995*).

Autoantibodies might be detectable several years before disease onset. In a study of 130 patients with SLE, at least one autoantibody was present in 88% of patients before diagnosis (Arbuckle et al, 2003*). On average, the time between the first appearance of autoantibodies and the diagnosis of SLE was 3.3 years, but the onset of disease could be delayed by up to 9.4 years. ANAs were present in 78%, anti-dsDNA antibodies in 55%, anti-Ro antibodies in 47%, anti-La antibodies in 34%, anti-Sm antibodies in 32%, anti-RNP antibodies in 26% and antiphospholipid antibodies in 18% of patients. ANAs, anti-Ro antibodies, anti-La antibodies and antiphospholipid antibodies were the first autoantibodies to appear, followed by anti-dsDNA antibodies and finally, anti-Sm and anti-RNP antibodies.

Direct comparison of mortality in patients with UCTD and other connective tissue diseases does not exist. Comparison of results from different studies, however, showed that the mortality of patients with UCTD was intermediate in comparison with other connective tissue diseases. In patients with UCTD, 5- and 10-year survival rates have been reported as 83% and 76%, respectively (Mosca et al, 2002). Two studies on patients with SLE reported survival rates of >90% after 5 and 10 years (Trager and Ward, 2001; Cervera et al, 2003). By contrast, patients with diffuse SSc have survival rates of about 63% after 7–10 years (Ferri et al, 2002; Scussell-Lonzetti et al, 2002). Nevertheless, comparability of these different studies is limited owing to several confounding factors, including patient selection, data acquisition, ethnic populations, available treatments and organ manifestations. For instance, patients with SLE-associated kidney disease or SSc-associated pulmonary arterial hypertension (PAH) had a poor prognosis, while patients with SLE and SSc with skin disease only had a relatively long survival compared with the overall survival of the disease groups of these studies.

2.4 Management of patients with UCTDs

Although most patients will continue to have a diagnosis of UCTD, they should be followed up closely since additional disease manifestations may develop, fulfilling the criteria for a defined rheumatological disease. Both new disease manifestations and the new diagnosis might change the further management of the patient. For instance, patients with accumulating symptoms suggestive of SLE need to be closely monitored for potentially life-threatening manifestations, such as glomerulonephritis. Patients with RP and anticentromere antibodies have a higher risk of developing PAH and need to be monitored by echocardiography.

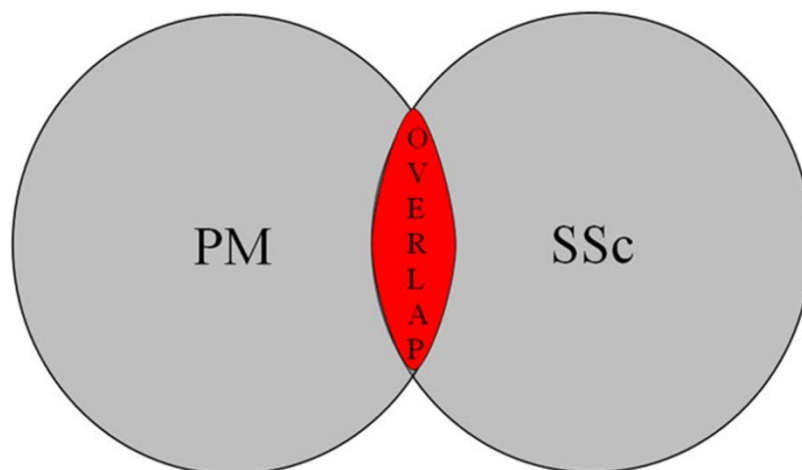
Treatment of patients with UCTD usually includes antimalarial agents, low doses of steroids and symptomatic drugs depending on the presenting clinical manifestations. Treatment options derive from study results and experiences in other rheumatic diseases. We will discuss later the treatment options for patients with UCTD together with management principles in patients with MCTD.

2.5 Overlap syndromes

Overlap syndrome is often defined as an entity that satisfies the classification criteria of at least two connective tissue diseases occurring at the same time or at different times in the same patient (Iaccarino et al, 2013). Virtually any combinations of coexisting rheumatic diseases have been reported in the literature. In this chapter, we will discuss selected overlap syndromes that are particularly characteristic or very common.

Cardinal signs of one specific connective tissue disease may also be part of the normal clinical spectrum of another, since many clinical findings and laboratory markers lack specificity. For instance, myositis or myopathies may occur in a subset of patients with SSc (Pope et al, 2002). Four large studies have evaluated the SSc/myositis overlap syndrome and reported 282/633 cases; SSc/myositis seemed to be the second most common SSc overlap syndrome after SSc/RA (Balbir-Gurman et al, 2001; Caramaschi et al, 2007; Pakozdi et al, 2011; Koschik et al, 2012; Iaccarino et al, 2013). Patients with this overlap syndrome do not necessarily fulfil the classification criteria for polymyositis and might have myositis as part of the clinical spectrum of SSc. To make this issue more complicated, classification criteria are of limited value in the early diagnosis of rheumatic diseases. Therefore, patients with SSc and myositis might still have an incomplete or early form of polymyositis as well as SSc. This example highlights the challenges in the diagnosis and classification of connective tissue diseases. Similar considerations may account for many overlap syndromes. In our own clinical practice, we reserve the diagnosis of overlap syndromes for patients who clearly present with classic features of two different rheumatic diseases, including the presence of specific autoantibodies (figure 2). Nevertheless, there is no general consensus about this subject.

Figure 2 The concept of overlap syndrome. PM, polymyositis; SSc, systemic sclerosis.



2.5.1 SLE–RA overlap

Paying tribute to the name of both diseases, the overlap of RA and SLE is called ‘rhumus’ (Panush et al, 1988). The exact definition of ‘rhumus’ syndrome is still debated. In some cases it has been defined as a condition in which patients present clinical features of SLE and RA, and this hypothesis is supported by the simultaneous

presence of SLE-specific autoantibodies (anti-DNA, anti-Sm) and RA-specific autoantibodies (anti-citrullinated protein antibodies (ACPA). Rhupus seems to be as common as the chance of simultaneously having both SLE and RA (Panush et al, 1988). This supports the concept that rhupus represents the coexistence of two separate diseases in the same patient, rather than an additional disease entity. Others authors prefer to consider the 'rhupus' syndrome as an erosive subset of SLE arthropathy (Iaccarino et al, 2013).

The serological overlap between RA and SLE is well known with up to 20% of RA patients exhibiting antinuclear antibodies. However, patients with a true concomitance of RA and SLE are rare. The real prevalence, clinical picture and the natural history of this condition are documented in the literature by case series and small cohorts with significant discrepancies among case definitions and assessment methods. Indeed, in most recent studies, the reported prevalence of rhupus in SLE cohorts ranges between <1% and 17% depending on the adopted inclusion criteria and assessment methods. (Li J, 2014, Tani C, 2013, Gormezano NM, 2016)

Although erosive changes are rarely noted on plain radiographs in patients with SLE, more sensitive imaging techniques, such as magnetic resonance imaging, can disclose erosions in up to 60% of patients (Ostendorf et al, 2003; Iaccarino et al, 2013). In addition, flexion deformities, ulnar deviation, soft tissue laxity and swan neck deformities, as seen in RA, have been noted in 15–50% of patients with SLE (fig.3). (Weissman et al, 1978; Cronin, 1988; Van Vugt et al, 1998).

Recently, the characteristics of a small series of patients with rhupus identified among SLE patients were assessed from the clinical, serological and the instrumental (US and MRI) point of view; in this series arthritis was responsible for the major disease burden at the time of the evaluation; indeed, clinical signs of active synovitis and clinically detectable joint deformities were present respectively in 90% and in 60% of the cases. Interestingly, the severity of the joint disease was also highlighted by the instrumental data which revealed a high prevalence of inflammatory signs (synovial effusion, synovial hyperplasia) and severe joint damage (bone oedema and erosions). From the laboratory point of view, high levels of ESR and CRP were a clinical hallmark of rhupus patients with respect to the entire SLE cohort (Tani C, 2013).

The prevalence of ACPA in 'rhupus' patients is estimated around 57% and 100% (Amezcu-Guerra et al, 2006; Iaccarino et al, 2013) that is significantly higher than in SLE patients; moreover, some studies report a lower prevalence of these antibodies in patients with non-erosive arthritis in comparison with those with erosive disease (Chan et al, 2008; Iaccarino et al, 2013).

In patients with 'rhupus', severe SLE extra-articular manifestations (such as glomerulonephritis and neurological involvement) are less common than in patients with SLE. (Li J, 2014; Tani C et al, 2013)

Figure 3 Picture showing the left hand of a patient with rhupus. Please note that the clinical appearance is indistinguishable from RA.



Figure 4 Hand-wrist plain radiograph of a patient with rhupus. Please note extensive carpal collapse, erosions and subluxations.



2.5.2 SSc overlap syndromes (PM-SSc and RA-SSc overlap)

Symptoms of SSc can occur in combination with those of other connective tissue diseases (CTD); this condition is defined as SSc-overlap syndrome. No classification criteria for SSc-overlap syndrome are available, however, it is generally considered when musculoskeletal involvement (myositis, arthritis) or clinical signs of other rheumatic diseases are substantially greater than usually found in SSc patients (Pakozdi A, 2011). It is reported that up to 20% of patients with SSc have overlapping features with other rheumatologic diseases, being polymyositis/dermatomyositis (43%) and rheumatoid arthritis (32%) the most frequently reported (Pakozdi A, 2011)

Recently, 10% of SSc-overlap syndromes have been identified among the 3240 SSc patients registered in the database of the German Network for Systemic Scleroderma and prospectively followed between 2003 and 2013; interestingly, these subgroup of patients showed distinct serological and clinical profile with respect to the rest of cohort thus supporting the concept that SSc-overlap syndromes should be regarded as a separate SSc subset, distinct from both the limited and the diffuse cutaneous SSc. (Moinzadeh P, 2015)

Autoantibodies are helpful to separate SSc-overlap syndromes from other SSc subsets. In particular, two distinct autoantibody specificities have been associated with the PM-SSc overlap. However, these antibodies can also be found in other connective tissue diseases or overlap syndrome in 17% of cases (Jablonska and Blaszyk, 2004; Iaccarino et al, 2013). In the study of Pakozdi et al, anti-PM-Scl antibodies were found in 33.1% of the patients with SSc/myositis (Pakozdi et al, 2011). In the United States, anti-PM-Scl antibodies are significantly more common in patients with PM-SSc overlap (Targoff et al, 1992). This association could not be confirmed in a Japanese population. By contrast, anti-Ku antibodies were predictive of PM-SSc overlap in the Japanese study population. The differences between the American and the Japanese study might be—at least in part—explained by different frequencies of HLA-DR3 in the two populations, since the genotype is closely associated with anti-PM-Scl antibodies (Ioannou et al, 1999). Other studies showed a prevalence of anti-Ku antibodies in patients with PM-SSc, ranging from 2.3% to 55% (Cavazzana et al, 2008; Belizca et al, 2010; Pakozdi et al, 2011).

Inflammatory joint involvement is another frequent manifestation in patients with SSc-overlap syndromes. These patients are often identified by typical SSc-clinical symptoms (usually limited skin involvement) together with high titers of anticyclic citrullinated peptides (ACPA) and/or higher rheumatoid factor (Ueda-Hayakawa M, 2010, Szucs G, 2007)

Among all patients with SSc, ACPA positivity has been reported in 1.7–14.8% (Avouac et al, 2006; Szucs et al, 2007; Iaccarino et al, 2013). In these patients, ACPA were strongly associated with erosions detected by X-ray examination or with arthritis. In the study by Szucs et al the metacarpophalangeal, carpal, proximal interphalangeal joints and the ulnar heads were found to be more frequently affected by arthritis in patients

with SSc–RA. Most of these subjects had a limited SSc. The extra-articular manifestations included RP, present in 100% of patients, and pulmonary fibrosis, present in 77.3% (Iaccarino et al, 2013).

Overlap-syndrome management

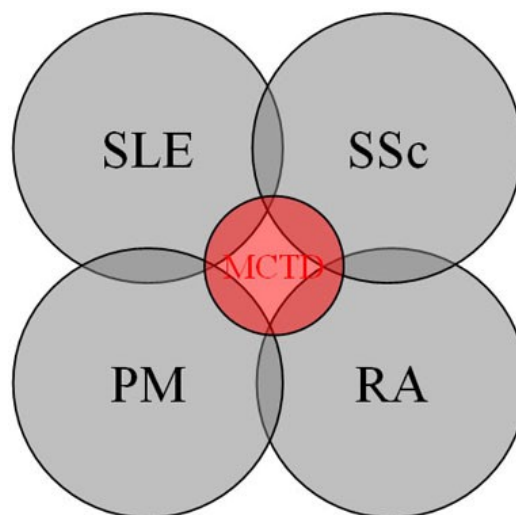
Patients with overlap syndromes are treated according to study protocols and experience with the underlying rheumatic diseases and mainly based on the type of organ involvement. Owing to small patient numbers and poor definition of overlap syndromes, randomized controlled trials have not been performed, and separate guidelines for the treatment of overlap syndromes have not been established.

3 Mixed connective tissue disease

3.1 Introduction

Although the terminology might be misleading, MCTD (formerly, Sharp's syndrome) is a distinct rheumatic disorder. Sharp and colleagues first described the disease in 1972 as a connective tissue disease with features of SLE, SSc and polymyositis. High titres of anti-U1-RNP autoantibodies further defined this disease (Sharp et al, 1972*; Tani et al, 2014). Later, a high prevalence for the development of arthritis resembling the RA joint pattern was seen in patients with MCTD (figure 5).

Figure 5 The concept of mixed connective tissue disease. *MCTD, mixed connective tissue disease; PM, polymyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.*



The clinical features of MCTD often develop over several years and the complete clinical findings are rarely present at the start of the disease. In early stages, patients often present with one of the following features: Raynaud's phenomenon, puffy fingers of the hands (figure 4), sclerodactyly, arthralgias, arthritis, myalgias, myositis and malaise. These clinical features are the most frequently reported in the different cohorts during the course of the disease, together with lung involvement and oesophageal symptoms (Tani et al, 2014).

Figure 6 Swollen fingers.

Mixed connective tissue disease is rare with a prevalence of 3.8 per 100 000 adults (as assessed in a Norwegian population). There is a female predominance with a male to female ratio of about 1:3 (Gunnarsson et al, 2011).

3.2 Mixed connective tissue disease: a distinct disease entity?

Since the initial description, several authors challenged the concept of MCTD as a distinct clinical entity for the following reasons (Smolen and Steiner, 1998*): First, most patients diagnosed as MCTD also satisfy the criteria for another connective tissue disease, especially in later stages of the disease. Second, there are not any commonly classification criteria for MCTD, although several criteria sets have been tested successfully. Third, the initial description of MCTD as a benign connective tissue disease not involving major organ systems and promptly responding to low-dose glucocorticoids has not been confirmed by other studies.

Several genetic, serological and clinical features, however, argue for MCTD as an distinct rheumatic disease and against the concept of an early form of other connective tissue diseases such as SLE, SSc, PM or RA: MCTD is associated with HLA-DR1, HLA-DR4 and to a lesser degree with HLA-DR2 (Black et al, 1988; Kaneoka et al, 1992). In contrast, SLE is associated with HLA-DR2 and HLA-DR3, SSc with HLA-DR3 and HLA-DR5 and PM with HLA-DR3. The linkage disequilibrium and the association with different HLA class II molecules argues for MCTD being distinct from SLE, SSc and PM. Similar to MCTD, RA is associated with HLA-DR1 and HLA-DR4. Apart from erosive arthritis, however, RA barely shares clinical features with MCTD and usually does not show autoantibodies against U1-snRNP.

Serological features also support the concept of MCTD as a distinct disease entity. Although 20–30% patients with SLE might also express anti-U1-snRNP antibodies, per definition a sine qua non for the diagnosis of MCTD,

high titres of these antibodies are specific for patients with MCTD (Habets et al, 1985). Furthermore, SLE patients with anti-U1-snRNP antibodies often retain IgM-U1-snRNP, instead of showing a class switch to IgG antibodies as found in MCTD (Vlachoyiannopoulos et al, 1996). Finally, anti-U1-RNP antibodies in patients with SLE seem to differ from those in patients with MCTD by their antigen recognition (Barakat et al, 1991). Thus, high titres of IgG-autoantibodies against U1-snRNP seem to be specific for MCTD.

In addition to genetic and serological differences, certain clinical manifestations are also unique for patients with high titres of anti-U1-snRNP antibodies. Patients with high titres of antibodies against U1-snRNP rarely develop severe CNS (eg, psychosis, seizures or diffuse) or renal manifestations (eg, diffuse proliferative glomerulonephritis). By contrast, they develop RF-positive, erosive arthritis more frequently. Furthermore, they are more likely to develop pulmonary arterial hypertension than patients with other connective tissue diseases except for SSc. Thus, we agree with many other experts that MCTD is a distinct clinical entity based upon genetic, serologic and clinical features (table 1).

Table 1 Mixed connective tissue disease (MCTD) as a distinct disease entity?

MCTD as a distinct disease entity?	
Pro	Contra
<ul style="list-style-type: none"> • Association with certain HLA types • High titres of anti-U1-RNP IgG autoantibodies with unique antigen recognition • Specific set of clinical manifestations 	<ul style="list-style-type: none"> • Patients might satisfy the classification criteria of other connective tissue diseases in later stages of the disease • Not one commonly accepted set of criteria

3.3 Anti-U1-RNP antibodies

MCTD was initially described as a connective disease with high titres of autoantibodies directed against a complex named 'ribonuclease-sensitive extractable nuclear antigen'. Further studies showed that the U1-RNP particle is a major component of the spliceosome, which is a nuclear particle processing pre-messenger RNA (mRNA) splicing into mRNA (Routsias et al, 2010). Different parts of the spliceosome represent targets of autoimmunity in several connective tissue diseases. The immunogenic potential of spliceosomal components may be increased by post-translational modifications during apoptosis (Mamula et al, 1999).

The small nuclear ribonucleoprotein particles (snRNPs) and the heterogeneous nuclear ribonucleoprotein particles (hnRNPs), two spliceosomal subunits, are the major targets of autoimmunity. SnRNPs contain small RNAs ranging from 80 to 350 nucleotides complexed with proteins. U1-RNPs are a subset of snRNPs with high amounts of uridine nucleotides (called U1-RNA). The U1-RNA molecules form double-stranded secondary structures, which make up the backbone of the U1-RNP complex. The protein components of the U1-RNP complex can be further classified into proteins specific for the U1-RNP complex and non-specific proteins.

Specific proteins are U1-A, U1-C and U1 68 kDa proteins. Non-specific proteins include the Smith proteins (Sm proteins) and the SR proteins, a group of splicing factors rich in serine (S) and arginine (R). Autoantibodies against U1-RNP and other snRNPs mainly recognise the protein components of the complex. Sm proteins are common targets of autoimmunity in SLE, whereas patients with MCTD usually have high antibody titres for the U1 68 kDa protein (Fenning et al, 1995).

hnRNPs contain pre-mRNAs and a variety of structurally related proteins with molecular weights between 33 and 43 kDa. Anti-RA33 antibodies target 33 kDa hnRNP-A2 proteins of the hnRNP complex. Raised titres of anti-hnRNP-A2 antibodies are present in about 30% of patients with RA, SLE and MCTD. The antigen recognition pattern in MCTD, however, differs from that of RA and SLE (Smolen and Steiner, 1998*).

In an animal model of MCTD, mice expressing the HLA-DR4 molecule (HLA-DRA*0101/DRB1*0401) develop anti-U1-RNP antibodies after a single exposure to the 70 kDa polypeptide/U1-RNA autoantigen. Clinically, these mice develop pulmonary inflammatory infiltrates characteristic of MCTD. They do not develop anti-Sm or anti-DNA antibodies, which distinguishes the model from SLE (Greidinger et al, 2008).

Molecular mimicry may lead to the development of anti-U1-RNP antibodies. This hypothesis suggests the presence of antigens (eg, infectious agents) that closely resemble the U1-RNPs and cause the production of cross-reactive antibodies. While the exogenous antigen might be cleared over time, the immune reaction against the endogenous U1-RNP structures might persist. Although some evidence for the role of molecular mimicry in connective tissue disease exists, including associations of Epstein–Barr virus with anti-Sm antibodies, and cytomegalovirus with anti-U1 68 kDa antibodies (McClain et al, 2003; Newkirk et al, 2001), it still needs further scientific proof.

Apart from anti-U1-RNP antibodies, a variety of other antibody specificities, may be present in patients with MCTD; in a recent study, Anti-Ro52 antibodies were present in 29%, anti-Ro60 in 19% and anti-SSB in 6% of the MCTD sera. Interestingly, anti-Ro52 antibodies were significantly associated with lung fibrosis (Gunnarsson R, 2016).

Antigen spreading to molecules in close proximity to the original antigen (ie, the U1-RNP complex) may play a role. Nevertheless, several antigens do not show structural homologies or colocalize with the U1-RNP complex. In these cases, defective clearance of apoptotic material with a high immunogenic potential, might lead to the formation of antibodies against other antigens (Rosen and Casciola-Rosen, 2001). Ro/SSA antigens, for example, occur in high concentrations on apoptotic blebs. Incomplete B or T cell tolerance to apoptotically modified antigens might also be of importance (Casciola-Rosen et al, 1999).

Although anti-U1-RNP antibodies are a sine qua non for the diagnosis of MCTD, their role in the pathogenesis of MCTD is unclear. In this context, recent data from an animal model suggest that anti-U1-RNP antibodies can

mediate tissue injury (Provost et al, 1987; Mason et al, 2004). Mice immunized with apoptotically modified U1 68 kDa proteins developed a MCTD-like interstitial lung disease, whereas mice immunized with control antigens did not. This animal model is of interest because a diversifying autoimmune response is seen in response to immunization with apoptotically modified U1 68 kDa proteins. In addition to antibodies against the exogenous U1 68 kDa protein complex, these animals also show antibody formation against epitopes on endogenous U1 68 kDa proteins and non-U1-RNP proteins. This mimics, at least in part, the situation in human MCTD.

3.4 Sequential clinical and laboratory features of patients with anti-U1-RNP antibodies

MCTD evolves over time and patients typically develop new clinical and laboratory features in the course of the disease. Thus, patients might display few features of the disease and may not fulfil the classification criteria for MCTD at their initial presentation. Furthermore, patients with antibodies against U1-RNP might meet the classification criteria for rheumatic diseases other than MCTD (Reichlin, 1976*; Habets et al, 1985).

In the first prospective study on patients with anti-U1-RNP antibodies, 60% of patients presented with symptoms compatible with a specific connective tissue disease other than MCTD. After a mean follow-up of 6 years, however, 90% fulfilled the criteria for MCTD (Sullivan et al, 1984*).

At the start of another study of 32 patients with high- and low-titer anti-U1-RNP antibodies, only three patients fulfilled the classification criteria for MCTD and 11 patients for other connective tissue diseases. The remaining 18 patients were classified as having UCTD. After a mean observation period of 6 years, 15 of the 18 patients (83%) initially diagnosed with UCTD met the classification criteria for specific connective tissue diseases: 11 for MCTD, two for SLE and two for both MCTD and SLE (Lundberg et al, 1991b).

Diagnosis of other rheumatic diseases (in particular, UCTD) may evolve into a diagnosis of MCTD over time. The initial diagnosis of MCTD may also change into the diagnosis of another rheumatic disease. In a study on 46 patients positive for anti-U1-RNP antibodies, 33 were classified with MCTD, 10 were diagnosed with SLE, two with RA and one with SSc (Van den Hoogen et al, 1994). After 5 years, 55% of the patients initially diagnosed with MCTD fulfilled the classification criteria for another connective tissue disease. Twenty-one per cent developed SSc, 15% SLE, 9% RA and 9% an overlap syndrome. Of the 10 patients in this study, who fulfilled the criteria for SLE at the initial presentation, four developed clinical SSc features. In a recent retrospective study, 161 patients had initially been diagnosed as having MCTD by three different sets of classification criteria (Sharp, Alarcon-Segovia and Kasukawa (discussed in detail in the next section)). After a mean follow-up of 7.9 years, 57.9% of patients still had the diagnosis of MCTD. By then, the other patients carried a diagnosis of SSc (17.3%), SLE (9.1%), RA (2.5%), UCTD (11.5%) and overlap syndrome (1.7%).

Interestingly, the presence of autoantibodies and specific clinical features helped to predict the evolution into

another rheumatic disease: the presence of anti-dsDNA antibodies was associated with evolution into SLE, hypomotility or dilatation of the oesophagus and sclerodactyly with evolution into SSc (Cappelli et al, 2011).

3.5 Proposed classification criteria for MCTD

For MCTD, there is not one widely accepted set of classification criteria. Four different sets of classification criteria for MCTD are available—namely, the criteria of Sharp, Alarcon-Segovia, Kahn and Kasukawa (Alarcon-Segovia and Villareal, 1987; Kasukawa et al, 1987; Sharp, 1987; Kahn, 1991). Since none of those criteria is convincingly better than the others, all four sets of criteria may be used.

Sharp's criteria consist of five major and 11 minor criteria to distinguish between definite MCTD and probable MCTD (table 2). In contrast to the three other sets of criteria, Sharp's criteria do not demand the presence of high titres of U1-RNP antibodies for the diagnosis of MCTD. According to Sharp, a patient can have probable MCTD in the absence of anti-U1-RNP antibodies. Nevertheless, for the diagnosis of definite MCTD, anti-U1-RNP antibodies are necessary.

Table 2 Sharp's criteria for mixed connective tissue disease

Major criteria	Minor criteria
1. Severe myositis	1. Alopecia
2. Lung involvement with a TLCO <70% and/or PAH and/or proliferative vascular lesions on biopsy	2. Leucopenia
3. Raynaud's phenomenon and/or oesophageal hypomotility	3. Anaemia
4. Swollen hands and/or sclerodactyly	4. Pleuritis
5. anti-ENA \geq 1:10 000, positive for anti-U1-RNP antibodies and negative for anti-Sm antibodies	5. Pericarditis
	6. Arthritis
	7. Trigeminal neuralgia
	8. Malar rash
	9. Thrombocytopenia
	10. Mild myositis
	11. History of swollen hands

- Definite MCTD: four major criteria, no anti-Sm antibodies, anti-U1-RNP antibodies >1:4000
- Probable MCTD: three major criteria and no anti-Sm antibodies or two major criteria plus one minor criterion plus anti-U1-RNP antibodies >1:1000

ENA, extractable nuclear antigen; PAH, pulmonary arterial hypertension; RNP, ribonucleoprotein; TLCO, carbon monoxide transfer factor.

Table 3 Alarcon–Segovia’s criteria for mixed connective tissue disease

Clinical criteria	Serological criterion
<ol style="list-style-type: none"> 1. Swollen hands 2. Acrosclerosis with or without proximal SSc 3. Raynaud’s phenomenon 4. Myositis: biologically or histologically proved 5. Synovitis 	Anti-RNP antibodies with a titre of >1:1600 at the haemagglutinin assay
Diagnosis of MCTD, if the serological criterion is present and three or more clinical criteria (if 1, 2 and 3 are present, 4 and 5 are also required to distinguish MCTD from SSc)	

MCTD, mixed connective tissue disease; RNP, ribonucleoprotein; SSc, systemic sclerosis.

Kahn’s criteria (table 4) are similar to those of Alarcon-Segovia. Besides the presence of high titres of anti-RNP antibodies, four clinical criteria are included.

Table 4 Kahn’s criteria for mixed connective tissue disease

Clinical criteria	Serological criterion
<ol style="list-style-type: none"> 1. Raynaud’s phenomenon 2. Swollen fingers 3. Myositis 4. Synovitis 	High titres of anti-RNP antibodies, corresponding to a speckled ANA titre of $\geq 1:2000$
Diagnosis of MCTD, if the serological criterion is present plus Raynaud’s phenomenon plus two or all of the other three clinical criteria	

ANA, antinuclear antibodies; MCTD, mixed connective tissue disease; RNP, ribonucleoprotein.

Kasukawa’s criteria (table 5) include anti-snRNP antibodies, as well as common clinical symptoms and features of the defined connective tissue diseases SLE, SSc and PM.

Table 5 Kasukawa’s criteria for mixed connective tissue disease

Common symptoms	Symptoms of SLE, SSc and PM	Serological criterion
<ol style="list-style-type: none"> 1. Raynaud’s phenomenon 2. Swollen fingers 	<p>SLE:</p> <ol style="list-style-type: none"> 1. polyarthritis 2. adenopathies 3. malar rash 4. serositis 5. leucopenia and/or thrombocytopenia <p>SSc:</p> <ol style="list-style-type: none"> 1. sclerodactyly 2. pulmonary fibrosis and/or restrictive changes and/or reduced TLCO 3. oesophageal hypomobility or dilatation <p>PM:</p> <ol style="list-style-type: none"> 1. muscle weakness 2. raised muscle enzymes 3. myogenic changes in EMG 	anti-snRNP antibodies

Diagnosis of MCTD, if one or two common symptoms plus one or more symptom of the mentioned signs of two or three of the defined connective tissue diseases SLE, SSc and PM plus the serological criterion

EMG, electromyogram; MCTD, mixed connective tissue disease; PM, polymyositis; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TLCO, carbon monoxide transfer factor.

Sharp's, Alarcon-Segovia's and Kasukawa's criteria have been tested for their specificity by applying them to patients with other rheumatic diseases, including SLE, RA, SSc, DM/PM and Sjögren's syndrome (Alarcon-Segovia and Cardiel, 1989). These studies were limited by the lack of a commonly accepted, typical clinical presentation of patients with MCTD to test the criteria. Alarcon-Segovia's and Kasukawa's criteria both had a very high specificity for patients with MCTD. Only one of 200 patients with SLE was diagnosed as having MCTD according to Alarcon-Segovia's criteria and none according to Kasukawa's criteria. According to these two sets of criteria, none of the patients with RA, SSc and DM/PM was diagnosed with MCTD. Finally, one of 80 patients with Sjögren's syndrome was positive for MCTD according to the Alarcon-Segovia and Kasukawa criteria.

The specificity of Sharp's criteria, however, was significantly lower and several patients were falsely identified as having probable MCTD. Sharp's criteria distinguished patients with RA and Sjögren's syndrome well (100% and 96%, respectively), but was less accurate for patients with SLE, DM/PM and, in particular, SSc (88%, 84% and 55%, respectively). Of 80 patients with high anti-RNP antibody titres with the genuine diagnosis of MCTD, Sharp's criteria and Alarcon-Segovia's criteria had a sensitivity of 100%. Using Kasukawa's criteria, two of the 80 patients were not identified (Alarcon-Segovia and Cardiel, 1989).

In another comparative study of the four classification criteria evaluating 45 patients with anti-U1-RNP antibodies, the criteria by Alarcon-Segovia and Kahn performed best (Amigues et al, 1996). Twenty-five of the 45 patients included in the study had other rheumatological diseases such as SLE, RA, SSc or overlap syndromes. Sixty-four per cent of the patients with anti-U1-RNP antibodies fulfilled Sharp's criteria, 42% those of Kasukawa and 14% each those of Alarcon-Segovia and Kahn. Of the 25 patients with other rheumatic diseases, 56% also fulfilled Sharp's criteria, 40% Kasukawa's and 14% each Alarcon-Segovia's and Kahn' criteria.

Except for Sharp's criteria, the diagnosis of MCTD depends on high titres of anti-U1-RNP antibodies. Thus, the method of detection and the cut-off point between high and low titres should be well defined. Several methods are used to measure the titres of U1-RNP antibodies but a defined cut-off value is lacking (Venables, 2006). In early studies, the haemagglutinin assay was the standard test. Other assays used are immunodiffusion, immunoblotting and immunoprecipitation. Nowadays, enzyme-linked immunosorbent assays with cloned antigens as standards are widely used.

3.6 Clinical manifestations of MCTD

The first clinical symptoms of MCTD are usually non-specific. At this stage of the disease, patients often have malaise, myalgias, arthralgias, Raynaud's phenomenon and low-grade fever. In later stages of the disease, a set of five cardinal signs should lead to the suspicion of MCTD:

- the presence of high titres of anti-U1-RNP autoantibodies—in particular, IgG antibodies that recognise the 68 kDa protein of the U1-RNP complex;
- the lack of severe kidney and central nervous system (CNS) involvement;
- severe arthritis and the presence of RF;
- pulmonary arterial hypertension;
- Raynaud's phenomenon in association with puffy hands.

Apart from these classic manifestations, almost any other organ system may be affected (Sharp et al, 1972*; Bennett and O'Connell, 1980; Alarcon-Segovia, 1994), including the vascular system, skin, gastrointestinal tract, musculoskeletal system, lungs, heart, haematological system, kidneys and CNS. Table 6 compares the clinical features of patients with UCTD and MCTD at presentation and after 5 years of follow-up.

3.6.1 Musculoskeletal manifestations of MCTD

In MCTD, joint involvement may vary from mild arthralgias to severe arthritis in small or large joints that sometimes may lead to erosions typical of RA and to mutilating arthritis (Ortega-Hernandez and Shoenfeld, 2012). As described above, the joint involvement in MCTD tends to be more severe than in SLE and SSc. Inflammatory arthritis is a frequent presenting symptom of MCTD and occurs in 60–100% of patients. Most commonly, joint involvement is present in a RA-like pattern with symmetrical, polyarticular involvement of the small joints of the hands and feet. As with RA, mono- or oligoarticular presentations can also occur (Piirainen, 1990). The arthritis in patients with MCTD is erosive in 30–70% of cases as shown by X-ray examination. In patients with MCTD, RF is a risk factor for erosive joint disease (O'Connell et al, 1977; Udoff et al, 1977; Bennett and O'Connell, 1980). Periarticular osteopenia, subchondral cysts and subluxations are also common. In addition, swan neck deformities and boutonniere changes are seen in up to 30% of affected patients.

Another very common feature, which might occur in up to 60% of patients, is resorption of the digital tuft. Arthritis mutilans can occur in rare cases. Non-erosive Jaccoud's arthropathy and atlantoaxial subluxation may be present in single cases (Alarcon-Segovia and Uribe-Uribe, 1979; Bennett and O'Connell, 1980; Catoggio et al, 1983; Piette et al, 1988). Nevertheless, despite the close resemblance to joint disease in RA, the course of MCTD-associated arthritis is more benign than in erosive RA, with erosions being small and scattered even after several years of active arthritis.

Between 80% and 90% of patients with MCTD develop muscle involvement, with proximal muscles being more frequently involved (Ortega-Hernandez and Shoenfeld, 2012). The prevalence of myositis in MCTD varies from 15% to 75% in different studies. This considerable variation might be explained by differences in the diagnostic methods. Myositis is often present early in the course of the disease. The clinical presentation is identical to that of other inflammatory myopathies. Most patients show weakness of the proximal muscles of the

shoulders and pelvic girdle and little if any wasting. Focal myopathies, however, have been reported in single cases. Diaphragmatic dysfunction and dysphagia due to myositis can occur, but are rare.

Table 6 Comparison of the clinical features of mixed connective tissue disease and undifferentiated connective tissue disease. Modified from Swanton and Isenberg (2005)

	MCTD (Burd et al, 1999)		UCTD (Danieli et al, 1999; Bodolay et al, 2003)	
	At the time of diagnosis (%)	Cumulative findings after 5 years (%)	At the time of diagnosis (%)	5 Years after the diagnosis (%)
Raynaud's disease	89	96	50–60	89
Arthralgias/arthritis	85	96	35–50	89
Puffy hands	60	66		
Oesophageal dysfunction	47*	66*	5†	7†
Reduced TLCO	43*	66*	7†	8†
Serositis	34	43	5–10	5–15
Haematological abnormalities	30	53	20–30	20–40
Skin rash	30	53	25–50	30–55
Myositis	28	51	0–1	0–1
PAH	9	23	†	†
Skin fibrosis	4	19	5	5
Neurological manifestations	0	17	5–10	5–15
Renal manifestations	2	11	0	0
Sicca symptoms	Up to 30 in other series		10–25	15–25

*Functional test performed on all patients, including asymptomatic patients.

†No functional tests performed in asymptomatic patients.

MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; TLCO, carbon monoxide transfer factor; UCTD, undifferentiated connective tissue disease.

On histological examination, patients with MCTD-associated myositis show histological findings similar to those of patients with PM or SLE (Ortega-Hernandez and Shoenfeld, 2012), or perivascular and endomysial lymphocytic infiltrates, similar to the histological findings in DM (Cooke and Lurie, 1977; Bennett and O'Connell, 1980). Myositis in patients with MCTD commonly manifests as acute flares and can be associated with high-grade fever. Less often, myositis presents as a smouldering process. Several case studies report myasthenia gravis in patients with MCTD, suggesting that there might be some association between these two diseases (Yasuda et al, 1993).

3.6.2 Vascular manifestations of MCTD

The majority of patients with MCTD display vascular changes (Grader-Beck and Wigley, 2005). About 75–90% of patients have Raynaud's phenomenon, which may precede the appearance of other clinical manifestations by years (Sharp et al, 1972*; Ortega-Hernandez and Shoenfeld, 2012). In addition, microvascular changes, similar to those seen in patients with SSc occur. Typical SSc-like findings of MCTD on nailfold capillaroscopy, such as avascular fields, micro-haemorrhages, bushy capillaries and giant capillaries with a general reduction of the capillary density and reduced blood flow, are present in 54% of patients with MCTD (Blockmans et al, 1993). Furthermore, Hejas et al observed a capillaroscopic 'scleroderma pattern' in 31.4% of patients at the time of diagnosis and in 40.3% after a mean of 13.1 years of follow-up, with significant progression of microvascular alterations (Hejas et al, 2013). In addition to changes of the capillaries, small and medium-sized arteries often show signs of occlusion on arteriographic studies. These occlusions, however, are asymptomatic in most cases. Interestingly, an imbalance of angiogenic and angiostatic factors reflects the capillaroscopic alterations in both MCTD and SSc, although there appear to be differences in the expression profiles of these two diseases. In MCTD, levels of vascular endothelial growth factor (VEGF) were higher in patients with PAH, acrosclerosis and myositis, suggesting that VEGF levels might help to predict the development of these disease manifestations (Distler et al, 2011).

A severe vascular manifestation of MCTD is PAH. Patients with PAH show a pulmonary artery pressure of >25 mm Hg at rest and pulmonary capillary wedge pressure <15 mm Hg, as tested by right-heart catheterisation (Simonneau et al, 2009). PAH is seen in 20–30% of patients with MCTD (Burdett et al, 1999) and the presence of anticardiolipin antibodies is associated with its development. In addition, a higher prevalence of anti-endothelial cell antibodies was found in patients with MCTD plus PAH than in those patients with MCTD but no PAH (Vegh et al, 2006). In a recent follow-up study of patients with MCTD, PAH developed in 17.8% of patients at a mean of 14.5 ± 3.71 years after diagnosis. All these patients showed a continuously high level of anti-RNP and 84% of them were positive for anti-endothelial cell antibodies (Hejas et al, 2013).

In contrast to other forms of pulmonary hypertension, which might occur in patients with MCTD, PAH is characterised by hypertrophy of the intima and proliferation of smooth muscle cells in small pulmonary arteries and arterioles, leading to a reduction of the vascular lumen. Since PAH is the major cause of death in MCTD, regular evaluation for PAH is essential. Patients with PAH usually present with a history of progressive dyspnoea on exertion. Many other clinical symptoms and signs are suggestive of PAH but are not always present.

Physical examination may disclose an accentuated second pulmonary heart sound and might also show a systolic pulsation at the left sternal border. Chest X-ray examination may demonstrate a dilatation of the pulmonary arteries and right atrial enlargement and ventricular hypertrophy. Similarly, signs of right atrial and

ventricular hypertrophy may be seen on electrocardiography. The sensitivity and specificity of chest X-ray examination and electrocardiography, however, are relatively poor; the PAH-related findings often occur late, after haemodynamic changes are already established.

Screening tests for patients at risk, however, need to detect PAH at earlier stages. Transthoracic echocardiography is becoming the first choice for PAH screening. Despite the need for a highly experienced sonographer, echocardiography is a non-invasive, cheap and feasible screening test. Transthoracic echocardiography may be inaccurate in patients with borderline or slightly raised pulmonary pressure, resulting in both false-negative and false-positive results. Serum biomarkers, such as pro-brain-type natriuretic peptide (pro-BNP), may help to increase sensitivity of echocardiographic PAH screening (Allanore et al, 2003). A Delphi consensus study has detected the tests that may lead to a suspicion of PAH in patients with SSc. Additionally, N-terminal pro-BNP and echocardiography, and also pulmonary function tests, may provide additional information, as a decrease of the carbon monoxide transfer factor (TLCO) of <50% in the absence of pulmonary fibrosis may suggest that right heart catheterisation should be carried out. There is general consensus that a suspicion of PAH needs verification by right heart catheterisation, which is the diagnostic 'gold standard' (Avouac et al, 2014).

In the study of Khanna et al, new recommendations for screening and detection of PAH associated with connective tissue disease, in particular SSc and connective tissue diseases with scleroderma features, have been published. According to these recommendations, patients should be evaluated with pulmonary function tests (including TLCO), transthoracic echocardiography and N-terminal pro-BNP initially and at least once a year thereafter. If patients have new signs or symptoms, complete screening needs to be repeated (Khanna et al, 2013).

3.6.3 Pulmonary manifestations of MCTD

A significant number of patients with MCTD have a pulmonary involvement. However, in most patients with MCTD, pulmonary changes are mild and many patients are asymptomatic (Bodolay et al, 2005). PAH, a severe complication of the disease, is the major cause of death in patients with MCTD. Apart from PAH, pleural effusions and interstitial lung disease (non-specific interstitial pneumonia or usual interstitial pneumonia pattern) are also common in MCTD. The prevalence of interstitial lung disease may be as high as 67% based on high-resolution computed tomography (HRCT) and DTPA scans (Black and Isenberg, 1992). Applying strict HRCT-based diagnostic criteria, 35 of the patients in the Norwegian nationwide MCTD cohort showed reticular patterns consistent with lung fibrosis. Lung fibrosis was quantified as minor in seven, moderate in nine and severe in 19 of all patients. Mortality was significantly increased in patients with severe lung fibrosis compared with patients with normal HRCT findings (20.8 vs 3.3 during a 4.2 years' follow-up) (Gunnarsson et al, 2012).

Reductions of the transfer factor for carbon monoxide are the most common abnormality in lung function tests (Black and Isenberg, 1992). Most patients with this abnormal finding, however, are asymptomatic and only a minority have exertional dyspnoea. Pleural disease is found in up to 40% of patients with MCTD. It can manifest as pleural effusion and pleural thickening. As with interstitial lung disease, pleural involvement is often asymptomatic. Rare pulmonary manifestations of MCTD are diaphragmatic dysfunction, alveolar haemorrhage, pulmonary vasculitis and thromboembolic disease. Table 7 summarizes the pulmonary manifestations of MCTD.

Table 7 Overview of the pulmonary manifestations of mixed connective tissue disease

Common manifestations	Rare manifestations
Interstitial lung disease	Diaphragmatic dysfunction
Pleural effusion	Alveolar haemorrhage
Pulmonary arterial hypertension	Pulmonary vasculitis
	Thromboembolic disease
	Aspiration pneumonia

3.6.4 Mucocutaneous manifestations of MCTD

Patients with cutaneous involvement often present with typical SSc- or SLE-like skin manifestations (Sharp et al, 1972*; Baurle and Hornstein, 1979; Magro et al, 1997; Sen et al, 2014). Swollen digits or oedema of the entire hands, also known as puffy hands, are a common feature of MCTD and are often the presenting signs of the disease. These findings can also occur during the early course of SSc. Other common features of both diseases are sclerodactyly and calcinosis cutis. In contrast, truncal skin fibrosis does not usually occur in MCTD. Patients might also develop digital ulcers and gangrene due to severe Raynaud's phenomenon or telangiectasias. SLE-like manifestations of MCTD include discoid plaques, subacute lupoid skin changes, photosensitivity and malar rashes, which can be indistinguishable from SLE. A recent study, evaluating cutaneous manifestations in 23 patients who fulfilled the Alarcon-Segovia and Villareal criteria, showed that five patients presented malar rash (21.7%) and two patients had discoid lupus erythematosus. Acrosclerosis and hand oedema were identified as the commonest cutaneous features (in 17 and nine patients, respectively) (Sen et al, 2014). Besides SSc- and SLE-like features, livedo reticularis, livedo vasculitis and cutaneous leucocytoclastic vasculitis have been described. Manifestations of MCTD at the mucosal membranes, which occur in a small percentage of patients, are oral and genital ulcerations and nasal septum perforation.

MCTD often overlaps with, or may reflect, features of Sjögren's syndrome. Forty per cent to 95% of patients with MCTD have sicca symptoms, including dry eyes, dry mouth and salivary or lachrymal gland inflammation. Many of these patients are positive for anti-Ro/SSA and some also for anti-La/SSB (Alarcon-Segovia 1976; Helenius et al, 2001; Setty et al, 2002).

3.6.5 Gastrointestinal manifestations of MCTD

Oesophageal hypomotility is found in 45–85% of patients with MCTD and initially it is often subclinical. As for SSc, oesophageal manometry and barium swallow can demonstrate a reduction of the peristalsis, particularly in the lower third, and a decline of the lower sphincter pressure. Consequently, patients have gastro-oesophageal reflux and might have swallowing problems in later stages. Nevertheless, oesophageal manifestations may be less severe in MCTD than in SSc. One study compared the lower oesophageal sphincter pressure in patients with MCTD and SSc. The prevalence of oesophageal involvement was similar in SSc and MCTD, but the lower oesophageal sphincter pressure in patients with MCTD was higher than in patients with SSc (Doria et al, 1991).

Besides the oesophagus, disturbed peristalsis might also occur in other parts of the gastrointestinal tract. Delayed gastric emptying was noted in 6% of patients and up to 75% of patients in one study had abnormal findings in a small bowel series, including slow transit and dilatation. Malabsorption might occur owing to bacterial overgrowth and small bowel dilatation. Pseudo-diverticula and colonic perforation are also found with increased frequency in patients with MCTD. Rare gastrointestinal manifestations that can be associated with MCTD are serositis, protein losing enteropathy, mesenteric vasculitis, Budd–Chiari syndrome, autoimmune hepatitis, primary biliary cirrhosis and pancreatitis (Marshall et al, 1990; Weston et al, 1998).

3.6.6 Cardiac manifestations of MCTD

Cardiac disease may occur in 20–30% of patients (Dutschmann et al, 1989; Smolen and Steiner, 1998*). Pericarditis is the most common manifestation, but is often mild (Lundberg et al, 2005). A recent review including 616 patients showed that the prevalence of cardiac involvement varies from 13% to 65% according to patient selection and method used for its detection. However, it highlighted that pericarditis was the most common cardiac diagnosis, with a prevalence ranging from 30% to 43% in two prospective studies (Patampong et al, 2014). In MCTD mitral valve prolapse (in up to 25%) and conduction defects may also occur. In rare cases potentially lethal myocarditis may occur. Other abnormalities such as right atrial enlargement or right ventricular hypertrophy are secondary due to PAH. Finally, patients with MCTD may have a higher risk for cardiovascular events, sometimes due to accelerated atherosclerosis—similar to patients with other chronic inflammatory diseases (eg, RA). Cardiovascular risk factors, including dyslipidaemia, low vitamin D levels and endothelial stiffness, may occur in patients with MCTD and require aggressive treatment to reduce the long-term risk for cardiovascular events (Bodolay et al, 2008; Hajas et al, 2010; Soltesz et al, 2010).

3.6.7 Renal manifestations of MCTD

Renal involvement is one of the most common complication in MCTD (Ortega-Hernandez and Shoenfeld, 2012), occurring in 11–40% of patients (Kobayashi et al, 1985; Kitridou et al, 1986). In contrast to SLE, severe

renal disease is very rare in MCTD, and the presence of anti-RNP antibodies may be protective against the development of an important renal manifestation with a diffuse proliferative glomerulonephritis (Lemmer et al, 1982). This is true for patients with MCTD and also for patients with SLE carrying anti-U1-RNP antibodies. Nevertheless, few cases of patients with MCTD and renal crisis, a potentially life-threatening complication with abrupt onset of severe hypertension and renal dysfunction, have been reported. In these patients, similar histopathological findings to those of scleroderma renal crisis have been reported (Satoh et al, 1994).

Other rare renal manifestations of MCTD are renal amyloidosis and renal infarcts in patients with anticardiolipin-positive MCTD. Finally, membranous nephropathy may occur. Usually, membranous nephropathy is mild in patients with MCTD, but might also be associated with significant proteinuria.

3.6.8 Neuropsychiatric manifestations of MCTD

Like renal disease, severe CNS manifestations are usually absent in MCTD, although there are a few case reports of CNS haemorrhage, myelitis, retinal vasculitis and progressive multifocal leucoencephalopathy in patients diagnosed with MCTD. Although severe manifestations are unusual, mild CNS involvement occurs in 25% of patients. As in patients with SSc, neuropathy of the trigeminal nerve is a common problem in MCTD. Headaches are an unspecific symptom. Vascular headaches are another frequent problem. Aseptic meningitis is a rare problem, but may be more common in MCTD than in the general population. Of note, anti-U1-RNP antibodies in the cerebrospinal fluid are associated with central neuropsychiatric manifestations, including aseptic meningitis, demyelinating syndromes, cognitive dysfunction, seizures and psychosis in patients with SLE and MCTD (Sato et al, 2010).

3.6.9 Haematological manifestations of MCTD

Anaemia and lymphopenia are commonly seen in patients with MCTD (Segond et al, 1978; Poullin et al, 1999). Low-grade anaemia, normally due to chronic disease, is observed in up to 75% of patients. In rare cases, patients present with Coombs positive haemolytic anaemia. Leukopenia and lymphopenia tend to correlate with disease activity. Autoimmune-mediated thrombocytopenia can become severe and manifest as thrombocytopenic purpura. Thrombocytopenia may be associated with the presence of antiphospholipid antibodies.

3.6.10 Laboratory abnormalities associated with MCTD

All patients diagnosed with MCTD have by definition high titres of ANAs with specificity against U1-RNP. Anti-IgG-U1-RNP autoantibodies against the 68 kDa protein of the U1-RNP complex of the spliceosome are particularly specific for MCTD. By immunofluorescence, anti-U1-RNP antibodies produce a speckled ANA pattern, very similar to that of anti-Sm and anti La/SSB autoantibodies.

The titres of U1-RNP autoantibodies tend to correlate with disease activity. A significant reduction of the anti-U1-RNP antibody titres was seen in patients in remission, whereas persistently raised titres were measured in patients with chronically active disease (Burdett et al, 1999).

Fifty per cent to 70% are also positive for RF. Antibodies directed to single-stranded DNA occur in 80% of patients, but anti-dsDNA-antibodies are rare. Antiphospholipid antibodies occur in about 15% of patients with MCTD compared with almost 40% of patients with SLE (Komatireddy et al, 1997). Unlike in SLE, most anticardiolipin antibodies in MCTD are β 2-glycoprotein independent (Mendonca et al, 1998). Antiphospholipid antibodies tend to correlate with thrombocytopenia, but not with thrombosis or abortion.

Other autoantibodies often detected in patients with MCTD are anti-hnRNP-A2, anti-fibrillin-1 and antinucleosome antibodies. A false-positive Venereal Disease Research Laboratory test is seen in about 10% of patients. Besides the presence of autoantibodies, hypergammaglobulinaemia is a common feature of MCTD. Furthermore, hypocomplementaemia or cryoglobulins might be found, but they seem not to be associated with renal disease or involvement of other organs in patients with MCTD (Smolen and Steiner, 1998*).

3.6.11 Clustering of clinical and laboratory features in MCTD

To identify specific subtypes of patients with MCTD, Szodoray and colleagues applied statistical cluster analysis to a group of 201 patients fulfilling the Alarcon-Segovia diagnostic criteria. The authors identified the three following clusters: (1) 77 patients with increased likelihood of having PAH, Raynaud's phenomenon and livedo reticularis; (2) 79 patients prone to interstitial lung disease, myositis and oesophageal hypomotility; and (3) 45 patients with a high rate of anti-CCP positivity and erosive arthritis. Survival was worst in cluster (1) with PAH being the major disease complication, resulting in the death of patients. Despite limitations in diagnosing certain disease manifestations (eg, PAH), this study may provide a preliminary system for further classification of the broad disease spectrum of MCTD (Szodoray et al, 2012).

3.7 MCTD and pregnancy

The data for the outcome of pregnancy in patients with MCTD are limited to a few retrospective studies and some case reports (Bennett and O'Connell, 1980; Kaufman and Kitridou, 1982; Siamopoulou-Mavridou et al, 1988; Lundberg et al, 1991a; Kitridou, 2005; Hoshino et al, 2008). Prospective, controlled studies of foetal and maternal morbidity and mortality in MCTD are lacking. Several conclusions can be drawn from the available studies. First, there is no evidence that the fertility of patients with MCTD is impaired. Second, patients might have a new onset of MCTD or the disease might flare up during pregnancy. Third, most reports suggest that foetal outcome is favourable in patients with MCTD, like that in healthy individuals. One study, however, showed a poor outcome and the rate of live births was reduced to 31% compared with 83% in controls. Finally,

neonatal lupus manifesting predominantly at the skin can occur in MCTD even in the absence of anti-Ro/SSA and anti-La/SSB antibodies. Nevertheless, neonatal lupus seems to be very rare in MCTD.

To sum up, the reports available suggest a modest risk of maternal flares during pregnancy. The foetal outcome remains controversial. Based on these findings and experiences in patients with SLE, the following guidelines have been proposed:

- The pregnancy should be planned for times of controlled disease activity.
- Patients should be followed up closely by an obstetrician and a rheumatologist
- Anti-U1-RNP, anti-Ro/SSA, anti-La/SSB, anticardiolipin antibodies and lupus anticoagulant should be determined at the onset of pregnancy, if not already known.
- Disease flares should be treated promptly with glucocorticoids.

3.8 Prognosis of MCTD

MCTD was initially described as a connective tissue disease with a good prognosis and an excellent response to glucocorticoids (Sharp et al, 1972*). Indeed, the prevalence of severe renal and CNS manifestations, which are a major cause of morbidity and mortality in SLE, is low (Lemmer et al, 1982; Burdt et al, 1999). Nevertheless, the incidence of PAH, which shortens life significantly, is high in MCTD (Burd et al, 1999). The excellent response to glucocorticoids was challenged by the results of subsequent follow-up studies (Nimelstein et al, 1980; Sullivan et al, 1984*). In general, the prognosis of MCTD is better than that of SLE and diffuse SSc (Burd et al, 1999). In many patients, the disease follows a benign course and goes into remission. Other patients show an aggressive disease course and may only have a partial response to immunosuppressive therapies.

Several studies, which included almost 200 patients at tertiary referral centres, showed a mortality rate of 16–28% after 10–12 years (Nimelstein et al, 1980; Burdt et al, 1999). Comparison with mortality data from age- and sex-matched controls is missing. Nevertheless, since MCTD mainly affects young women, the reported mortality rate may indicate an increased risk of premature death in patients with MCTD. PAH remains the leading cause of death in MCTD (Harmon and Leatherman, 1988; Burdt et al, 1999; Szodoray et al, 2012; Hajas et al, 2013), followed by infections. Other causes of death are rare and include myocarditis and renal crisis (Lash et al, 1986; Burdt et al, 1999). In children, deaths due to haemolytic uremic syndrome and glomerulonephritis have been reported. Death due to cardiovascular disease seems to be less common than in RA and SLE.

The morbidity in patients with MCTD can be high. Patients commonly have fatigue, arthralgias and arthritis, myalgias and myositis, serositis or gastrointestinal problems. In rare cases, patients may be disabled owing to deforming or mutilating arthritis. Secondary fibromyalgia with widespread musculoskeletal pain might also develop.

Treatment-induced increase of morbidity and mortality is another concern in patients with MCTD, and is mainly due to the prolonged use of glucocorticoids. The side effects of glucocorticoids include osteoporosis, aseptic bone necrosis, steroid myopathy, hypertension, steroid diabetes, acne, Cushing syndrome, gynecomastia and an increased risk of infections.

3.9 Treatment of MCTD

Unfortunately, no randomised controlled trials on the treatment of MCTD have been carried out. Thus, the management of patients with MCTD relies on interpolation of treatment guidelines for equivalent manifestations in SLE, SSc, RA and PM. In general, inflammatory manifestations such as arthritis, myositis, SLE-like skin disease and autoimmune-mediated anaemia and thrombocytopenia respond to immunosuppressive therapy. In contrast, other features such as Raynaud's phenomenon, acrosclerosis and most gastrointestinal manifestations are usually unresponsive to immunosuppression. Furthermore, treatment should be individualised for each patient, depending on the specific organs affected and the severity of the disease.

3.9.1 Treatment of the musculoskeletal manifestations of MCTD

All patients with MCTD with arthritis should have a radiographic evaluation of the hands and feet to screen for erosions. Arthralgias and mild non-erosive arthritis can be treated symptomatically with non-steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs, however, might increase the risk of aseptic meningitis in MCTD. In more severe cases of arthritis, or if arthritis persists despite NSAID treatment, a trial of low-dose glucocorticoids and/or hydroxychloroquine should be started. For refractory cases or erosive arthritis, methotrexate is the first choice. If methotrexate fails to induce remission or if it is contraindicated, other DMARDs such as leflunomide may be used (Ortega-Hernandez and Shoenfeld, 2012).

Experience with biological agents targeting tumour necrosis factor α (TNF α) is limited. Two case reports of the use of TNF α antagonists for refractory, polyarticular arthritis in MCTD have been published. Both papers reported beneficial effects on the joint symptoms. Both patients, however, developed a SLE-like syndrome with fever, generalised arthralgias and myalgias, malaise and anaemia. In addition, anti-dsDNA antibodies became detectable and transient hypocomplementaemia developed, which resolved after discontinuation of the TNF α antagonists. Thus, TNF α antagonists cannot be recommended for treatment of arthritis in MCTD.

Myalgias in the absence of myositis can be treated with NSAIDs. Patients with diffuse musculoskeletal complaints should be evaluated carefully for the presence of reactive depression or fibromyalgia. In the absence of myositis, glucocorticoids should be avoided. Myositis in MCTD is often acute and can be accompanied by high-grade fever and in this case, it may respond to treatment with glucocorticoid in doses of 0.5–1.0 mg/kg/day prednisolone equivalent (Nimelstein et al, 1980; Burdt et al, 1999). Azathioprine,

methotrexate or intravenous immunoglobulins are further options for escalating treatment in severe cases with persistently raised muscle enzymes (Ortega-Hernandez and Shoenfeld, 2012).

3.9.2 Treatment of the vascular manifestations of MCTD

The management of Raynaud's phenomenon and PAH in patients with MCTD is dealt with in the online in-depth discussions. Briefly, conservative approaches, such as avoiding cold exposure, maintaining high core body temperature, gloves, smoking cessation and exogenous vasoconstrictors such as caffeine and sympathomimetic drugs, are the mainstay for treatment of Raynaud's disease (Sinnathurai and Schirber, 2013). Calcium channel blockers are the first line of medical treatment. Other medical approaches are topical glyceryl trinitrate and infusion of prostaglandins, which is particularly useful in patients with digital ulcers and gangrene. Smaller studies reported good effects of the angiotensin receptor blocker losartan and the selective serotonin reuptake inhibitor fluoxetine, which might be alternative choices for treatment of refractory cases. Randomised controlled trials show prophylactic effects of the endothelin receptor antagonist bosentan in patients with multiple digital ulcers. Bosentan, however, neither accelerated the healing of digital ulcers nor could it completely prevent their development (Korn et al, 2004; Matucci-Cerinic et al, 2011). Digital sympathectomy treatment should be reserved as the last resort for patients with critical ischaemia.

Almost all the presented data and recommendations on pharmacological and non-pharmacological treatment of Raynaud's phenomenon and digital ulcers derive from studies of patients with SSc or primary Raynaud's phenomenon. There are virtually no studies on patients with MCTD. One case report suggests that microvascular alterations in patients with MCTD might regress upon autologous haematopoietic stem cell transplantation (Aschwanden et al, 2008). The severely pathological scleroderma-like pattern at baseline improved to almost normal at most fingers of this patient after stem cell transplantation.

The treatment of PAH is complex and should be adjusted to the functional WHO class. Patients should be managed at specialised centres. General measures include diuretics (in patients with oedema), continuous oxygen supply (in patients with hypoxaemia), digoxin (in patients with supraventricular tachycardias associated with right ventricular dysfunction) and adapted regular cardiopulmonary exercise. Although evidence may be good for idiopathic PAH, data that support these general measures (therapeutic anticoagulation) in PAH associated with MCTD and other connective tissue diseases are limited.

Like Raynaud's phenomenon, the treatment suggestions for MCTD-associated PAH are mainly based on studies with idiopathic PAH or PAH associated with other connective tissue diseases, mainly SSc. PAH-specific drugs include prostacyclins, PDE5 inhibitors or endothelin receptor antagonists. In idiopathic PAH, patients who have a positive vasoreactivity testing during right heart catheterisation may respond well to calcium channel blockers. Recommendations for the use of calcium channel blockers in patients with CTD-associated PAH are changing. Since it is negative in most patients with CTD-associated PAH, vasoreactivity testing will be no longer

recommended in this group of patients. In parallel, calcium channel blockers will no longer be routinely used in CTD-associated PAH.

A report on 28 patients with connective tissue disease-associated PAH, including eight patients with MCTD, suggested that some patients might respond to immunosuppressive therapy with cyclophosphamide and glucocorticoids. Three out of eight patients with MCTD and PAH responded to the treatment and had a significantly improved 6 min walking distance and an improvement in haemodynamic function after 1 year of immunosuppressive therapy (Sanchez et al, 2006). A similar response rate was also seen in patients with SLE, whereas none of the patients with SSc responded.

The same group reported recently the outcome of 23 patients with MCTD- and SLE-associated PAH treated with immunosuppressant agents alone or in combination with pulmonary vasodilators for 6 months (Jais et al, 2008). All patients were in New York heart Association (NYHA) class II or III and most patients had not received disease-modifying antirheumatic drugs (DMARDs) before. Twelve patients responded to the treatment with cyclophosphamide and prednisolone with improvements in NYHA class, 6 min walking distance and mean pulmonary arterial pressure. Most responders had NYHA class II disease and a cardiac index >3.1 at baseline, suggesting that patients, particularly those with milder disease, might benefit from immunosuppressive therapy.

In another case, IL-6 blockade with tocilizumab improved functional activity and haemodynamic parameters in a patient with a severe and refractory form of MCTD-associated PAH (Furuya et al, 2010). The efficacy of immunomodulatory drugs for the treatment of MCTD- and SLE-associated PAH, however, needs to be confirmed in randomised controlled trials, before recommending them for routine treatment of connective tissue-associated PAH.

3.9.3 Treatment of the gastrointestinal manifestations of MCTD

Treatment of gastrointestinal symptoms of MCTD is often difficult and follows the same principles as the treatment of gastrointestinal involvement in SSc. Gastro-oesophageal reflux disease should be treated with proton pump inhibitors. In contrast to SSc, patients with MCTD with severe oesophageal dysfunction might benefit from glucocorticoid treatment (Marshall et al, 1990). A longitudinal study showed that patients with MCTD receiving oral glucocorticoids at an average dose of 25 mg/day had a significant increase of the lower oesophageal sphincter pressure and a trend to an improvement in oesophageal body peristaltic pressures. Secondary complications such as dysphagia due to strictures or mucosal rings should no longer occur with the consequent use of proton pump inhibitors but, if present, might require the use of endoscopic dilatation. Screening for Barrett's oesophagus might be indicated in patients with severe and longstanding gastro-oesophageal reflux disease.

Constipation is common in patients with MCTD. These patients should be advised to increase their fibre ingestion and fluid intake and to exercise. In more severe cases with pseudo-obstruction or intestinal pneumatosis, hospitalisation and bowel rest might be required. Case reports in patients with SSc report positive effects of octreotide, but the clinical experience is less encouraging.

3.9.4 Treatment of the pulmonary manifestations of MCTD

Pulmonary disease is common in MCTD, but is often asymptomatic and does not require specific treatment. Symptomatic pleuritis can often be managed with NSAIDs alone. In more severe cases, oral glucocorticoids should be added in a dose of 0.5–1.0 mg/kg/day. DMARDs are rarely indicated for pleural disease. Active alveolitis might warrant aggressive treatment: this includes oral glucocorticoids in doses of 1 mg/kg/day or intravenous pulses of high-dose steroids in severe cases as well as cyclophosphamide. The efficacy of oral cyclophosphamide for the treatment of active alveolitis and interstitial lung disease in patients with SSc has been analysed in a multicentre, placebo-controlled trial (Tashkin et al, 2006). After 12 months of treatment with a maximum dose of 2 mg/kg of body weight per day, a modest, but significantly higher forced vital capacity (2.53) was seen in the cyclophosphamide group than in the placebo group. This difference was maintained through the follow-up period of 1 year after treatment. In contrast, the TLCO did not differ significantly between the groups.

3.9.5 Treatment of the mucocutaneous manifestations of MCTD

Patients with SLE-like skin manifestations should be instructed to avoid sun exposure and to use sunscreen lotions. If these conservative approaches are not sufficient, patients might benefit from topical steroids or hydroxychloroquine. Systemic glucocorticoids or DMARDs should be avoided, but might be needed for severe, refractory cases.

3.9.6 Treatment of the cardiac manifestations of MCTD

Pericarditis in patients with MCTD is usually mild and can be treated with NSAIDs. In persistent cases, patients benefit from a short trial of glucocorticoids in doses of 0.5–1.0 mg/kg. In the rare cases of large effusions with cardiac tamponade, percutaneous or even surgical drainage might be necessary.

Myocarditis is a potentially life-threatening manifestation, which requires more aggressive treatment. Milder cases can be treated with oral glucocorticoids in a dose of 1 mg/kg/day. Severe cases often require intravenous pulses of glucocorticoids for the first 3 days followed by oral glucocorticoids. Since myocarditis tends to relapse, remission maintenance with azathioprine, mycophenolate mofetil or cyclophosphamide is often needed. Treatment for heart failure might be needed in severe cases. Digoxin should be avoided in patients with MCTD and myocarditis because it predisposes to ventricular arrhythmias.

3.9.7 Treatment of the renal manifestations of MCTD

Although severe renal manifestations are rare, some patients with MCTD might present with raised serum creatinine or high-grade proteinuria. These patients undergo renal biopsy to clarify the underlying pathology and guide treatment. Membranous glomerulonephritis is the most common manifestation. Milder forms with low-grade proteinuria can often be treated with ACE inhibitors alone. In the case of overt nephrotic syndrome, glucocorticoids are indicated, sometimes in combination with mycophenolate mofetil or cyclophosphamide. Supportive treatment with aggressive blood pressure control and lowering of cholesterol levels plays an important role in the long-term outcome of renal disease.

Renal crisis, which has been described in few cases, is managed according to the guidelines for SSc. High-dose ACE inhibitors with aggressive control of the blood pressure are the mainstay of treatment and should be started immediately upon suspicion. Angiotensin receptor antagonists might also be beneficial.

3.9.8 Treatment of the neural manifestations of MCTD

Although rare, neurological manifestations of MCTD can be severe. No randomised clinical trials in MCTD are available and all evidence is provided by SLE trials or case reports (Ortega-Hernandez and Shoenfeld, 2012). Vascular headache is a common problem in patients with MCTD. These can be treated with NSAIDs, low-dose tricyclic antidepressants or selective serotonin reuptake inhibitors. Triptans should be used with caution, because they can induce vasospasms and aggravate Raynaud's phenomenon. NSAIDs themselves might also be the cause of headaches in patients with MCTD. The prolonged use of high doses of NSAIDs might result in analgesia-induced headaches.

NSAIDs can also trigger aseptic meningitis, and in this case, all NSAIDs should be discontinued. Aseptic meningitis often responds promptly to a short course of glucocorticoids. The incidence of trigeminal neuropathy is also significantly increased in MCTD. Trigeminal neuropathy, the most common neurological symptom, is less responsive to glucocorticoids or immunosuppressive agents (Hagen et al, 1990). Patients with chronic pain may benefit from analgesics, antidepressants or anticonvulsant drugs.

3.9.9 Treatment of the haematological manifestations of MCTD

Mild anaemia or leukopenia tends to correlate with disease activity in MCTD and improves usually without specific treatment when the overall disease activity declines. Anaemic patients should be analysed for iron deficiency and, if present, treated appropriately. In cases of severe immune-mediated anaemia or thrombocytopenia, steroids at high doses of 1 mg/kg/day may be effective. In refractory cases, intravenous immunoglobulins, danazol, rituximab or splenectomy might be considered, and evidence from case studies for the use of rituximab is accumulating. These studies highlight a potential effect in correcting haematological disorders and other manifestations of patients with MCTD; they also demonstrate, however, that serious

adverse events (eg, serum sickness) might occur when treating patients with MCTD, and highlight the urgent need for controlled trials (Fearnley et al, 1978; Haroon et al, 2007; Rudolph et al, 2009).

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SUMMARY POINTS

- Patients presenting with features of rheumatological diseases, who do not fulfil the criteria for a defined rheumatic disease, are diagnosed as having undifferentiated connective tissue disease (UCTD).
- In most patients with UCTD, no defined rheumatological disease will be diagnosed after several years of follow-up. For the remaining patients with UCTD, development of a defined rheumatological disease is more common than resolution of symptoms.
- Patients with overlap syndromes fulfil the criteria for two or more rheumatological diseases.
- Mixed connective tissue disease (MCTD) shares several features of systemic lupus erythematosus, systemic sclerosis, polymyositis and rheumatoid arthritis. Specific genetic, serological and clinical features, however, support the concept of MCTD as a separate clinical entity.
- Anti-U1-RNP antibodies directed against the U1-RNP complex of the spliceosome are the key biomarker for the diagnosis of MCTD.
- Four different classification criteria have been proposed for MCTD
- Characteristic, even not exclusive, clinical features of MCTD are Raynaud's phenomenon, puffy hands, the presence of severe arthritis, the high incidence of pulmonary arterial hypertension.
- Pulmonary arterial hypertension is the major cause of death in patients with MCTD.
- The prognosis of MCTD seems to be better than that of other defined connective tissue diseases such as systemic lupus erythematosus. The mortality of patients with MCTD, however, is significantly increased compared with age- and sex-matched controls.
- No clinical trials are available to guide the treatment of UCTD, overlap syndromes or MCTD. Treatment is based on experience with therapeutic approaches in other rheumatological diseases.

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Connective tissue diseases: Concepts and pathogenesis, overlap syndromes, mixed CTD and undifferentiated CTD

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IN-DEPTH DISCUSSION I

**Raynaud's syndrome and its treatment in patients with
UCTD and MCTD**

Raynaud's phenomenon (RP) is a well-defined clinical syndrome caused by a disorder of microvasculature and it is characterized by recurrent episodes of digital vasospasm triggered by exposure to physical/chemical or emotional stress. These episodes generally affect the fingers and toes, however also other extremities, as nose, ears and nipples may be involved [Prete M et al, 2014; Maverakis et al, 2014]. RP is often sub-classified in primary (with a relative benign course) and secondary, that is usually associated with an underlying disease, generally a connective tissue disease [Maverakis et al, 2014]. The majority of RP are primary forms that require only follow-up. In both cases, RP occurs after cold exposure or emotional stress. The onset of primary RP is often characterized by symmetric attacks involving both hands and patients do not present necrosis or tissue gangrene [LaRoy et al, 1992]. All patients should be assessed for the presence of associated symptoms/signs, to exclude the presence of an underlying connective tissue disease and to properly classify patient as having a primary or secondary form of RP. The most common symptoms/signs to investigate are: xerostomia, joint pain, photosensitivity, migraines, cutaneous sclerosis, telangiectasias, dysphagia, heartburn, and dyspnoea [LaRoy et al, 1992; Maverakis et al, 2014; Goundry et al, 2012]. Nailfold capillaroscopy and autoantibody profile play a central role in the assessment of patients with RP. Patients with primary RP have a normal capillaroscopy and a negative test for antinuclear antibodies [LaRoy et al, 1992].

In a recent study in RP patients, Trombetta C et al showed that capillary diameter on nailfold capillaroscopy is an independent predictor for development of SSc-associated RP while progression to secondary RP is unlikely when average capillary diameter is under 30 μm (Trombetta C, 2016).

Recently, Van Room AL et al. demonstrated that the degree of vasospasm and ischaemia provoked by stepwise cooling and recovery are positively associated with the severity capillaroscopic abnormalities in patients with primary and secondary RP (Van Room AL, 2016).

RP is a very common manifestation in UCTD and MCTD and can be associated with severe morbidity. Raynaud's syndrome occurs in about 50% of patients with UCTD and in more than 90 % of patients with MCTD. No clinical trials have specifically investigated the treatment of Raynaud's syndrome in patients with UCTD and MCTD. Therefore, the treatment principles for Raynaud's syndrome in UCTD and MCTD are based on guidelines from primary or secondary Raynaud's syndrome from other connective tissue diseases (e.g., SSc). The therapeutic options encompass supportive, alternative, pharmaceutical and surgical approaches.

Supportive therapies

Supportive therapies are the mainstay of the treatment of Raynaud's syndrome. Thus, patient education is extremely important. All patients should avoid cold exposure, which is not restricted to the extremities but includes the whole body [Gregory, 2013]. Patients should be encouraged to wear warm, isolating, or heatable gloves and shoes [Ko GD et al, 2002], but also cover their heads. Patients should stop cigarette smoking, in particular when they suffer from secondary Raynaud's syndrome and peripheral ischemia [Goodfield et al,

1990; Sinnathurai et al, 2013]. Avoiding emotional stress can also help to prevent Raynaud's attacks. Finally, patients with Raynaud's syndrome should avoid sympathomimetic drugs, which can stimulate vasoconstriction. If these conservative approaches are insufficient to reduce symptoms, more intensive therapies are needed.

Alternative therapies

Biofeedback and autogenic training might be beneficial in treating Raynaud's syndrome. Nevertheless, an evidence-based recommendation cannot be given for any of these approaches. A study on more than 300 patients did not demonstrate benefit of biofeedback on the frequency of Raynaud's attacks [Arch Intern Med. 2000; 160(8): 1101-8]. No clinical trials are available for autogenic training. Conflicting data exist regarding the efficacy of acupuncture. One study demonstrated a beneficial effect on primary Raynaud's phenomenon, which may be explained by increased release of sensory nerves and vasodilators such as substance P and calcitonin gene related peptide, whereas a small controlled study on patients with secondary Raynaud's syndrome did not demonstrate benefit [Appiah et al, 1997; Hahn et al, 2004; Gregory, 2013].

Drug therapies

Topical therapies

Topical therapies with isosorbide dinitrate and minoxidil did not improve symptoms in clinical studies. On the other hand, transdermal glyceryl trinitrate patches may reduce the number and the severity of RP [Sinnathurai et al, 2013]. However, side effects such as headaches are reported by up to 80% of patients. This side effect together with symptomatic hypotension reduce the usefulness of patches [The et al, 1995]. Topical glyceryl trinitrate improved peripheral blood flow and showed positive effects on the intensity and frequency of Raynaud's attacks in smaller studies [Anderson et al, 2002]. New formulations might be more effective and show less side effects (e.g., headaches, dizziness, skin irritation) [Chung et al, 2009]. Systemic nitrates should not be used because of the high incidence of side effects such as headaches.

Calcium channel blockers

Three different meta-analyses demonstrated a positive effect of calcium channel blockers for patients with primary and secondary Raynaud's syndrome [Thompson et al, 2005; Thompson et al, 2001, Ennis H, 2016]. This effect, however, was modest with a small reduction of frequency and severity of the attacks. The most recent Cochrane systematic review by Ennis H et al was focused on primary Raynaud's phenomenon; the randomised controlled trials included in this review provided moderate quality evidence that oral calcium channel blockers are minimally effective on frequency of the attacks and high-quality evidence that they have little effect on severity.

In addition, the individual response varied strongly between patients. Most evidence exists for nifedipine, which has been used in the large majority of studies. The efficiency of amlodipine and felodipine has also been demonstrated in single controlled trials [Kallenberg et al, 1991; La Civita et al, 1993; Schmidt et al, 1989]. In contrast, conflicting data exist for other calcium channel blockers such as diltiazem. It seems to produce a decrease in the severity and frequency of primary Raynaud's phenomenon but not in the secondary one. Unwanted side effects such as hypotension, dizziness, headache, peripheral oedema, and flush occur quite frequently. In addition, the reduction of the lower oesophageal sphincter tone might increase the incidence of gastro-oesophageal reflux disease. Thus, treatment should start with a low dose (e.g. nifedipine retard 10 mg) and increase further as tolerated by the patient.

Prostaglandin analogues: Iloprost

The synthetic prostacyclins analogue iloprost does not only induce vasodilatation, but also inhibits platelet aggregation and modulates the expression of adhesion molecules on endothelial cells. Intravenous iloprost significantly reduces the frequency of attacks and improves the healing of fingertip ulcers in SSc patients on the evidence level of a meta-analysis, while oral iloprost has no consistent effects [Pope et al, 2000]

The application schemes for i.v.-iloprost vary considerably between different studies. Doses between 0.5 – 2.0 ng/kg/min for 6 to 8 hours are commonly used. Application periods of 10 days every three month have been suggested to be particularly beneficial [Milio et al, 2006]. The published experience with iloprost in patients with primary Raynaud's syndrome or other connective tissue disease is limited. Common side effects include hypotension, headache, gastrointestinal problems and an increased bleeding risk in patients receiving platelet aggregation inhibitors or oral anticoagulants. Beneficial effects were also observed in smaller studies for alprostadil and misoprostol.

Angiotensin-II receptor type 1 antagonists (AT-1 antagonists)

A study on patients with primary and secondary Raynaud's phenomenon demonstrated that the AT-1 antagonist losartan has beneficial effects similar to that of nifedipine [Dziadzio et al, 1999]. The reduction of the frequencies of attacks was even better than for nifedipine. However, no significant differences were found between the two groups in laser Doppler-flow examination following cold challenge. The major side effect was dizziness. In general, the frequency of side effects was lower than with nifedipine.

Selective serotonin re-uptake inhibitors (SSRI)

The serotonin reuptake inhibitor fluoxetine at a dose of 20 mg/d was more effective in one study than nifedipine [Coleiro et al, 2001]. In this study, no statistically significant effect was observed for nifedipine. Side effects of fluoxetine were apathy and concentration deficits. The rate of side effects was lower than with nifedipine [Gregory, 2013]

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors interfere with the degradation of the vasodilative mediator cGMP. The phosphodiesterase 5 inhibitor sildenafil significantly reduced the frequency and duration of attacks at a dose of 50 mg twice daily in patients with secondary Raynaud's syndrome [Fries et al, 2005]. Vardenafil, another phosphodiesterase 5 inhibitor, had similar effects in an uncontrolled study [Caglayan et al, 2006]. Evidence for the long-acting PDE V-inhibitor tadalafil is conflicting; Tadalafil did not show efficacy in a randomized placebo-controlled trial with 39 SSc patients suffering from Raynaud's syndrome [Schiopu et al, 2009] by contrast, tadalafil as add-on therapy improved symptoms of Raynaud's syndrome, healed and prevented new digital ulcers, and improved quality of life in another double-blind randomized cross-over trial with SSc and MCTD patients [Shenoy et al, 2010]

In 2014, Lee EY et al published the results of a double-blind, randomized, cross-over study comparing the efficacy on secondary Raynaud's phenomenon of a new phosphodiesterase type 5 inhibitor udenafil with amlodipine. Amlodipine and udenafil similarly decreased the rate of the attacks significantly. In addition, udenafil was more effective in improving the blood flow in digital arteries compared with amlodipine (Lee EY, 2014)

The endothelin receptor antagonist

The non-selective endothelin receptor antagonist bosentan, also used in treatment of pulmonary arterial hypertension, has an emerging role in the treatment of Raynaud's phenomenon and digital ulcers. In SSc case reports, patients treated with this drug for PAH reported to have an improvement of Raynaud's phenomenon and digital ulcers [Sinnathurai et al, 2013; Arefievk et al, 2011]. Bosentan prevents the development of fingertip ulcers in patients with SSc as shown in two randomized, controlled trials (RAPIDs-1 and 2). Bosentan, however, did not improve the healing process of digital ulcers. It was effective in reducing the relapse of multiple (≥ 3 DUs) – but not single- ulcers [Korn et al, 2004; Matucci-Cerinic et al, 2011]. There are no proven effects on primary or secondary Raynaud's phenomenon.

Recently, Bellando-Randone S et al reported in a small cohort of patients with Raynaud's phenomenon secondary to SSc a significant improvement of the Raynaud Condition Score and nailfold capillaroscopy pattern after 6 months of combination therapy with bosentan and sildenafil (Bellando-Randone S, 2016)

Other drug treatments

The alpha receptor blocker prazosin had modest efficiency in two controlled studies, but its clinical use is limited due to sometimes severe and frequent orthostatic hypotension [Pope et al, 2000]. The data for ACE inhibitors are inconsistent. The selective serotonin receptor antagonist ketanserin reduced only mildly the duration of attacks, but demonstrated otherwise no significant benefits.

Since statins can slow down the progression of vascular injury in cardiovascular disease, their effects on SSc-related Raynaud's phenomenon and DUs have been addressed by two recent randomized controlled trials; while atorvastatin at a dose of 40 mg/d for four months improved Raynaud's phenomenon and reduced the number DUs in an Egyptian study [Abou-Raya et al, 2008], a European study did not find any significant differences between atorvastatin at a dose of 20 mg/d for two months and placebo [Sadik et al, 2010]. Apart from treatment dose and duration, disease duration and severity of vascular injury might account for these different results. Given the good tolerability and the relatively low costs for statins, however, future studies should identify patients with CTD-associated Raynaud's phenomenon and DUs who might benefit from a statin therapy.

Medications to improve rheological properties have also been tested in patients with Raynaud's syndrome. No effect has been observed for low-dose acetylsalicylic acid. Mild effects have been suggested by single studies for low-molecular heparin and ginkgo-biloba preparations. Two studies analysed the effects of pentoxifylline in patients with primary Raynaud's syndrome. Pentoxifylline did not reduce the frequency and duration of the attacks in one study, but was suggested to improve peripheral hemodynamic in a small controlled trial.

Surgical therapies

Surgical approaches are proximal cervical and localized digital sympathectomy. A persisting beneficial effect was observed in only a minority of patients in a retrospective study for proximal cervical sympathectomy. A smaller study demonstrated an improved microvascular perfusion in 22 SSc patients treated with localized digital sympathectomy. The long-term outcome of this therapy, however, remains unknown [De Trafford et al, 1988; Ruch et al, 2002]. More recently, digital periarterial sympathectomy demonstrated to be a simple and relatively nonaggressive technique without adverse side effects and with excellent medium-term results in a large series of patients with post-traumatic Raynaud syndrome (Letamendia A, 2016).

Thus, surgical approaches should be restricted to treatment-resistant, acute critical ischemia and should be performed at experienced centres.

Other therapies

Botulinum toxin A has been proposed for the treatment of Raynaud's phenomenon because of their ability to modulate sympathetic nerve conduction and thus reduce vasoconstriction; however, a recent systematic review concluded that despite many promising reports, there is insufficient evidence to assess the efficacy of botulinum toxin A in Raynaud's phenomenon and further research is warranted before recommending this therapy in clinical practice.

Summary

There are no evidence-based therapies for Raynaud's syndrome in patients with UCTD or MCTD due to the lack of specific studies with these patient populations. Considering the evidence for primary and secondary Raynaud's phenomenon (the latter one in patients with SSc), the following conclusions can be drawn: Two of the mentioned therapeutic approaches, nifedipine and intravenous iloprost, can be recommended with evidence grade I a (evidence based on the meta-analysis of randomized controlled studies). The evidence for intravenous iloprost is mainly based on studies with secondary Raynaud's syndrome. Grade I b evidence (evidence based on at least one randomized controlled study) exists for amlodipine, felodipine, losartan, fluoxetine and sildenafil. For all other approaches, the evidence is lower, because (i) randomized, controlled trials demonstrated conflicting results, (ii) positive effects have only base on case reports or uncontrolled studies or (iii) the effects were small and only involved certain aspects (e.g. the frequency of attacks, but not hemodynamic and intensity of attacks).

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Connective tissue diseases: Concepts and pathogenesis, overlap syndromes, mixed CTD and undifferentiated CTD

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IN-DEPTH DISCUSSION II

Diagnosis of pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) occurs as a severe manifestation of several connective tissue diseases such as systemic sclerosis (SSc) mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), overlap syndromes and undifferentiated connective tissue diseases [Shahane, 2013].

In the most recent literature, the highest rates of PAH are reported in MCTD (2–24%) followed by systemic lupus erythematosus (SLE) (up to 17.5%), and systemic sclerosis (SSc) (nearly 10%) [Gunnarsson et al, 2013; Wigley FM et al, 2005; Pèrrez-Penate GM et al, 2016; Avouac J et al, 2010]. PAH is more rarely observed in inflammatory myopathies and Sjögren syndrome.

Estimates of its prevalence among different cohorts are variable; this wide prevalence is explained by the patient's selection criteria, the lack of a standard definition for PAH, and the different PH diagnostic approaches [Doppler echocardiography or right heart catheterization]. Echocardiography, indeed, tends to overestimate pulmonary artery pressures and can have a high rate of false-positive results. Thus, the real prevalence might be somewhat lower than reported in some studies using estimated right ventricular systolic pressure on echocardiography as the only diagnostic method.

Moreover, challenges of PAH management include clinically undetected CTDs at the time of PAH clinical presentation and diagnosis; this is a crucial point as CTD-associated PAH has a poorer prognosis and worse cardiac dysfunction compared with idiopathic PAH. In a recent study, Cavagna L et al showed a high prevalence (17/49 pts) of undiagnosed CTDs in patients with iPAH without a previous rheumatological assessment (Cavagna L, 2016).

Regardless of the challenges in determining its prevalence, PAH is a major cause of morbidity and mortality in connective tissue diseases. Three-year survival rates in idiopathic PAH are as low as 48% after diagnosis – even after exclusion of risk factors and associated diseases. Survival is worse for those with respiratory disease-associated SSc-PAH (3-year survival, 28%), whereas survival among patients with exercise-induced SSc-PAH is superior (3-yr survival, 86%) [Condiffe et al, 2009].

PAH is the most serious complication and the major cause of death in patients with MCTD [Shahane, 2013. Tani et al, 2014]. A recent study showed that in patients with CTD-PH, the 3-year survival rate was 87% [Kang et al, 2015]. In the longitudinal study of patients with MCTD mentioned above, 9/11 deaths were due to PAH. These poor outcomes highlight the need for careful follow-up and early diagnosis because therapies are available to treat patients with PAH associated with connective tissue diseases. In addition to therapies for idiopathic PAH and PAH associated with SSc, PAH associated with MCTD might respond to immunosuppressive therapy with intravenous cyclophosphamide and systemic glucocorticosteroids, which appears to prolong survival in these patients [Legendre et al, 2014].

Clinical symptoms

Clinical symptoms of PAH are diverse and unspecific. The cardinal sign is dyspnoea on exertion, but many patients do not mention these symptoms during past medical history. Therefore, it is important to ask specific, individual questions (e.g. “Are you short of breath when climbing the stairs to your flat” instead of “Do you experience shortness of breath on exertion”). Other symptoms that should alert the clinical suspicion of PAH include fatigue, weakness, angina, and syncope/pre-syncope and pleuritic chest pain [Ortega-Hernandez et al, 2012. Hajas et al, 2013]. Physical signs such as left parasternal lift, accentuated pulmonary component of S2, pan systolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency and right ventricular S3 are indicative but require considerable experience to be detected [Galié et al, 2004]. Other findings on physical examination include jugular vein distension, hepatomegaly, peripheral oedema, and ascites. Notably, these symptoms are late manifestations of the disease. Hemodynamic as well as morphological changes in the pulmonary vasculature occur long before these clinical findings are detectable [Distler et al, 2006].

Diagnostic screening tests

Unspecific and late clinical signs and symptoms raise a need for diagnostic screening tools in patients at risk of PAH. The best characterized and most often used screening test is transthoracic Doppler-echocardiography (TTE). Regular TTE screening, as recommended for patients with SSc, might also be useful in patients with MCTD because of the high prevalence of PAH [Galié et al, 2009]. For patients with SSc, regular TTE screening protocols can both detect PAH in milder stages and improve survival of SSc-PAH patients [Humbert et al, 2011].

TTE is a non-invasive, readily available and feasible diagnostic test. Nevertheless, there are limitations: first, TTE is strongly dependent on the experience of the examiner. Second, TTE is imprecise in patients with borderline or mild pulmonary hypertension, both under- as well as overestimating the right ventricular systolic pressure (RSVP, equivalent to the pulmonary artery systolic pressure in the absence of pulmonary outflow obstruction). This can lead to both false negative and positive results in the screening process [McQuillan et al, 2001].

According to the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension [Galiè N, 2016] the echocardiographic probability of pulmonary hypertension in symptomatic patients is strictly related to the tricuspid regurgitation velocity measurement and other echocardiographic signs (see tables 1 and 2)

Table 1: Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension (adapted from Galiè N et al, 2016)

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs' ^a	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

Table 2: Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of pulmonary hypertension in addition to tricuspid regurgitation velocity measurement (adapted from Galiè N et al, 2016)

A: The ventricles ^a	B: Pulmonary artery ^a	C: Inferior vena cava and right atrium ^a
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm ²
	PA diameter >25 mm.	

a: Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.

Additional tests such as 6-minutes-walk-test and circulating brain natriuretic peptide (BNP) levels might increase the specificity of PAH screening in patients with MCTD and other connective tissue diseases [Ortega-Hernandez et al, 2012; Distler et al, 2006]. A significant decrease in DLCO without concomitant changes of restrictive parameters is the strongest risk factor for the later development of PAH in patients with SSc [Steen et al, 2003]. Whether the same holds true for patients with MCTD, however, is unknown. The 6-minute walk

distance is established and, at least in part, validated to assess the severity in patients with PAH. It is also used for follow-up to assess treatment response. [Avouac et al, 2010]. However, in what extent the musculoskeletal manifestations of connective tissue diseases can interfere with the validity of this outcome measure has still to be established. Recently, 6MW stress echocardiography has been evaluated in a prospective 5-years cohort of patients with CTD-associated PAH; the authors demonstrated that this test can provide an incremental prognostic value of PH development in CTD. (Kusunose K et al, 2015)

Finally, rising, rather than elevated, NT-pro BNP levels may indicate increased right ventricular load in early stages of PAH but are not specific for pulmonary hypertension.

New recommendations for screening and detection of CTDs associated PAH, concerning in particular SSc and CTDs with scleroderma features, have been published by Khanna et al. According to these recommendations, patients should be evaluated with PFT (including DLCO), transthoracic echocardiography and NT-proBNP initially and at least once annually thereafter. If patients complain new signs or symptoms, the complete screening needs to be repeated [Khanna et al, 2013]. The DETECT algorithm, generated to guide RHC in SSc patients with increased risk of PAH, has not been validated in MCTD. See Table 3 for Recommendations for screening and early detection of CTD-PAH [Khanna et al, 2013].

Right heart catheterization

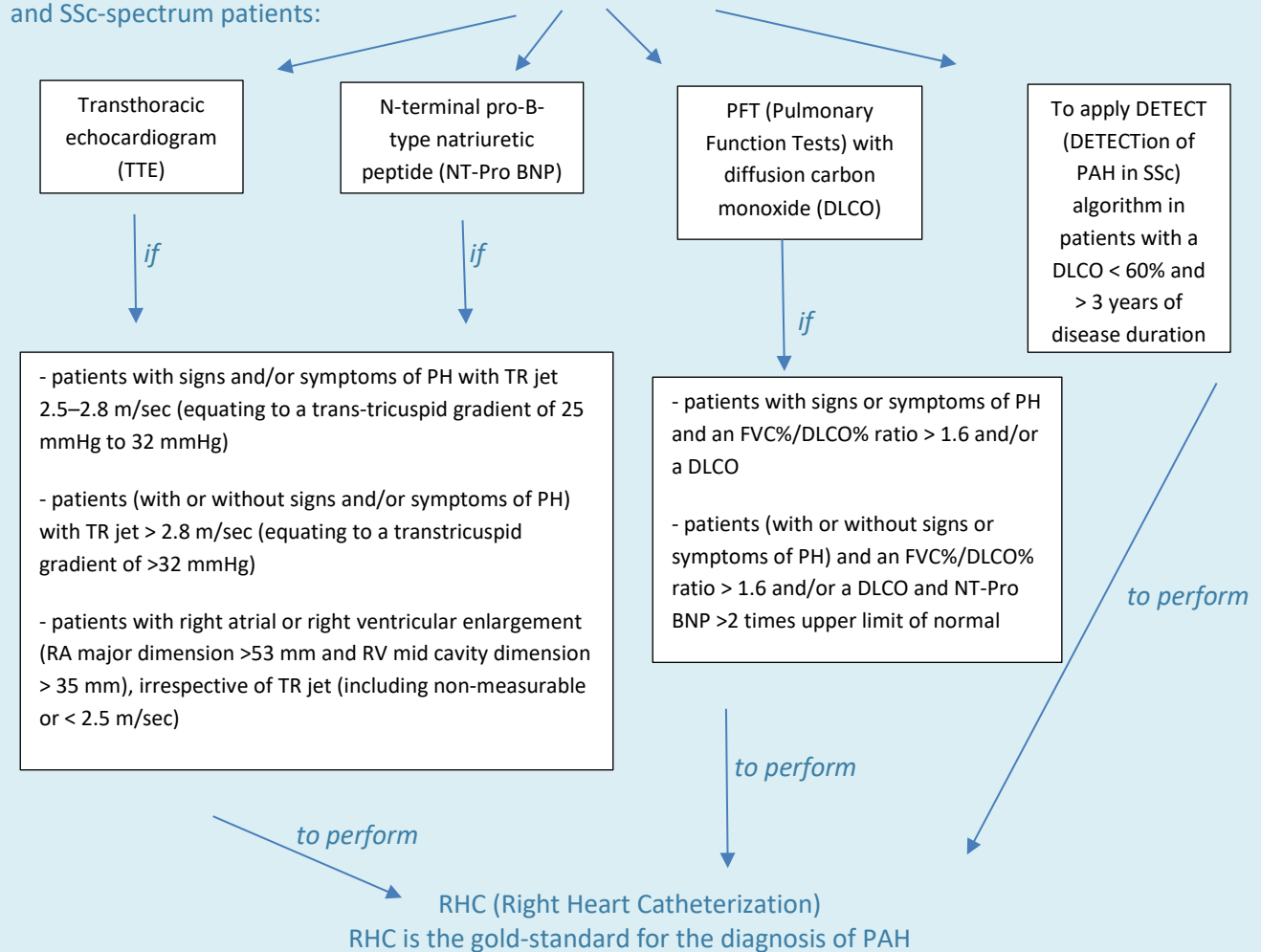
Once the diagnostic screening tests suggest PAH, the diagnosis must be confirmed by direct measurement of the pulmonary haemodynamics by right heart catheterization. Right heart catheterization is the gold-standard for the diagnosis of PAH. The hemodynamic parameters that characterize PAH include a pulmonary arterial pressure ≥ 25 mmHg and a normal pulmonary capillary wedge pressure of ≤ 15 mmHg on right heart catheterization [Simmonneau et al, 2009].

Vasoreactivity, as shown by a decrease of the pulmonary arterial pressure upon challenge with inhaled NO in patients with PAH during right heart catheterization, is rare in patients with connective tissue diseases, including MCTD. Thus, upcoming guidelines may no longer recommend vasoreactivity testing in patients with CTD-associated PAH in routine clinical practice. Finally, it is important to exclude other causes of pulmonary hypertension, such as interstitial lung disease (e.g., by high resolution CT) and chronic thromboembolic disease (e.g. by ventilation and perfusion lung scan). Chronic thromboembolic disease might be particularly relevant for patients with MCTD considering the increased prevalence of anti-phospholipid-antibodies. On the other hand, the presence of anti-phospholipid-antibodies does not appear to correlate with thrombotic events in patients with MCTD [Komatireddy et al, 1997; Hoeper et al, 2013].

Table 3 Recommendations for screening and early detection of CTD-PAH, adapted from Khanna et al, 2013.

Patients with MCTD or other CTD with scleroderma features should be evaluated and screened for PAH similar to patients with SSc.

Blood and instrumental examinations to perform annually or at the onset of any new signs/symptoms in SSc and SSc-spectrum patients:



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Systemic lupus erythematosus: pathogenesis and clinical features

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LEARNING OBJECTIVES

- ➔ Use epidemiology and evidence about the disease course to support clinical decisions
- ➔ Understand the key events in the pathogenesis of systemic lupus erythematosus (SLE)
- ➔ Describe and explain the clinical manifestations of SLE in the mucocutaneous, musculoskeletal, renal, respiratory, nervous, cardiovascular, pulmonary, haematological, gastrointestinal and eye domains
- ➔ Make a diagnosis of SLE based on history, physical examination, and interpretation of serological and laboratorial results
- ➔ Critically evaluate the classification criteria, their uses and limitations
- ➔ Assess patients according to the activity and damage indices as part of a decision-making process
- ➔ Recognize the specificities in the assessment of different clusters of patients (children, childbearing women, elderly)
- ➔ Monitor aspects related to the chronicity of SLE as damage, comorbidities and their impact on patient quality of life

1 Introduction

1.1 Definition

Systemic lupus erythematosus (SLE) is the prototypic multisystem autoimmune disease with a broad spectrum of clinical presentations encompassing almost all organs and a chronic course, which can vary from mild to life-threatening.

1.2 Major milestones in the history of lupus

The term 'lupus' was first used during the Middle-Ages to describe erosive skin lesions evocative of a 'wolf's bite'. In 1846 the Viennese physician Ferdinand von Hebra (1816–1880) introduced the butterfly metaphor to introduce the malar rash. He also used the term 'lupus erythematosus' and published the first illustrations in his Atlas of Skin Diseases in 1856. Lupus was first recognised by Moriz Kaposi (1837–1902) as a systemic disease with visceral manifestations. The systemic form was further established by Osler in Baltimore and by Jadassohn in Vienna.

2 Epidemiology

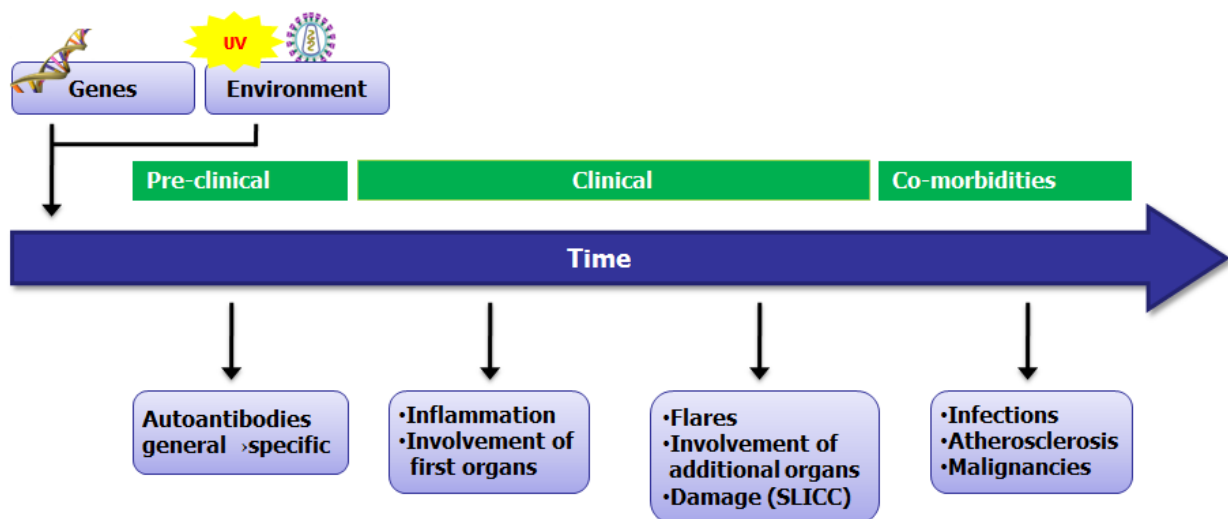
Estimated incidence rates of SLE in North America, South America and Europe range from 1 to 23 per 100 000 per year (Pons-Estel et al, 2010; Somers et al, 2014). Prevalence in adults is as high as 150 per 100 000 people in the USA. Age, gender, geographical differences and ethnicity are risk factors for SLE and influences clinical presentation and patient outcomes (Duarte et al, 2011*; Lewis et al, 2016). In Europe, prevalence ranges from 20 to 97 per 100 000 (Alonso et al, 2011; Bertsias et al, 2013; Arnaud et al, 2014 ; Rees et al, 2016a). Women are affected up to twelve times more frequently than men; African-American and Hispanics are affected much more often than Caucasians, and have higher disease morbidity (Rivest et al, 2000; González et al, 2014; Ugarte-Gil et al, 2016). In USA, the average incidence and prevalence rates of childhood SLE is 2.2 and 9.7 cases per 100 000 per year, respectively, with nearly 40% having renal involvement (Hiraki et al, 2012). Disease onset is between the ages of 16 and 55 in 65% of patients, 20% present before age of 16 and 15% after the age of 55. Men with lupus tend to have less photosensitivity, more serositis and nephritis, an older age at diagnosis and a higher mortality rate than women (Gonçalves et al, 2015; Riveros Frutos 2016). SLE tends to be milder in the elderly with lower frequency of renal and central nervous system (CNS) involvement (Mina and Brunner, 2013).

2.1 Natural history and disease course

SLE is a chronic disease and has a waxing and waning course with significant morbidity (figure 1). The disease starts with a preclinical phase characterised by nonspecific autoimmune abnormalities and proceeds to a more disease-specific autoimmunity phase (Bertsias et al, 2010b). Likewise, the clinically overt disease may start with single manifestations that are nonspecific, such as Raynaud's phenomenon, arthritis or autoimmune

thrombocytopenia. It may take years for patients to develop enough clinical and immunological disturbances leading to SLE diagnosis, although some patients present from inception with a full-blown disease. For these reasons, time of disease onset is often uncertain and diagnosis may be delayed. Flares of disease activity are mostly unpredictable in time and can include a varying combination of old and new manifestations early in the disease course. With time, clinical presentation may result not only from lupus flares, but also from damage accrual related to disease, treatment (namely glucocorticoids and immunosuppressives) and comorbidities, such as infections, chronic kidney disease, osteonecrosis, osteoporotic fractures, cataracts, Jaccoud's arthropathy, atherosclerosis, and malignancy. Current survival rates of SLE patients at 10 years after diagnosis in Europe are 90% or higher, but life expectancy is still lower than in the general population (Rees et al, 2016b). Predictors of mortality include high disease activity, damage accrual and low socioeconomic status. Infections, cardiovascular disease, malignancy and disease activity are major causes of death (Cervera et al, 2003; Doria et al, 2006; Duarte et al, 2011*; Lopez et al, 2012; Bruce et al, 2015*).

Figure 1 Natural history of systemic lupus erythematosus.



SLICC, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. (Reproduced from Bertsias et al, 2010b)

2.2 Aetiology

The aetiology of SLE includes genetic, hormonal and environmental components. These factors lead to an irreversible breakdown of immunological tolerance manifested by aberrant immune responses against endogenous nuclear and other self-antigens (Tsokos et al, 2011).

2.2.1 Genetic factors

Siblings of patients with SLE are 30 times more likely to develop SLE than people without an affected sibling. Large genome-wide association studies have confirmed the importance of genes associated with immune response and inflammation, DNA repair, adherence of inflammatory cells to the endothelium and tissue

response to injury (Guerra and Vyse, 2012; Bentham et al, 2015). They also highlight the importance of transcription factors acting as upstream regulators, Toll-like receptors and type 1 interferon (IFN) signalling pathways. Some of the genetic loci may explain the susceptibility to disease and also its severity (Taylor et al, 2008; Rullo and Tsao, 2013). The genetic risk for SLE may be influenced by epigenetic effects, such as DNA methylation and post-translational histone modifications, which can be either genetically determined or environmentally induced (Patel and Richardson, 2013). The most well understood type of epigenetic factor is DNA methylation, which plays a role in a variety of human processes. Differences in the methylation status of genes may explain, at least in part, the discordance for SLE in 3 out of 4 pairs of identical twins (Javierre et al, 2010).

2.2.2 Environmental factors

Candidate triggers of SLE include ultraviolet light, drugs, smoking, cosmetic products, occupational exposures and infectious or endogenous viruses or viral-like elements (Cooper et al, 2010; Duarte et al, 2011*; Zandman-Goddard et al, 2012). Sunlight and ultraviolet radiation exposure, namely to UV-B, is a widely recognized risk factor for SLE onset. Certain drugs can induce autoantibodies, some of whom develop signs of autoantibody-associated disease (Bukhari 2012). Over 100 drugs have been reported to cause drug-induced lupus, the most common being tetracyclines. A genetic predisposition may play a role, particularly in the case of agents that are metabolised by acetylation such as procainamide and hydralazine, with the disease being more likely to develop in slow acetylators (Reidenberg et al, 1993). Anti-TNF-alpha drugs were also reported to induce lupus, usually self-limiting after stopping therapy (Williams et al, 2009). From potential viral triggers, there is better evidence for an association with Epstein-Barr virus infection (Parks et al, 2005). Current smoking was associated in a meta-analysis with an increased risk of SLE (Costenbader et al, 2004). There is evidence for an increased risk with silica exposure. Available studies found no association with alcohol, hair dyes, or silicone-containing implants.

2.2.3 Hormonal factors

The marked predominance of women with SLE, its highest incidence and prevalence found in women of childbearing age, and the equal prevalence in men compared to women before puberty and after menopause suggests an important role of endogenous oestrogens and androgens in SLE aetiology (Duarte et al, 2011*). In murine models, experimental data support a role of oestrogens in lupus development, while androgens delay lupus onset and are associated with a milder disease. There is conflicting data from observational studies on a potential effect of oral contraceptives and hormonal replacement therapy in risk of developing SLE. No association was found between pregnancies and risk of developing SLE in two case-control studies (Bengtsson et al, 2002; Cooper et al, 2002).

3 Pathogenesis

3.1 Key systemic events

The pathogenesis of SLE involves the interplay of susceptibility genes, environmental risk factors, immune cells and molecules that participate in apoptosis, innate and adaptive immune responses (Tsokos et al, 2016*). In genetically predisposed individuals, environmental factors act as triggers of loss of tolerance to self-antigens, eliciting autoimmunity. Downstream elements that drive a self-sustained loss of tolerance, spreading and maintenance of autoimmunity are still poorly understood. Pathogenic processes are heterogeneous across different disease features, patients, populations and ethnic groups. An overview of key events in immunopathogenesis of SLE is presented in figure 2.

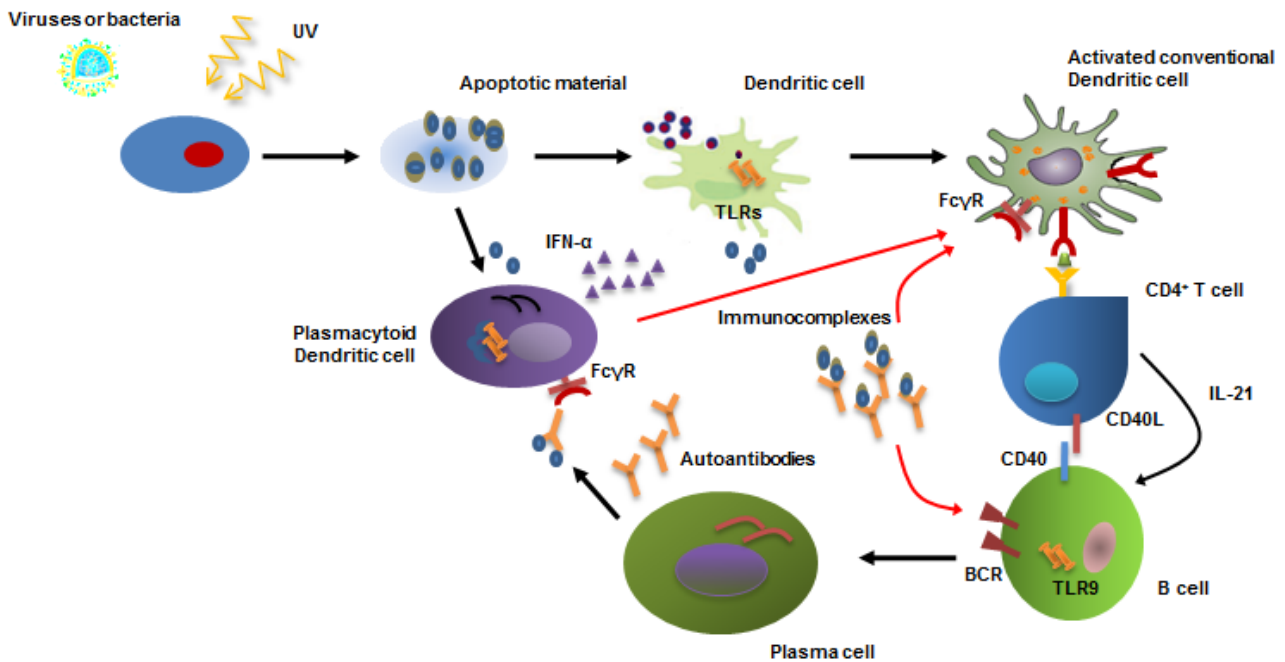
Over 40 genetic loci identified through genome-wide association studies (GWAS) are confirmed to be associated with SLE (Cui et al, 2013). Many of these genetic factors also confer susceptibility to other autoimmune diseases. Susceptibility to SLE conferred by each gene is limited, generally with a relative risk less than 2. A number of rare monogenic disorders are also implicated in SLE and lupus-like disease (Belot et al, 2012). The susceptibility genes are connected with three major immune pathways: (1) apoptotic waste clearance; (2) nucleic acid innate sensing by Toll-like receptors (TLR) and downstream interferon (IFN) signalling pathways; (3) lymphocyte signalling within T or B cells. Epigenetic mechanisms are potentially implicated in SLE susceptibility and disease activity: these include processes such as DNA methylation, post-translational histone modifications, and noncoding RNAs that can durably modify gene expression. DNA hypomethylation typically causes overexpression of genes and was found globally increased in T cells from patients with active SLE and specifically in IFN-stimulated genes (Tsokos et al, 2016*).

A key concept in the pathogenesis of SLE is an imbalance between production of apoptotic waste and its disposal: when the burden of apoptotic cells exceeds clearance rate, the accumulated apoptotic debris can illicit abnormal immune responses (Casciola-Rosen et al, 1994). Increased apoptotic cell load can be generated by exposure to ultraviolet light, infections and other environmental risk factors for SLE. Abnormal apoptotic pathways contribute to failure of the mechanisms that usually prevent immune activation in response to endogenous cellular debris. Neutrophils are key inflammatory participants that extrude nuclear material, forming neutrophil extracellular traps (NETs), a source of yet more nucleic acid antigens in SLE (Dieker et al, 2016). Nucleic acids (DNA, RNA) contained in apoptotic debris can stimulate an inflammatory response through activation of nucleic-acid recognition receptors, such as Toll-like receptors (TLR), which are constituents of the innate immune system (Tsokos et al, 2016*). The TLRs are expressed in immune cells, including dendritic cells (DC), B and T cells, and macrophages, as well as nonimmune cells (epithelial cells, fibroblasts). TLRs reside in the endoplasmic reticulum, with TLR3, TLR7 and TLR8 recognizing RNA, while TLR9 senses DNA. Experimental data support more strongly a role for TLR7 and TLR9 in SLE susceptibility, with more

limited evidence implicating TLR3 and TLR8 (Wu et al, 2015). Current models of SLE pathogenesis postulate a central role for TLRs in which they engage self-nucleic acids, drive loss of tolerance and induce a strong type I interferon (IFN) production (Tsokos et al, 2016*).

The plasmacytoid DCs (pDC) are immune cells that produce the highest levels of type I IFN after activation by TLRs. Hydroxychloroquine, a cornerstone of SLE treatment reduces TLR7/9 activation and Type I IFN production by pDC (Sacre et al, 2012). Type I IFN and other cytokines promote B-cell differentiation and loss of tolerance. B-cell activating factor (BAFF or BLyS) is upregulated by type I IFN and is an important driver of B-cell activation, survival and autoantibody production in SLE (Liu et al, 2011). BAFF is the target of belimumab, a drug approved for SLE treatment. Once activated, B cells mature, expand and secrete antibodies, which enhance the adaptive immune response. Type I IFN also induces differentiation of conventional myeloid DC (mDC) and auto-antigen presentation by mDCs to CD4-positive T cells in SLE (Blanco et al, 2001). Thus, both pDCs and mDC are thought to be pivotal to the disease process in SLE (Tsokos et al, 2016*).

T-cell and B-cell abnormalities are considered central to SLE pathogenesis and include: loss of T-cell tolerance; aberrant T-cell to B-cell interactions leading to stimulation of autoreactive B cells; differentiation and expansion of pro-inflammatory interleukin-17 (IL-17) producing T-cells; defective or deficient regulatory T-cells (T_{reg}), that represent an important checkpoint against autoreactive lymphocytes; aberrant development of B-cells, leading to a break in B-cell tolerance and increased survival of autoreactive clones (Dörner et al, 2016; Tsokos et al, 2016*). B-cells contribute to SLE through their response to autoantigens, with production of the autoantibodies that constitute a hallmark of the disease, as well as by autoantibody- independent mechanisms. Autoantibodies bind to self-antigens, forming immune complexes that activate complement, and through binding Fc receptors, drive inflammation at target tissues, such as the skin and kidney. Other roles of B-cells in SLE include their ability to present autoantigenic peptides to T cells, drive innate responses mediated by the expression of TLRs, and production of an array of proinflammatory and regulatory cytokines (Dörner et al, 2016). Co-stimulatory cell receptors and ligands, such as CD40-CD40L or ICOS-ICOS ligand are important determinants of B-cell-T-cell interactions that may be implicated in SLE (Dörner et al, 2016).

Figure 2 Overview of key events in immunopathogenesis of SLE.

BCR, B cell receptor, FcγR, Fcγ receptor, TLR, Toll-like receptor. (Reproduced from Bertias et al, 2010b)

3.2 Organ-specific disease mechanisms and tissue damage

In SLE patients, potentially predisposing genetic loci for lupus nephritis (LN) and for central nervous system (CNS) involvement were identified (Chung et al, 2014; Ho et al, 2016a). The pathogenesis underlying different lupus disease activity and organ damage features is varied.

Anti-dsDNA antibodies are considered central to the pathogenesis of LN and integrate immune complexes that deposit in the kidney. Glomerular immune complexes mostly form *in situ* by binding of autoantibodies to nucleosomes from renal cells. Potential intrarenal sources of nucleosomes include neutrophils releasing NETs. Anti-dsDNA and immune complexes activate endothelial and mesangial cells and the complement system, driving inflammation through a variety of mechanisms. Cytotoxic T cells, Th17 cells as well as B cells and macrophages infiltrate the kidney in LN. A large number of mediators, including cytokines, chemokines and adhesion molecules, expressed by infiltrating and activated renal cells amplify the inflammatory process and collude to inflict progressive damage (Lech et al, 2013).

Exposure to ultraviolet light (UV) is a major trigger to development of lupus skin lesions. UV causes apoptosis of keratinocytes, and there is an accumulation of apoptotic keratinocytes in the epidermis of patients with lupus skin lesions (Deng et al, 2015). This may precipitate the immunopathogenic events leading to inflammatory skin lesions in SLE patients and, hypothetically, to systemic flares. Deposits of immune complexes, immunoglobulins and complement can be found along the dermoepidermal junction in sun-exposed non-lesional skin specimens of most SLE patients (the 'Lupus band').

A dysfunction of the blood-brain barrier may play a pivotal role in the pathogenesis of CNS lupus, allowing autoantibodies, soluble mediators and immune cells to abnormally reach the brain tissue. Autoantibodies may have a direct pathogenic role in CNS lupus, which is best established for antiphospholipid antibodies, but others, including anti-ribosomal P and anti-neuronal antibodies may also be implicated (Ho et al, 2016b). Many of the CNS lupus manifestations can be the end result of different pathogenic insults. Neuropsychiatric lupus is a highly heterogeneous group of clinical syndromes and may result from a wide variety of pathogenic mechanisms that is poorly understood.

4 Clinical features

4.1 Mucocutaneous features

Mucocutaneous involvement is one of the commonest clinical manifestations in SLE patients. These includes both lupus-specific and non-specific lesions (table 1) (Kuhn et al, 2014*; Okon et al, 2013).

4.1.1 Acute lupus-specific mucocutaneous lesions

The classic lupus ‘butterfly’ or malar rash presents acutely as a fixed, confluent, sharply outlined erythema, flat (macular) or raised (maculopapular) lesion, located at the malar eminences and over the nose, tending to spare the nasolabial folds. It can be pruritic, especially the papular lesions. It may evolve with fine scaling, erosions and crusts (figure 2A). Typically, acute cutaneous lupus erythematosus (ACLE) resolve over the course of days or weeks, without scarring. Malar rash was reported in 20-60% of large SLE cohorts (Cervera et al, 2003; Inês et al, 2015*). Differential diagnosis can be challenging and includes sunburn, polymorphous light eruption, facial flushing, telangiectasias, acne rosacea, seborrheic dermatitis, atopic and contact dermatitis, and glucocorticoid-induced dermal atrophy (Okon et al, 2014). Besides malar rash, ACLE lesions may present localized on the dorsa of the fingers and hands with periungual erythema but typically sparing the knuckles. Patients may also develop a more generalized maculopapular lupus rash (figure 2B).

Both localized and generalized ACLE are commonly, but not always, precipitated by exposure to sunlight or other sources of UV radiation, and in that case involve exposed skin areas. For SLE classification purposes, the ACR revised classification criteria for SLE (1997) defines the photosensitivity criterion as a skin rash resulting from unusual reaction to sunlight (by patient history or physician observation). In lupus patients without previous history of photosensitivity, risk associated with sunlight exposure is difficult to predict, even with photo testing procedures (Kuhn et al, 2010). The SLICC classification criteria for SLE (2012) redefined photosensitivity as an (acute) ‘photosensitive lupus rash’ and extended the scope of ACLE features for classification purposes, to include (acute) ‘maculopapular lupus rash’ (figure 2) and the rare manifestations ‘toxic epidermal necrolysis variant of SLE’ and ‘bullous lupus’. It also newly included the subacute cutaneous lupus lesions (Petri et al, 2012a*).

Table 1 Classification of lupus-associated mucocutaneous lesions

LE specific lesions	LE non-specific lesions
Acute cutaneous LE	Cutaneous vascular disease
Localised	Vasculitis
Generalised	Leucocytoclastic
Subacute cutaneous LE	Palpable purpura
Annular	Urticarial vasculitis
Papulosquamous (psoriasiform)	Polyarteritis nodosa-like
Chronic cutaneous LE	Vasculopathy
'Classic' DLE	Dego's disease-like
Localised	Atrophy blanche-like
Generalised	Periungual telangiectasia
Hypertrophic (verrucous) DLE	Livedo reticularis
Lupus panniculitis (profundus)	Thrombophlebitis
Mucosal LE	Raynaud's phenomenon
Lupus tumidus	Erythromelalgia
Chilblain lupus	LE non-specific bullous lesions
Discoid lupus/lichen planus overlap	Epidermolysis bullosa acquisita-like
	Dermatitis herpetiformis-like
	Pemphigus erythematosus
	Bullous pemphigoid
	Porphyria cutanea tarda
	Mucosal ulcerations
	Papulonodular mucinosis
	Anetoderma/cutis laxa
	Acanthosis nigricans
	Erythema multiforme
	Leg ulcers
	Lichen planus
	Alopecia (non-scarring)
	'Lupus hair'
	Telogen effluvium
	Alopecia areata
	Sclerodactyly
	Rheumatoid nodules
	Calcinosis cutis
	Urticaria

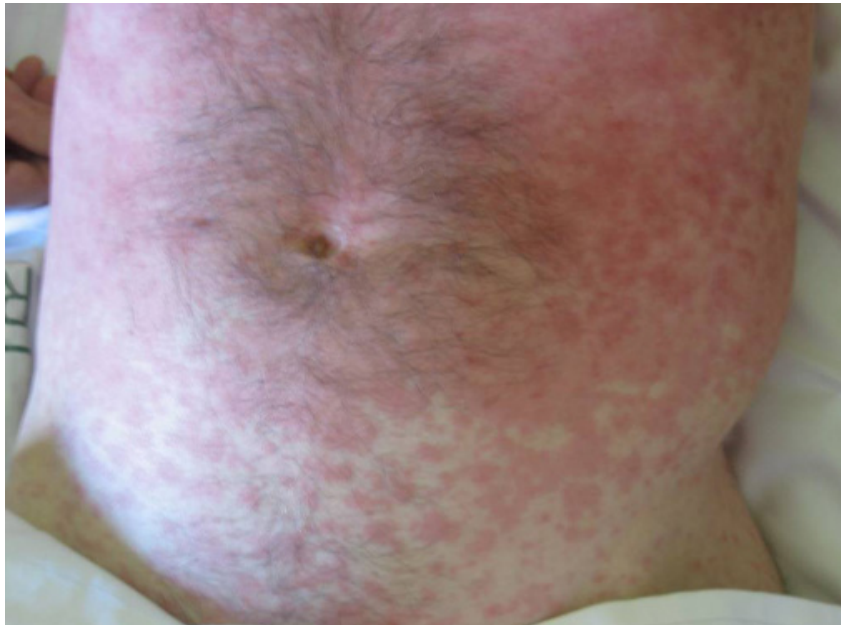
DLE, discoid lupus erythematosus; LE, lupus erythematosus.

Figure 3 *Acute cutaneous lupus erythematosus.*

A



B



(A) Localised (malar rash) and (B) diffuse (maculopapular rash).

4.1.2 Subacute lupus-specific mucocutaneous lesions

Subacute cutaneous lupus erythematosus (SCLE) is not uniformly associated with SLE (Okon et al, 2014). Patients with purely cutaneous lupus or with primary Sjögren's syndrome may also develop SCLE. About 50% of affected patients have SLE and about 10% of patients with SLE have this type of skin lesion (Wollina et al, 1999). Patients with SCLE have a high incidence of photosensitivity and lesions characteristically develop in sun-exposed areas (upper back, shoulders, extensor aspects of the arms, V-area of the neck, and less frequently on the face). SCLE lesions begin as erythematous macules or papules that evolve into scaly, papulosquamous (psoriasiform) or annular form. The latter often coalesce to form polycyclic plaques (figure 3). A few patients develop both types.

The central areas of annular SCLE lesions typically become hypopigmented. Differential diagnosis includes psoriasis, erythema multiforme and erythema annulare centrifugum. Lesions typically heal without scarring, although they can leave long-lasting or even permanent depigmentation and telangiectasias. Patients with active SCLE may also present coexisting acute and chronic mucocutaneous lesions. Subacute cutaneous lupus erythematosus has been associated with anti-Ro/SSA antibodies, genetic deficiencies in C2/C4, and certain drugs, such as hydrochlorothiazide.

4.1.3 Chronic lupus-specific mucocutaneous lesions

The most common feature of chronic rashes in SLE is classic discoid lupus erythematosus (DLE) that develop in up to 25% of patients with SLE (Pistiner et al, 1991). Patients with DLE have approximately a 5–10% risk of developing SLE, which tends to be mild. Risk is even higher with numerous and widespread skin lesions (Okon et al, 2014). DLE lesions start as flat or slightly elevated and well demarcated erythematous, scaly, macules or papules. These frequently evolve into larger, round ('discoid') infiltrated plaques covered by a well-formed adherent scale that extends into dilated hair follicles (follicular plugging) (figure 4). DLE commonly presents on the face, neck, extensor aspects of the arms and the scalp, but also occurs on the ears, and infrequently on the upper torso. DLE lesions slowly expand with active inflammation at the periphery and then heal, leaving depressed central scars, atrophy, telangiectasias and depigmentation (hyper- or hypopigmentation). Involvement of the hair follicles is a prominent feature of DLE and may lead to permanent hair loss, resulting in scarring alopecia. DLE occurring only on the head and neck is referred to as 'localized DLE', whereas lesions both above and below the neck is named 'generalized DLE'. Lesions solely below the neck are rare. DLE can be precipitated by UV exposure or any form of skin trauma. The differential diagnosis includes a variety of disorders that can clinically simulate some phases of DLE, such as polymorphous light eruptions, psoriasis, actinic keratosis, sarcoidosis, and tertiary syphilis. The histopathology usually distinguishes these conditions from DLE. In the ACR classification criteria, only the classic DLE was included as a criterion, while in the newer SLICC classification set, other chronic LE-specific features are also counted.

In rare cases, DLE can present with very prominent hyperkeratosis, which is named hypertrophic DLE. Very infrequently, lesions can have overlapping features with lichen planus (discoid lupus/lichen planus overlap).

Lupus erythematosus profundus or lupus panniculitis is characterised by inflammatory lesions in the lower dermis and subcutaneous tissue. It presents in up to 3% of SLE patients. Clinically it presents as deep, firm nodules, 1 to 3 cm in diameter, with or without overlying superficial lesions and are often painful. They usually appear on the scalp, face, arms, chest, back, thighs and buttocks. As the lesions mature, the overlying skin progressively becomes attached to the subcutaneous nodules, producing saucerized depressions with areas of scarring skin atrophy.

Chilblain lupus is precipitated by cold exposure, presenting as red-purple patches and plaques involving most frequently fingers and toes during the winter season. As the lesions mature, they can take the typical clinical aspect of DLE. These lesions are sometimes named ‘perniosis lupus erythematosus’, that is distinct from ‘lupus perniosis’ (a form of cutaneous sarcoidosis).

Lupus tumidus, a rare variant, is characterised by succulent, oedematous, urticaria-like plaques occurring in sun-exposed skin.

Mucosal membranes can be involved in DLE, most frequently in the mouth (buccal, palate, alveolar processes, tongue, lips), and more rarely in the nasal, conjunctival and genital mucosae. Lesions begin as painless erythematous patches and mature into chronic DLE plaques which may be hard to distinguish from oral lichen planus. Involvement of the nasal mucosa can rarely cause perforation of the nasal septum.

Bullous lesions rarely develop in SLE, as a result of dissolution of the basal cell layer with sub epidermal cleavage plane, within lesions with lupus-specific skin histopathology. These bullous presentation may occur in acute or subacute cutaneous lupus (‘toxic epidermal necrolysis variant ACLE and SCLE’ and ‘vesiculobullous annular SCLE’) and as bullous DLE. In addition, there are also several LE non-specific bullous lesions that can present in SLE.

Figure 4 Subacute cutaneous lupus lesions.



Figure 5 Facial discoid lupus rash with a malar distribution.



Erythema, keratin plugged follicles and dermal atrophy. The typical pattern of hyperpigmentation at the active border and hypopigmentation at the inactive centre is particularly evident in black patients. DLE in the face usually spares the nasolabial folds and must be differentiated from acute malar rash. (Patient consent obtained)

4.1.4 Pathology of lupus-specific mucocutaneous lesions and the 'lupus band test'

Histopathology of lupus-specific skin lesions presents characteristic features including mononuclear cell infiltration around the dermal-epidermal junction, dermal oedema, hyperkeratosis and basal cell degeneration. These features are present in ACLE, SCLE and DLE, so that it may be impossible to differentiate between them from histopathology. Skin biopsy samples of non-lesional, sun-protected areas from SLE patients can present the 'lupus band' of immunoglobulins and complement components, including the membrane attack complex (C5b through C9) at the dermal–epidermal junction (Biesecker et al, 1982). This positive non-lesional 'lupus band test' may be of diagnostic usefulness in selected cases, considering it has a fairly good specificity but a limited sensitivity.

4.1.5 Lupus erythematosus non-specific mucocutaneous lesions

A wide variety of non-specific mucocutaneous lesions can be found in SLE patients, some of them with high prevalence (i.e., photosensitivity, oral and nasal ulcers, Raynaud's phenomenon, non-scarring alopecia). Despite the lack of specificity, some of these are included in the SLICC lupus classification criteria (i.e., photosensitivity, oral and nasal ulcers, non-scarring alopecia). Furthermore, some of these features are included in SLE disease activity indexes, such as the SLEDAI and BILAG index, and cutaneous vasculitis heavily weights the disease activity score in SLEDAI. In clinical practice, correct attribution of these lesions to SLE or other causes is frequently challenging, and of utmost importance for appropriate management decisions.

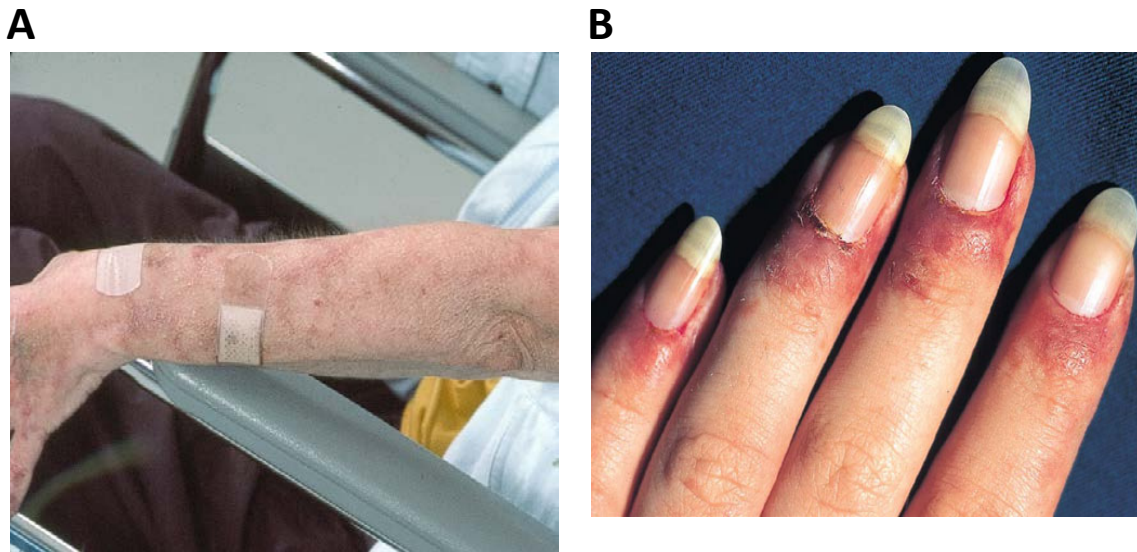
Photosensitivity is defined as the development of an inflammatory rash after exposure to UV-B radiation coming from sunlight or fluorescent lights that may last several days or even weeks. It occurs in 60–100% of patients with SLE. Some patients are also sensitive to UV-A radiation. The clinician should be wary of diagnosing photosensitivity based on history alone, and other causes or mimics must be considered.

Livedo reticularis can present in SLE patients, as a mottled reticulated purplish pattern on the arms and legs (figure 5 A), caused by swelling of the venules in the skin. It is frequently aggravated by cold exposure, similarly to the more frequent Raynaud's phenomenon.

Cutaneous vasculitis, usually a small vessel vasculitis, can present in SLE with a variety of lesions, such as punctuate lesions, erythematous plaques or macules, urticaria-like lesions, periungual erythema (figure 5 B), splinter nailfold haemorrhages, palpable purpura, ulcerations, digital gangrene, and cutaneous infarctions. Cutaneous vasculitis may be associated with systemic vasculitis. Ulcerations and gangrene may also result from secondary antiphospholipid syndrome.

Non-scarring alopecia, defined as diffuse thinning or hair fragility with visible broken hairs, occurs in most patients with SLE (Yun et al, 2007). Clinically observed diffuse hair thinning results from a synchronization of hair shedding, often with an acute onset (telogen effluvium), which is a reactive process caused by a systemic lupus flare, an acute illness, hormonal or physical stress. Diffuse lupus-related alopecia is typically self-limited and the hair spontaneously returns to normal after reduction of the underlying SLE activity. Hair fragility with visible broken hairs is denominated 'lupus hair' and is frequently seen with lupus-related alopecia. As with photosensitivity, the clinician should be wary of diagnosing lupus-related alopecia based alone in a subjective history of exaggerated hair loss. It must be differentiated from the usually patchy and potentially scarring alopecia accompanying discoid lupus in the scalp.

Mucosal ulcers occur in 25–45% of patients (Khatibi et al, 2012). Most commonly present on the soft or hard palate or buccal mucosa, but they may also involve the nasal and upper airway mucosa (Jonsson et al, 1984). These mucosal ulcers usually resolve without scarring. Differentiation from mucosal DLE should be made. Oral ulcers in SLE are usually asymptomatic; by contrast, those not lupus-related are commonly quite painful. Differential diagnosis of ulcers attributable to SLE disease activity from other conditions is challenging, including lichen planus, candidiasis, aphthous stomatitis, intraoral herpes, Behçet's disease, bite marks, leucoplakia and malignancy.

Figure 6 (A) Livedo reticularis and (B) periungual erythema.

4.2 Musculoskeletal features

The musculoskeletal system is affected in 53–95% of patients with SLE. These features, especially lupus arthritis, are frequently the first clinical manifestation of SLE. It is a particularly common presenting manifestation motivating referral to rheumatology. Many of these patients do not have at presentation any clinical manifestations from other organ systems; however, appropriate laboratory tests may reveal other, often asymptomatic but potentially severe organ involvement, such as lupus nephritis. Some patients may present at early arthritis clinics with undifferentiated arthritis that with time will evolve in to SLE. In young women presenting with arthritis, the differential diagnosis should include SLE.

4.2.1 Lupus arthritis

Joint involvement is typically non-erosive, non-deforming inflammatory arthritis primarily affecting the small joints of the hands (especially the proximal interphalangeal joints), wrists and knees, most frequently as a polyarthritis (Grossman 2009). It may first present at clinical onset of SLE or at any time during the disease course. Patient's symptoms (inflammatory pain and morning stiffness) are usually more prominent than the synovitis on physical examination, which is usually mild. Lupus arthritis is often evanescent, but tends to be recurrent. A few patients have a chronic polyarthritis with a pattern indistinguishable from rheumatoid arthritis (sometimes called 'rhumus'). Patients with chronic polyarthritis are more prone to develop joint deformities, in particular Jaccoud-type arthropathy similar to rheumatoid arthritis hand deformities except that the deformities are usually reducible and due to ligamentous laxity and not to bony damage (figure 6). In rare cases, lupus arthritis is erosive and most of these patients have positive anti-cyclic citrullinated peptide antibodies (anti-CCP). In a meta-analysis, estimated sensitivity and specificity of anti-CCP for erosive arthritis in SLE patients was 47.8% and 91.8%, respectively (Budhram et al, 2014).

Diagnosis of lupus arthritis may be challenging, due to the frequently mild synovitis. Clinicians should be wary of diagnosing it solely based on patient history, when objective synovitis is not found at clinical examination. Alternative causes must be ruled out, including fibromyalgia and in older patients, flares of osteoarthritis.

Tenosynovitis may be an early manifestation and tendon rupture can occur. Subcutaneous nodules similar to rheumatoid nodules can be rarely found in SLE. Chest pain or discomfort secondary to costochondritis has been reported. Relapsing polychondritis can also occur.

Figure 7 Jaccoud-type (deforming) arthropathy.



(Courtesy of Dr D Vassilopoulos).

4.2.2 Myositis

Generalised myalgia and muscle tenderness are common during disease exacerbations and should be differentiated from fibromyalgia complaints. Inflammatory myositis affecting the proximal muscles has been reported in 4–16% of adult patients and in up to 31% of paediatric SLE patients and may develop at any time during the course of the disease (Record et al, 2011). Myopathy caused by exposure to statins, glucocorticoids, antimalarials or other drugs should be excluded.

4.2.3 Avascular bone necrosis

Avascular necrosis of bone is an important cause of morbidity and disability in SLE, which occurs in 5% to 10% of patients. Acute or subacute localized joint pain, most often in shoulders, hips and knees, may indicate avascular necrosis. MRI is useful for early diagnosis and differentiating from other causes such as synovitis and osteoarthritis. Factors that can induce bone ischaemia and necrosis include Raynaud's phenomenon, vasculitis, fat emboli, glucocorticoids and the antiphospholipid syndrome. Osteonecrosis often develops shortly after the onset of high-dose glucocorticoid therapy.

4.2.4 Osteoporosis and fragility fractures

Factors contributing to increased risk of osteoporosis and fragility fractures in SLE include the disease activity, lupus damage (such as chronic renal failure), low vitamin D due to sun avoidance and use of sunscreens (advised for photosensitivity), medications (glucocorticoids in particular), and traditional risk factors in a mostly female population (Carli et al, 2016).

4.3 Renal features

4.3.1. Epidemiology

Lupus nephritis (LN) is the most frequent major organ involvement in SLE patients. Approximately 50% of patients with SLE develop LN during the disease course, with about 15-20% presenting with LN at time of SLE diagnosis. It is an important cause of morbidity and reduced survival of SLE patients (Cervera et al, 2003). In paediatric-onset SLE, risk of LN is higher and its prognosis more severe (Amaral et al, 2014). Patients with non-European ancestry (African-Americans, African-Caribbean, American-Hispanics and Asian ethnicities) present with LN more frequently and are more likely to develop renal damage than patients of European descent (Korbet et al, 2007). LN can progress to chronic renal failure requiring dialysis and renal transplantation.

4.3.2. Clinical diagnosis with indication for renal biopsy

The most frequent presenting manifestation of LN is proteinuria, usually without evident clinical signs of renal disease. This poses important diagnostic challenges, particularly when LN is an inaugural feature of SLE. Patients with newly active LN, either inception SLE cases or those with established disease, may or may not present any concomitant clinical manifestations of SLE. An early diagnosis of LN is of paramount importance for initiating timely and appropriate treatment, in order to optimize prognosis. A dipstick urinalysis is a readily available screening tool, with abnormalities requiring confirmation by other tests. Urinalysis must be systematically done in the diagnostic workup of suspected SLE and in every clinical assessment of SLE patients.

A diagnosis of LN is defined in SLE patients as urinary findings of: (i) persistent proteinuria >0.5 g per day in a 24-hour urine collection or a spot urine sample protein/creatinine ratio >0.5 , and/or (ii) 'active urinary sediment' (>5 red blood cells /high-power field (hpf) and/or >5 white blood cells/hpf in the absence of infection, and/or cellular casts of red or white blood cells) (Dooley et al, 2004). The ACR classification criteria for SLE rely in these findings for case definition of LN and do not require a renal biopsy for classification purposes. However, current ACR and EULAR guidelines recommend that all patients with clinical/analytical signs of active LN previously untreated undergo renal biopsy (unless strongly contraindicated) (Bertsias et al, 2012*; Hahn et al, 2012).

Proteinuria >0.5 g/day is an almost universal finding in active LN cases, ranging from low levels (<1.0 g/day) to >3.5 g/day (with nephrotic syndrome). Microscopic findings of 'active urine sediment' are less frequently found, and when present are almost invariably associated with proteinuria. Nevertheless, a renal biopsy may also be considered in the rare cases of SLE patients with unexplained persistent microscopic haematuria or leukocyturia, or elevated serum creatinine but without proteinuria >0.5 g/day (Bertsias et al, 2012*). Alternative causes for haematuria (i.e. menses, renal stones) and leukocyturia (i.e. urinary or gynaecological infection) should be excluded. Due to its convenience, the urinary protein excretion is most frequently gauged in the clinical practice in a random daytime spot urinary sample using the protein/creatinine ratio for quantification. It is however subject to spurious fluctuations, which may be contributed by orthostatic proteinuria and associated with changes in physical activity; to reduce these effects, a sampling of first morning urine may be more reliable. The 24-hour urine collection is also subject to spurious variations, in particular due to incomplete collections and changes in physical activity; quantification of creatinine excretion in the same sample can help appreciate if the collection was complete (Saxena et al, 2011). In clinical practice, when there is doubt if the proteinuria quantification was correct, a second confirmatory sampling, possibly using an alternative method, should be considered.

Some blood tests are useful in the diagnosis and monitoring of LN. Anti-dsDNA antibodies are usually high and complement levels of C3 and C4 low in patients with active LN, although this is not always the case. In longitudinal follow-up of SLE patients, increasing levels of anti-dsDNA and decreasing levels of C3 and C4 may precede a LN (or extra-renal) flare, justifying tighter monitoring of these patients. However, their accuracy is low. Other biomarkers, in particular anti-C1q antibodies, were associated with LN and their use in a combined panel of biomarkers may in the future improve the diagnosis and monitoring of LN (Orbai et al, 2015). Monitoring of blood pressure, serum creatinine, estimated glomerular filtration rate, albumin, and complete blood cell count is recommended in patients with LN (Bertsias et al, 2012*). Antiphospholipid antibodies should also be tested, as they can cause a distinct nephropathy (thrombotic microangiopathy), with different treatment requirements.

4.3.3. *Differential diagnosis of LN*

A variety of nephropathies other than LN can present with similar clinical and analytical features in SLE patients. The epidemiological and clinical context may help to raise suspicion of the appropriate alternative diagnosis. In some patients, other causes of nephropathy can coexist with LN. In patients with previous LN, an increased proteinuria and/or deteriorating renal function are not always due to a LN flare or related renal scarring, and appropriate alternative diagnosis should be considered.

Differential diagnosis of LN include tubule-interstitial nephritis, diabetic nephropathy, drug-induced nephrotoxicity, thrombotic microangiopathy associated with antiphospholipid syndrome, haemolytic-uremic

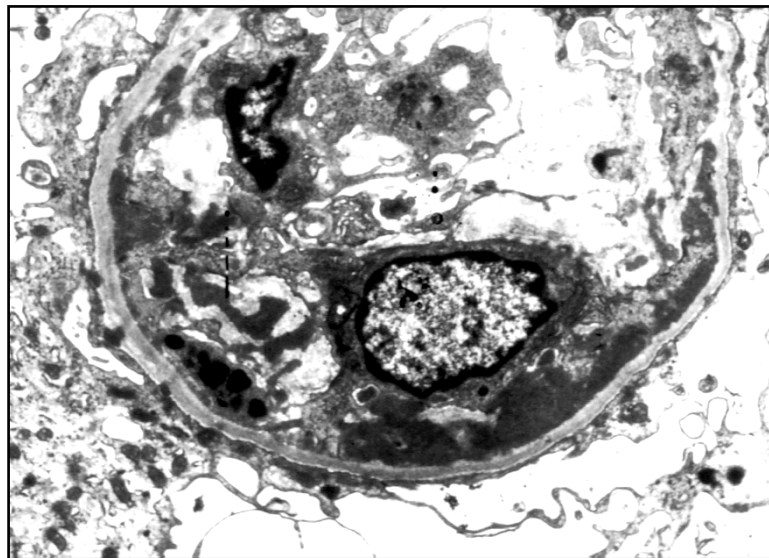
syndrome, preeclampsia (in pregnancy), hypertensive nephrosclerosis, or arterionephrosclerosis (Giannico et al, 2013*).

4.3.4. Renal histopathology

Renal biopsy is fundamental to confirm the LN diagnosis and exclude other causes of nephritis, establish the histopathological type of LN to guide treatment and estimate prognosis (Giannico et al, 2013*; Bertias et al, 2012*). Clinical and analytical results do not accurately reflect the histopathologic type and severity of LN. Even patients with low levels of proteinuria (0.5-1.0 g/day) may present significantly active LN (Christopher-Stine et al, 2007). Renal biopsy is usually well tolerated and carries only a small risk of bleeding and perirenal hematoma.

For pathological assessment of renal biopsy, the sample should include ≥ 8 glomeruli, to be examined under light microscopy (haematoxylin/eosin, periodic acid-Schiff, Masson's trichrome and silver stain), and include immunofluorescence or immunohistochemistry for immunoglobulin and complement deposits. Electron microscopy, if available, can be useful (figure 7) (Bertias et al, 2012*).

Figure 8 Electron microscopy demonstrating subendothelial deposition of electron-dense immune complexes in proliferative lupus nephritis.

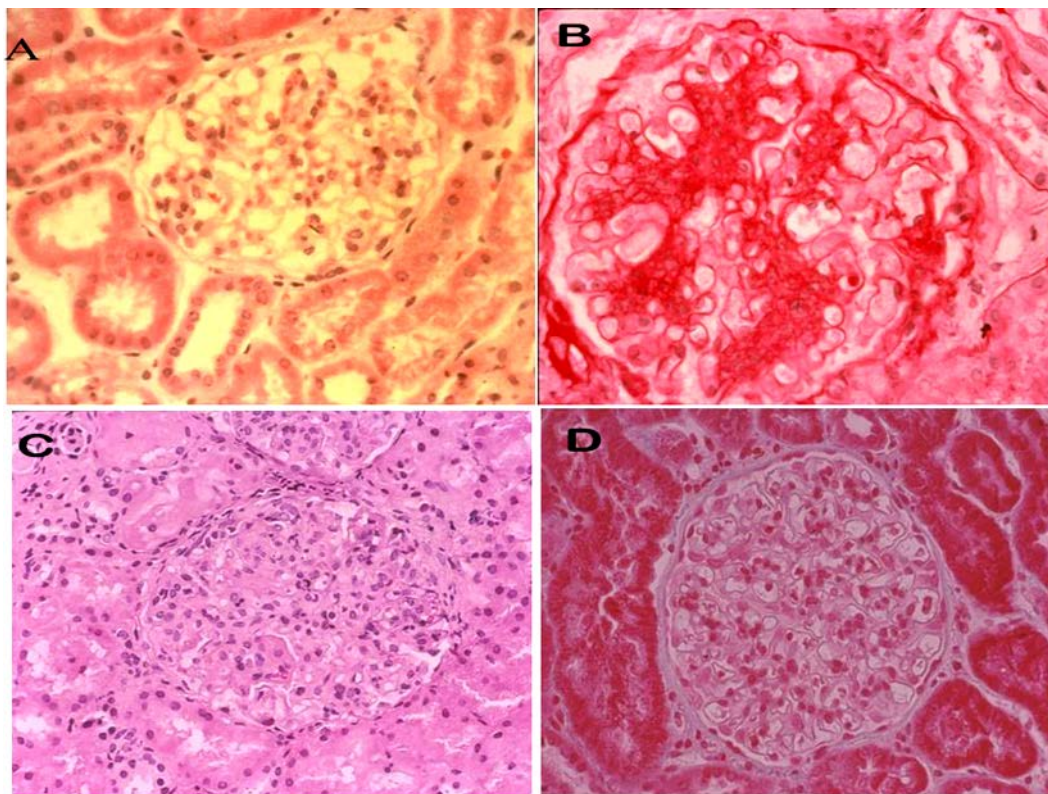


Electron microscopy helps to define distribution (subendothelial, epithelial, membranous deposits) of immune complexes and may be useful in the recognition of early proliferative changes when the light microscopy findings are subtler.

Histopathology of LN is currently classified using the 'International Society of Nephrology / Renal Pathology Society classification' (ISN/RPS) (Table 2; Figure 8) (Weening et al, 2004): Class I (minimal mesangial immune deposits on immunofluorescence with normal light microscopy); class II (mesangial hypercellularity or matrix expansion with immune deposits confined to mesangium); class III (subendothelial immune deposits and

proliferative changes in <50% of glomeruli); class IV (same as class III, with changes in >50% of glomeruli); class V (sub epithelial immune deposits and membranous thickening of glomerular capillaries); class VI (sclerosis of $\geq 90\%$ of glomeruli). There are also complex LN cases with combined class III or IV with V. Prognosis is best for classes I-II, but proliferative LN (classes III and IV) are the most prevalent. Class VI represents progression from other classes to end stage renal scarring. In repeat renal biopsies during subsequent flares of LN, some patients present a clinically relevant switch from non-proliferative to proliferative LN, while the opposite is uncommon (Daleboudt et al, 2009).

Figure 9 ISN/RPS histopathological classes of lupus nephritis.



(A) Minimal mesangial LN (class I). (B) Mesangial proliferative LN (class II). (C) Focal LN (class III) and Diffuse LN (type IV). (D) Membranous LN (type V).

Table 2 The 2003 ISN/RPS Classification of lupus nephritis (LN)

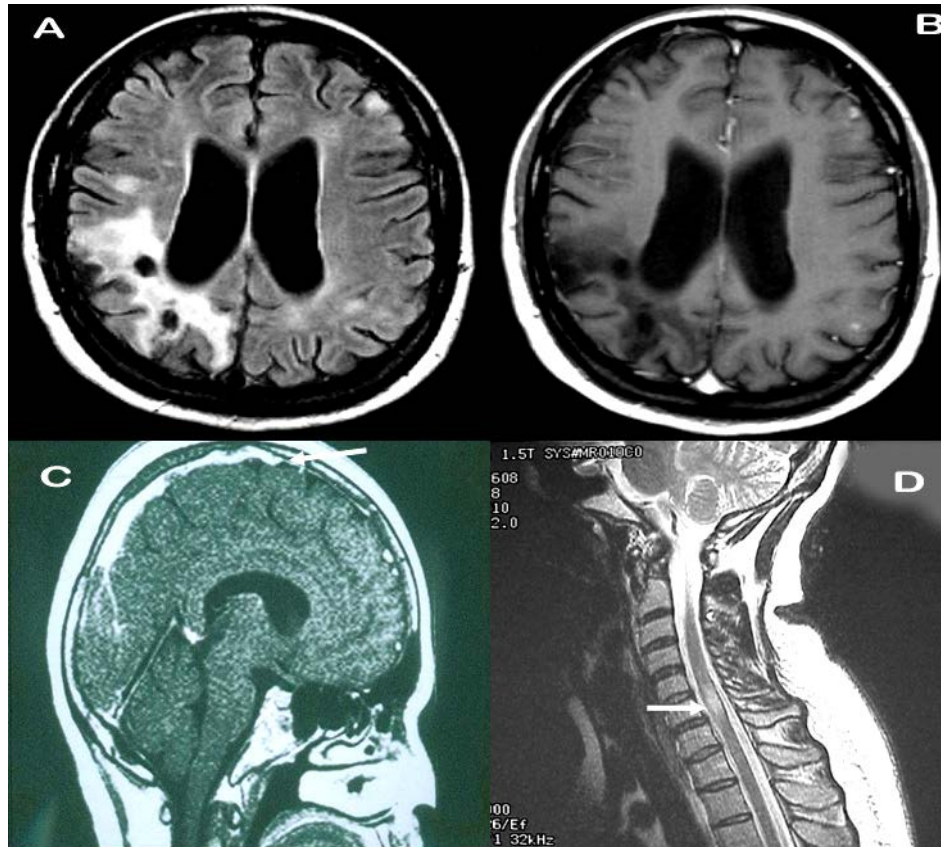
Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN (<50% of glomeruli) (A, C or A/C)
Class IV	Diffuse LN (>50% of glomeruli) (A, C or A/C, and S versus G)
Class V	Membranous LN
Class VI	Advanced sclerotic LN (≥90% of glomeruli globally sclerosed without residual activity)

A: active lesions; C: chronic lesions; A/C: active and chronic lesions; S: segmental; G: global

In addition to the diagnosis of glomerular disease according to ISN/RPS classes, tubulointerstitial and vascular changes should be evaluated. In cases with proliferative LN (Class III and IV), lesions should be scored as active (A) (*i.e.*, endocapillary proliferation, fibrinoid necrosis, and cellular crescents), chronic (C) (*i.e.*, sclerosis, fibrous crescents, and interstitial fibrosis) or combined A/C. The class IV is further classified as segmental (S) (<50% of the glomerular tuft involved) or global (G) (>50% of the glomerular tuft). Some studies suggest a differential prognostic value for these categories, although it remains controversial (Giannico et al, 2013*). Renal vascular lesions, including thrombotic microangiopathy, lupus vasculopathy and lupus necrotizing vasculitis are not frequent, but carry an increased risk of progression to chronic renal failure (Banfi et al, 1991).

4.4 Nervous system features

Neuropsychiatric (NP) manifestations in SLE include a wide range of neurologic and psychiatric features (Hanly et al, 2010*). The ACR established a widely used nomenclature system with detailed case definitions for the neuropsychiatric manifestations seen in SLE (ACR, 1999*). Importantly, these do not imply attribution to SLE-related pathogenesis. Therefore, a complete clinical assessment and appropriate investigations should be used to diagnose NP events and establish its aetiology to SLE or non-SLE causes and particularly to exclude infection (fig. 9) (Bertsias et al, 2010a*). Regardless of attribution, NP manifestations result in decreased quality of life, work disability and increased unemployment (Hanly et al, 2010*). Current therapeutic strategies are largely empiric, based on known immunopathogenetic mechanisms and observational studies (Hanly et al, 2014). For a comprehensive review on this topic, access the In-depth discussion I (Neuropsychiatric Manifestations in SLE).

Figure 10 Severe neuropsychiatric lupus.

MRI imaging showing cerebrovascular disease (A and B); thrombosis in the sagittal sinus in a patient with antiphospholipid antibodies (C); and acute transverse myelitis (D).

4.5 Cardiovascular features

Pericarditis occurs in 15–25% of patients with SLE. Pericardial effusions may be asymptomatic and are usually mild to moderate.

Myocardial involvement is rare and typically occurs in the presence of generalized lupus activity. The patient may present with fever, dyspnoea, tachycardia and congestive heart failure. Features of left ventricular dysfunction, non-specific ST/T wave changes, segmental wall motion abnormalities and decreased ejection fraction are found in >80% of patients with myocarditis. MRI has been used to detect both clinical and subclinical myocardial involvement in SLE.

Valvular heart disease is common in SLE and has been linked to antiphospholipid antibodies. The most frequent abnormality is diffuse thickening of the mitral and aortic valves followed by vegetations, valvular regurgitation and stenosis, in decreasing order of frequency. The combined incidence of stroke, peripheral embolism, heart failure, infective endocarditis and the need for valve replacement is about threefold higher in patients with valvular disease than in those without it. Pathological studies have shown active and healed valvulitis, as well as active Libman–Sacks vegetations with acute thrombus, healed vegetations with or without hyalinised thrombus, or both active and healed vegetations, in the same or different valves.

Patients with SLE have increased morbidity and mortality from cardiovascular disease. This includes accelerated, premature atherosclerosis and valvular heart disease. Studies have shown increased risk for myocardial infarction or stroke in lupus patients with significant risk of premature death and this risk cannot be fully explained by the traditional cardiovascular disease risk factors (Yee et al, 2015*).

4.6 Pleura and lungs features

The most common pleuropulmonary manifestation of SLE is pleuritis (table 3) (Mittoo et al, 2014). Pleuritic pain may occur with or without pleural effusion, with clinically apparent pleural effusions reported in up to 50%, but are usually mild and transient. Effusions are frequently bilateral, equally distributed between the left and right hemithoraces. The effusion is exudative with higher glucose and lower lactate dehydrogenase levels than those found in rheumatoid arthritis.

Clinically significant interstitial lung disease complicates SLE in 3–13% of patients and may be severe. It can rarely present as acute pneumonitis with cough, dyspnoea, pleuritic pain, hypoxaemia and fever. Chest radiographs show unilateral or bilateral infiltrates. Fibre optic bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsies is usually needed to establish the diagnosis of interstitial lung disease and to exclude infection. Pulmonary hypertension is a rare and severe feature, most frequently presenting with dyspnoea.

Pulmonary haemorrhage is a rare but potentially life-threatening complication of SLE, requiring emergency care. Clinical features are non-specific, with diffuse alveolar infiltrates, hypoxaemia, dyspnoea and anaemia. The 'shrinking lung syndrome' is a rare and enigmatic feature, further discussed in the in-depth discussion II.

Table 3 Pleuropulmonary manifestations of SLE

Pleuropulmonary manifestation	Presentation
Pleuritic chest pain or pleurisy	Common
Pleural effusion	Exudate; unilateral or bilateral
Acute pneumonitis	Uncommon; presentation includes: fever, non-productive cough, infiltrates, hypoxia; high mortality rates
Interstitial lung disease	Insidious onset of dyspnoea on exertion, non-productive cough, pleuritic chest pain
Bronchiolitis obliterans with organising pneumonia	Can be difficult to diagnose; requires biopsy; responds to glucocorticoids
Pulmonary capillaritis or diffuse alveolar haemorrhage	Rare, associated with antiphospholipid antibodies; poor prognosis
Shrinking-lung syndrome	Uncommon; presentation includes: dyspnoea on exertion, pleuritic chest pain
Pulmonary embolism or infarction	Usually in patients with antiphospholipid antibodies
Pulmonary hypertension	Insidious onset of dyspnoea on exertion, chronic fatigue, weakness, palpitations, oedema
Lymphadenopathy	Massive mediastinal lymphadenopathy uncommon in patients with SLE alone. Cervical and axillary common, correlates with disease activity
Infection	Typical and atypical pathogens. Due to immune dysfunction (low CD4 lymphocytes) and immunosuppressive drugs
Malignant tumour	Lung cancer especially in smokers; lymphoma

4.7 Lymphadenopathy and splenomegaly

Lymphadenopathy occurs in about 40% of patients, usually at the onset of disease or during disease flares (Shapira et al, 1996). Lymph nodes are typically soft, non-tender, discrete but fluctuating in size and are usually detected in the cervical, axillary and inguinal area. Clinically significant lymphadenopathy that raises diagnostic problems is less common. Patients with lymphadenopathy are more likely to have constitutional symptoms. A lymph node biopsy may be warranted when the degree of lymphadenopathy is out of proportion to the activity of the lupus especially with persistent fever, sweats and weight loss. It is important to consider lymphoma and tuberculosis in the differential diagnosis. Splenomegaly occurs in 10–45% of patients, particularly during active disease and is not necessarily associated with cytopenias. Splenic atrophy and functional hyposplenism have also been reported in SLE and may predispose to severe septic complications.

4.8 Haematological features

Haematological abnormalities are common and can be the presenting symptom or sign in SLE, especially lymphopenia. Major clinical manifestations include haemolytic anaemia, leukopenia, thrombocytopenia and thrombophilia due to antiphospholipid antibodies.

4.8.1 Anaemia

Anaemia in SLE is common and, depending on the cause, can correlate or not with SLE disease activity: some cases are SLE-related but most are not. The most frequent causes are iron deficiency anaemia and anaemia of chronic disease. Other less common causes include haemolysis (autoimmune or microangiopathic), chronic renal failure, drugs, infection, hypersplenism, myelodysplastic syndrome, myelofibrosis and aplastic anaemia.

Blood loss, either from the gastrointestinal tract (frequently secondary to non-steroidal anti-inflammatory drugs), or due to excessive menstrual bleeding commonly cause iron-deficiency anaemia. Suppressed erythropoiesis from chronic inflammation related to SLE disease activity may also cause anaemia. Autoimmune haemolytic anaemia was reported much less frequently, in up to 10% of patients; of note, patients with SLE may have a persistently positive direct Coombs' test without haemolysis. A microangiopathic haemolytic anaemia with or without the other features (fever, thrombocytopenia, kidney involvement and/or neurological symptoms) of thrombotic thrombocytopenic purpura (TTP) has been reported in SLE patients. The presence of schistocytes in the peripheral blood smear and increased lactate dehydrogenase levels are the hallmarks of this disorder which has a high mortality and warrants urgent plasma exchange. A similar syndrome can also occur in the presence of antiphospholipid antibodies. Red cell aplasia due to antibodies against erythrocyte progenitors has been rarely reported in patients with SLE.

4.8.2 Leukopenia and lymphopenia

Leukopenia is common in SLE; it can be the presenting symptom and is usually associated with disease activity. A white blood cell count $<4000/\text{mm}^3$ has been reported in up to 30–40% of patients, especially in presence of active disease, but it is usually mild. Severe leukopenia with neutrophil count $<500/\text{mm}^3$ is rare but carries a high risk of infection. Lymphopenia (variously defined as lymphocyte count $<1500/\text{mm}^3$ or $<1000/\text{mm}^3$) occurs in most patients with SLE and is frequently proportional to disease activity.

4.8.3 Thrombocytopenia

Mild thrombocytopenia ($50\,000$ – $100\,000/\text{mm}^3$) was reported in 25–50% of patients and is often associated with antiphospholipid syndrome; clinically significant thrombocytopenia ($<50\,000/\text{mm}^3$) with a risk of bleeding occurs in less than 10%. The most common cause of thrombocytopenia in SLE is immune-mediated platelet destruction, but increased platelet consumption may also occur owing to microangiopathic haemolytic

anaemia or hypersplenism. Impaired platelet production secondary to drug treatment is another possible contributing factor. Some patients present with autoimmune thrombocytopenia, especially in childhood, as a feature of undifferentiated connective tissue disease, with anti-nuclear antibodies, and years later may evolve to SLE.

4.8.4 *Thrombophilia*

Thrombosis may be the presenting feature of SLE with antiphospholipid syndrome or develop later during the SLE disease course. Antiphospholipid syndrome is discussed in another module.

4.9 Liver and gastrointestinal tract features

4.9.1 *Gastrointestinal tract*

Gastrointestinal (GI) manifestations are reported in 25–40% of patients with SLE, and commonly represent non-SLE related features, drug adverse events or more rarely, SLE GI involvement (Ebert et al, 2011).

Dyspepsia has been reported in 11–50% of patients, and peptic ulcers (usually gastric) in 4–21%. Xerostomia is relatively frequent and can be due to associated Sjögren's syndrome.

4.9.2 *Abdominal pain*

Abdominal pain may be the presentation of rare SLE-related conditions such as peritonitis, mesenteric vasculitis, intestinal infarction, and pancreatitis. The clinical presentation is usually an insidious abdominal pain that months later can evolve to an acute abdomen with nausea, vomiting, diarrhoea, GI bleeding and fever. Patients with acute presentation may also have peritonitis with or without ascites due to serositis (with or without pleuritic/pericarditis) or less commonly mesenteric thrombosis and infarction, often in association with antiphospholipid antibodies. Ascites is uncommon in SLE and, when detected, infectious causes and/or perforation must be excluded by paracentesis. Congestive heart failure and hypoalbuminaemia secondary to nephrotic syndrome or protein-losing enteropathy represent other possible causes of ascites in patients with SLE. Protein-losing enteropathy has been rarely described and can be the first manifestation of the disease. It usually occurs in young women and is characterized by oedema and hypoalbuminaemia. The diagnosis of mesenteric vasculitis is challenging and it is critical to exclude infection, for example diverticular abscess. Plain radiographic studies may show segmental bowel dilatation, air-fluid levels, 'thumb-printing' or narrowing of the lumen and pseudo-obstruction. Abdominal CT scan findings compatible with mesenteric vasculitis include prominence of mesenteric vessels with a comb-like appearance supplying dilated bowel loops, small bowel thickening and ascites. Vasculitis generally involves small arteries, so that angiography is frequently negative. Lupus pancreatitis may result from vasculitis or thrombosis and occurs in as many as 2–8% of patients.

4.9.3 Liver disease

The incidence of hepatomegaly is 12–25%. Steatosis is a common finding, commonly due to unrelated causes or secondary to glucocorticoids. Blood liver enzymes may be abnormal in patients with active disease or more frequently related to drug treatment or viral infections. An unrelated autoimmune hepatitis was in the past designed as ‘lupoid hepatitis’.

4.10 Ophthalmic features

Up to 8% of patients with SLE develop inflammation of the retinal artery during the course of their disease. An equal number of patients have infarction of the retinal vasculature secondary to antiphospholipid antibodies. Both conditions can lead to the presence of ‘cotton-wool’ spots in the retina visible on ophthalmoscopy or fluorescein angiography (where perivascular exudates and patches of dye leakage along the vessels are seen). Cotton-wool spots result from focal ischaemia and are not specific for lupus. Retinal vasculitis is usually associated with generalized active systemic disease and presents early in the disease process. Xerostomia is frequently found, as a feature of Sjögren’s syndrome associated with SLE, usually in patients with anti-SSA/SSB antibodies and may lead to corneal ulcers. Uveitis and scleritis are rare manifestations in SLE (<1% of patients). Optic neuritis is also rare.

5 Diagnosis

The “gold-standard” is a clinical diagnosis established by a clinician experienced in SLE, since there are no diagnostic criteria or any pathognomonic features. The clinical diagnosis is established based on the identification of several clinical and analytical features consistent with the diagnosis of SLE (described in the previous section), either concomitantly or cumulatively, while carefully considering other alternative explanations for the clinical picture.

5.1 Clinical presentation

The frequency of lupus manifestations in an international SLE inception cohort is presented in table 4 (Hanly et al, 2007). Possible combinations of clinical features are very heterogeneous, both at onset and during the disease course.

Table 4 Frequency of SLE manifestations defined according to ACR classification criteria in the SLICC inception cohort (n=572; mean disease duration \pm SD=5.2 \pm 4.2 months)

Cumulative ACR manifestations	%
Malar rash	37
Discoid rash	12
Photosensitivity	40
Oral/nasal ulcers	38
Serositis	27
Arthritis	74
Renal disorder	29
Neurologic disorder	5
Hematologic disorder	61
Immunologic disorder	76
Antinuclear antibody	95

5.2 Serological tests

5.2.1 Antinuclear antibodies (ANA)

The ANA assay is frequently used as screening test, in patients with a clinical picture suggestive of connective tissue disease, because of its very good sensitivity (>90% when using human cultured cells as the substrate) and wide availability. However, the specificity of ANA for SLE is low, since they are frequently found in many other conditions, as well as less frequently in the healthy population. Low serum titers (\leq 1:160) more frequently present without clinical significance. In contrast to the low positive predictive value of ANA testing, a patient with a negative test ($<$ 1:40) has less than a 3–5% probability of having SLE; thus, a negative ANA test is useful for excluding the diagnosis of SLE. However, when typical features of SLE are present, a negative ANA test cannot rule out the diagnosis (Bertsias et al, 2013). This is especially true for laboratories that employ enzyme immunoassays or other automated assays, which display marked inter-manufacturer variation in performance. In such cases, reported sensitivity against positive immunofluorescence-ANA with titre at 1:160 ranges from 70% to 98% (Meroni et al, 2010).

5.2.2 Anti-dsDNA antibodies

Antibodies to double-stranded (ds) DNA are found in about 70% of SLE patients at some point during the course of their disease, and are 95% specific for SLE. Their positivity may precede the clinical onset of the disease and are found in patients with undifferentiated connective tissue disease, some of whom will evolve to SLE. Clinical significance is more likely for moderate to high serum levels, taking into account the positivity cut-off of the assay used.

5.2.3 Antibodies to extractable nuclear antigens (ENA)

The main anti-ENA antibodies are: anti-Sm, anti-SSA(Ro), anti-SSB(La), anti-RNP, anti-topoisomerase I (Scl-70) and anti-Jo1. The ENA designation derives from its original identification in a saline extract of cell nuclei, despite that later it was found to include both nuclear and cytoplasmic proteins, which are associated with various RNA molecules. The anti-Sm antibodies are detected in 10–30% of lupus patients and are very specific for SLE. Anti-RNP antibodies, anti-SSA and anti-SSB are frequently found in SLE patients but are not disease specific.

5.2.4 Other auto-antibodies

Anti-ribosomal antibodies are specific for SLE but less sensitive than anti-dsDNA or anti-Sm antibodies. Anti-nucleosome antibodies were reported to present good sensitivity and specificity for SLE, but remain little used. Antiphospholipid antibodies can be quantified as anticardiolipin and anti-beta2-Glycoprotein I antibodies (IgG, IgM, and IGA) or indirectly detected in the lupus anticoagulant test; they are frequently found in SLE patients but are not specific. The anti-C1q antibody is associated with lupus nephritis. The direct antiglobulin (Coombs) test is positive in about 10% of SLE patients; is usually positive in those with autoimmune haemolytic anaemia but is not specific.

5.2.5 Serum complement levels

The complement system plays a major role in SLE pathogenesis and disease activity. The serum levels of complement fractions C3 and/or C4 are below normal in about 70% of SLE patients at some point during the disease course, frequently at the disease onset. Sensitivity of low C3 is higher than that of low C4 for SLE, and moderately specific. It is a widely available test, and in addition to its diagnostic value, longitudinal measurement of C3 and C4 serum levels can be useful for monitoring changes in disease activity (Leffler et al, 2014).

5.3 Differential diagnosis

Other diseases that must be frequently considered include undifferentiated connective tissue disease, rheumatoid arthritis, primary Sjögren's syndrome, primary antiphospholipid syndrome, fibromyalgia with positive ANA, idiopathic thrombocytopenic purpura, drug-induced lupus, and autoimmune thyroid disease. Patients with fever or splenomegaly/lymphadenopathy must be differentiated from those with infectious diseases or lymphoma. Lupus may present with lymphadenopathy or splenomegaly but the size of lymph nodes is rarely >2 cm, while splenomegaly is mild to moderate. Patients with known or suspected SLE with prominent lymphadenopathy, massive splenomegaly or expansion of a monoclonal CD19+/CD22+ B cell population should raise the suspicion of non-Hodgkin's lymphoma. In patients presenting with neurological symptoms, infections, cerebrovascular accidents or immune-mediated neurological diseases, such as multiple

sclerosis or Guillain–Barré disease, must be considered. Finally, in patients presenting with pulmonary-renal syndrome, the disease must be differentiated from Goodpasture’s syndrome, or antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. The differential diagnosis of glomerulonephritis includes post infectious glomerulonephritis (streptococcal, staphylococcal, subacute bacterial endocarditis or hepatitis C virus), membranoproliferative glomerulonephritis or renal vasculitis (ANCA or antiglomerular basement membrane (anti-GBM) associated).

Patients with undifferentiated connective tissue disease account for 10–20% of patients referred to tertiary care centres, and some of these will evolve to SLE or other differentiated systemic rheumatic disease, usually in the first 5 years after clinical onset. There are also patients with overlapping features of SLE and other connective tissue diseases. These syndromes are presented in another module of the EULAR course.

6 Classification criteria

Criteria for SLE classification were developed by the American College of Rheumatology (ACR) in 1971, and revised in 1982 and 1997 (table 5) (Hochberg et al, 1997). Classification criteria were developed to ensure a consistent case definition of SLE for inclusion in clinical research and randomized controlled trial: they are intended to be applied in patients to whom a clinical diagnosis of SLE was previously established. Nonetheless, these criteria are often used to assist diagnosis despite there are some caveats about their use for this purpose. The ACR criteria were developed and validated in patients with longstanding established disease and may exclude patients with early or limited disease. Some systems are over-represented, such as the mucocutaneous manifestations (photosensitivity, malar rash, discoid lesions and oral ulcers) (Bertsias et al, 2013). All features contribute equally without any weight based upon sensitivity and specificity.

Table 5 The revised ACR and the SLICC classification criteria for SLE

Criteria	ACR criteria (1997 update) (Tan et al, 1982; Hochberg, 1997)	SLICC criteria (2012) (Petri et al, 2012a*)
Skin	<ol style="list-style-type: none"> Malar rash (fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds) Discoid rash (erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occur in older lesions) Photosensitivity (skin rash as a result of unusual reaction to sunlight, by patient history or physician observation) 	<ol style="list-style-type: none"> Acute cutaneous lupus (lupus malar rash, do not count if malar discoid ; bullous lupus ; toxic epidermal necrolysis variant of SLE ; maculopapular lupus rash ; photosensitive lupus rash), or subacute cutaneous lupus (non-indurated psoriasiform and/or annular polycyclic lesions that resolve without scarring) Chronic cutaneous lupus (classic discoid rash: localised or generalised ; hypertrophic verrucous lupus ; lupus panniculitis profundus ; mucosal lupus ; lupus

		erythematosus tumidus ; chilblain lupus ; discoid lupus/lichen planus overlap) 3. Non-scarring alopecia
Ulcers	4. Oral or nasopharyngeal ulceration	4. Oral or nasal ulcers
Synovitis	5. Non-erosive arthritis (involving ≥ 2 peripheral joints, characterised by tenderness, swelling or effusion)	5. Inflammatory synovitis (in ≥ 2 joints: a. Characterised by swelling or effusion, or b. Tenderness and ≥ 30 min of morning stiffness)
Serositis	6. Any of: a. Pleuritis (convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion) ; b. Pericarditis (documented by ECG or rub or evidence of pericardial effusion)	6. Any of: a. Typical pleurisy (lasting >1 day, or pleural effusions, or pleural rub) b. Typical pericardial pain (pain with recumbency improved by sitting forward, for >1 day), or pericardial effusion, or pericardial rub or pericarditis by electrocardiography
Renal disorder	7. Any of: a. Persistent proteinuria >0.5 g/day, or $>3+$ if measurement is not performed ; b. Cellular casts : red cell, haemoglobin, granular tubular or mixed	7. Any of: a. Urine protein/creatinine (or 24 h urine protein) representing ≥ 500 mg of protein/24 h, or b. Red blood cell casts
Neurological disorder	8. Any of: a. Seizures ; b. Psychosis (in the absence of offending drugs or known metabolic derangements)	8. Any of: a. Seizures ; b. Psychosis ; c. Mononeuritis multiplex ; d. Myelitis ; e. Peripheral or cranial neuropathy ; f. Cerebritis (acute confusional state)
Haematological disorder	9. Any of: a. Haemolytic anaemia (with reticulocytosis) ; b. Lymphopenia ($<1500/\text{mm}^3$); c. Thrombocytopenia ($<100.000/\text{mm}^3$)	9. Haemolytic anaemia 10. Leukopenia ($<4000/\text{mm}^3$), or 11. lymphopenia ($<1000/\text{mm}^3$) at least once 11. Thrombocytopenia ($<100\ 000/\text{mm}^3$) at least once
Immunological disorder	10. Any of: a. Anti-DNA antibody to native DNA in abnormal titer; b. Anti-Sm (presence of antibody to Sm nuclear antigen) ; c. Positive finding of antiphospholipid antibodies (based on: 1. an abnormal serum concentration of IgG or IgM anticardiolipin antibodies ; 2. a positive test result for SLE anticoagulant ; or 3. a false-positive serological test for syphilis, known to be positive for ≥ 6 months and confirmed by negative <i>Treponema pallidum</i> immobilisation or fluorescent treponemal antibody absorption test)	12. Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range) 13. Anti-Sm 14. Antiphospholipid antibody positivity: lupus anticoagulant, false-positive test for syphilis (rapid plasma reagin), anticardiolipin (medium or high titer IgG, IgM, or IgA), or anti- $\beta 2$ glycoprotein 1 (positive IgG, IgM, IgA) 15. Low complement : low C3, or low C4, or low CH50 16. Direct Coombs' test (in the absence of haemolytic anaemia)

Antinuclear antibody	11. Abnormal titre of ANA (by immunofluorescence or an equivalent assay at any time and in the absence of drugs known to be associated with drug-induced lupus)	17. ANA (above laboratory reference range)
Classification of SLE	At least 4 out of 11 criteria	Either biopsy-proven lupus nephritis in the presence of ANA OR anti-dsDNA as a 'stand-alone' criterion, OR four criteria with at least one of the clinical and one of the immunological/ANA criteria

ACR, American College of Rheumatology; ANA, antinuclear antibody; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics.

The Systemic Lupus International Collaborating Clinics (SLICC) group undertook a revision of the ACR criteria using 'real-case patient scenarios' (table 5) (Petri et al, 2012a*). A patient is classified as having SLE if: (a) has biopsy-proven lupus nephritis (LN) with positive antinuclear antibody (ANA) or anti-dsDNA as a stand-alone criterion; or, (b) the patient satisfies four of the revised criteria, including at least one of the clinical and one of the immunological/ANA criteria. This classification rule had better sensitivity than the ACR criteria (97% versus 83%), at the cost of lesser specificity (96% versus 84%), but, importantly, resulted in fewer misclassifications in regard to the "gold-standard" expert clinical diagnosis.

Main differences introduced by the SLICC criteria include: one cutaneous criterion includes a larger number of acute and subacute manifestations as they largely overlap; the scope of neurologic manifestations was also expanded but still counted in one criterion and low complement was integrated in the immunologic criteria, reflecting its importance to disease pathogenesis. Another important aspect is that applying the SLICC criteria, biopsy-proven lupus nephritis is sufficient for classification of SLE in the presence of ANA or anti-dsDNA antibodies. One study with the GLADEL South-American registry found that the SLICC criteria may delay (or miss) the classification of SLE in some patients because of combining malar rash with photosensitivity (Pons-Estel et al, 2014). On the contrary, a multicentre European study found that in SLE patients with earlier disease (≤ 5 years since onset) the sensitivity of the SLICC criteria was higher compared to the ACR (93.2% versus 85.6%, respectively), because of the increased scope of clinical and immunologic features included (Inês et al, 2015*).

7 Monitoring SLE patients

Recommendations for the initial assessment and frequency of monitoring for patients with SLE are shown in table 6 (Tunnicliffe et al, 2015).

Table 6 Recommended initial assessment and monitoring of systemic lupus erythematosus**History: review of all systems**

Evaluate all presenting symptoms, intercurrents, including, but not limited to:

- Joint pain/swelling, Raynaud's phenomenon
- Photosensitivity, rash, hair loss,
- Shortness of breath, pleuritic chest pain
- General symptoms (depression, fatigue, fever, weight change)
- Comorbidities

Physical examination

Evaluate all features as suggested by history/symptoms, including, but not limited to:

- Mucocutaneous lesions
- Arthritis and other musculoskeletal features
- Lymphadenopathy, splenomegaly
- Cardiovascular and respiratory system

Imaging: laboratory data

- Haematology with complete blood count*
- Blood chemistry*
- Coagulation tests (PT/PTT), antiphospholipid antibodies
- Urine analysis (with protein/creatinine ratio)*
- Serology (ANA, ENA, anti-dsDNA*, complement C3, C4*)
- Chest X-ray examination
- ECG
- Other tests as suggested by history/symptoms

Disease activity index

At each visit or at least when considering major changes in treatment

Treatment side effects and compliance

At each visit

Damage index (SLICC)

Every 1 year

**Every 3–6 months, if stable. Every 1–3 months in patients with active disease.*

ANA, antinuclear antibody; ENA, extractable nuclear antigen; PT, prothrombin time; PTT, partial thromboplastin time; SLICC, Systemic Lupus International Collaborating Clinics.

7.1 Monitoring disease activity

Disease activity needs to be distinguished from damage as this has important implications for the appropriate treatment and the long-term prognosis. Several validated activity indices are used in the evaluation of patients with SLE (Urowitz and Gladman, 1998; Rao and Gordon, 2014*; Romero-Diaz et al, 2011*) including the European Consensus Lupus Activity Measure (ECLAM), the British Isles Lupus Assessment Group Index (BILAG), the Lupus Activity Index (LAI), the National Institutes of Health SLE Index Score (SIS), the Systemic Lupus Activity Measure (SLAM) and the SLE Disease Activity Index (SLEDAI) (SLEDAI-2K or SELENA-SLEDAI versions). SLEDAI is the most widely used (table 7). A crucial issue with the application of any of these indexes is that only

features attributable to active SLE should be scored. The use of at least one of these indices for monitoring disease activity is highly recommended (Vitali et al, 1999; Fanouriakis and Bertsias, 2015). Its use helps the clinician to quantify the disease activity in an objective and standardized way at each visit and in longitudinal follow-up to appreciate changes and response to treatment. However, the clinician should be well aware of the limitations of these instruments and use them as an aid and not a substitute for clinical judgment. These indices were shown to be predictors of damage and mortality, and reflect changes in disease activity (Lopez et al, 2012). For clinical trials, composite endpoints and responder indexes may be more useful (Navarra et al, 2011). Practical issues on monitoring disease activity are explored in the interactive clinical cases of this module.

Table 7 The Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K)

Weight	Descriptor	Definition
8	Seizure	Recent onset, exclude metabolic, infectious or drug causes
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Includes hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganised or catatonic behaviour. Exclude uraemia and drug causes
8	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
8	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal haemorrhages, serous exudate or haemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes
8	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves
8	Lupus headache	Severe, persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia
8	Cerebrovascular accident	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages or biopsy or angiogram proof of vasculitis
4	Arthritis	>2 Joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion)
4	Myositis	Proximal muscle aching/weakness, associated with raised creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis
4	Urinary casts	Haem-granular or red blood cell casts
4	Haematuria	>5 Red blood cells/high-power field. Exclude stone, infection or other cause

4	Proteinuria	>0.5 g/24 h
4	Pyuria	>5 White blood cells/high-power field. Exclude infection
2	Rash	Inflammatory type rash
2	Alopecia	Abnormal, patchy or diffuse loss of hair
2	Mucosal ulcers	Oral or nasal ulcerations
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening
2	Pericarditis	Pericardial pain with at least one of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation
2	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory
1	Fever	>38°C. Exclude infectious cause
1	Thrombocytopenia	<100 000 platelets $\times 10^9/L$, exclude drug causes
1	Leukopenia	<3000 white blood cells $\times 10^9/L$, exclude drug causes

For an item to be scored the indicated weight, the manifestation must have been present in the past 10 days (original SLEDAI-2k) or 30 days (SLEDAI-2k 30- day version) at attributed to active lupus disease activity.

7.2 Monitoring damage and comorbidities

The SLICC/ACR Damage Index (SDI) is a validated instrument designed to ascertain damage in SLE patients (table 8) (Chambers et al, 2009; Nossent et al, 2010). SLE-related damage may be due to the disease itself or to drug treatment, particularly glucocorticoids (Petri et al, 2012b; Yee et al, 2015*). Of note, the SDI scores only irreversible damage starting after the SLE diagnosis, and regardless of its attribution to SLE-related or non-related causes. SDI records damage in 12 organs or domains; furthermore, to ensure that the damage recorded is irreversible, most features are required to be present for at least 6 months before being scored. The scoring in SDI is categorical, however a weight >1 is attributed to some features. Up to 40–50% of patients with SLE develop damage within 5 to 10 years from disease diagnosis. Most frequently affected domains are the musculoskeletal, eyes (cataract), skin (scarring alopecia), cardiovascular, renal and neurological (Urowitz et al, 2012). Organ damage is a strong predictor of further damage accrual and increased patient mortality (Bruce et al, 2015*). However, the SDI does not consider many important comorbidities or any damage starting before the SLE diagnosis, which may significantly influence in an individual patient's quality of life and survival.

Practical issues on monitoring damage are explored in the interactive clinical cases of this module.

Table 8 The SLICC/ACR Damage Index for SLE

Item	Score
Ocular (either eye by clinical assessment)	
Any cataract ever	1
Retinal change or optic atrophy	1
Neuropsychiatric	
Cognitive impairment (eg, memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) or major psychosis	1
Seizures requiring treatment for 6 months	1
Cerebrovascular accident ever (score 2 if >1)	1, 2
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate <50%	1
Proteinuria >3.5 g/24 h	1
or End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiographical)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina or coronary artery bypass	1
Myocardial infarction ever (score 2 if >1)	1, 2
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic murmur, or systolic murmur >3/6)	1
Pericarditis for 6 months or pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (eg, loss of digit or limb) (score 2 if >1 site)	1, 2
Venous thrombosis with swelling, ulceration or venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if >1 site)	1, 2
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture or upper gastrointestinal tract surgery ever	1
Chronic pancreatitis	1, 2
Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reversible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if >1)	1, 2

Osteomyelitis	1
Tendon rupture	1
Skin	
Scarring chronic alopecia	1
Extensive scarring of panniculum other than sculp and pulp space	1
Skin ulceration (excluding thrombosis for >6 months)	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if >1 site)	1

SLICC, Systemic Lupus International Collaborating Clinics.

7.3. Assessment in special situations

7.3.1 Women's health issues and pregnancy

Most patients with SLE are women and the diagnosis is generally established in childbearing age. These patients present special needs regarding education, assessment and management on reproductive and other women's health issues. Important conditions to consider include pregnancy risks posed by antiphospholipid antibodies, anti-SSA/SSB (Ro/La) antibodies, lupus disease activity and medication adverse effects. Appropriate contraception and family planning are of paramount importance. With adequate management, most SLE patients can expect successful pregnancies. Antiphospholipid syndrome and pregnancy issues are approached in another module. The EULAR recently elaborated recommendations on women's health issues in SLE patients (Andreoli et al, 2017*).

7.3.2 Lupus in childhood and adolescence

About 15–20% of all SLE cases are diagnosed in childhood (Jimenez et al, 2003). Paediatric SLE may differ from adult SLE, in disease expression, physiological, developmental and psychosocial features. Knowledge of paediatric-onset SLE is more limited as compared to adult-onset, regarding epidemiology, long-term outcome and optimal management specificities (Ardoin et al, 2005). Despite that assessment principles applied in the adults are used for paediatric lupus, special needs of these populations should be taken into consideration (Lattanzi et al, 2011).

7.3.3 Elderly age

Later-onset SLE, after 50 years of age, occurs in 10-20% of patients. These tend to present less frequently with lupus nephritis, cutaneous features or cytopenias. However, disease activity and damage are not milder in this subgroup (Lalani et al, 2010). Differential diagnosis in late-onset SLE patients can be challenging, due to low SLE incidence and presentation with clinical features similar to those of more common disorders in this age group. An increasingly more frequent group is constituted by elderly patients with longstanding SLE, with earlier age of onset. In older patients, damage from SLE related and unrelated causes, as well as comorbidities,

have high prevalence and require careful assessment. Attribution of a feature to active SLE versus damage or comorbidities is also challenging: an example is the differential diagnosis of lupus arthritis in hand joints with previous osteoarthritis versus a flare of osteoarthritis.

7.3.4 Drug-induced lupus (DIL)

A variety of drugs have been identified as possible causes of lupus. DIL should be suspected in patients with no diagnosis or history of SLE, who develop a positive ANA and at least one clinical feature of lupus after an appropriate duration of drug exposure, and whose symptoms resolve when the drug is stopped. Clinical features include fever, myalgias, rash, arthritis and serositis. Haematological abnormalities, kidney disease and CNS lupus are uncommon. Anti-histone antibodies are present in >95%, whereas hypocomplementaemia and anti-DNA antibodies are rare, with the exception of disease associated with use of IFN α and anti-tumour necrosis factor therapies.

7.3.5 Emergencies, hospitalization and life-threatening illness

Patients with SLE may visit the emergency room owing to complications related to lupus itself or its treatment, or for unrelated reasons. Risk of incorrect attribution to SLE disease activity of unrelated health problems, as well as failure to diagnosis potentially life-threatening acute lupus manifestations are important challenges in the assessment of these patients in the emergency room. Poor compliance, low education level, infections, and high disease activity or damage are risk factors for hospitalization (Lee et al, 2013).

Life-threatening illness may develop from: (a) exacerbation of pre-existing or new manifestations of SLE; (b) infections; (c) adverse effects of drugs used to treat SLE or other concomitant conditions; (d) malignancy; and (e) acute serious illnesses that are unrelated to SLE (but whose manifestations may be altered by it).

Differential diagnosis of infections and SLE disease activity is challenging, and they can coexist, especially in acutely ill patients treated with high-dose glucocorticoids. The clinical (i.e. fever) and analytical (i.e. acute-phase reactants) features of infections can be masked by moderate to high-dose glucocorticoids.

Vascular acute events (myocardial or cerebrovascular) due to premature atherosclerosis are a frequent cause of morbidity in SLE patients and tend to present at an earlier age as compared to the general population (Bruce et al, 2000; Asanuma et al, 2003; Roman et al, 2003). Most coronary occlusive disease in SLE results from atherosclerosis or thrombosis. Cerebrovascular accidents can be caused by intracranial haemorrhage from ruptured aneurysms, thrombotic events from atherosclerosis or antiphospholipid antibodies, or from cardiac emboli (Futrell and Millikan, 1989; Kitagawa et al, 1990). Spinal cord transverse myelopathy is a devastating acute manifestation of SLE.

Acute abdominal pain in SLE may be secondary to mesenteric arterial thrombosis, ischaemic bowel, ruptured hepatic aneurysms, cholecystitis, perforated rectal ulcer, appendix, caecum or colon and pancreatitis

(McCollum et al, 1979; Kojima et al, 1997). An acute abdomen presentation can be masked by moderate to high glucocorticoids treatment. Patients with active SLE presenting with acute or subacute abdominal pain and high disease activity are more likely to have active mesenteric vasculitis and should be promptly referred for abdominal CT scan.

8 Prognosis

8.1 Predicting disease course and flares

Although treatment of lupus has dramatically improved survival, prolonged and complete remission—defined as 5 years without clinical and laboratory evidence of active disease and receiving no treatment—has remained elusive for many patients. The incidence of flare is estimated to be up to 0.50 flares per patient-year. Moreover, a significant number of patients (10–20% in tertiary referral centres) do not respond adequately to immunosuppressive therapies. Predictors of increased risk of flare include those patients with an earlier age at SLE diagnosis (≤ 25 years), those with previous lupus nephritis, neurologic or vasculitis involvement, high serum levels of anti-dsDNA, low C3, and those requiring treatment with immunosuppressants (Inês et al, 2014*; Petri et al, 2013).

8.2 Morbidity, comorbidities and mortality

The incidence of hospital admissions for patients with SLE is 0.69 admissions per patient-year. Infections, severe lupus disease activity in major organs, coronary artery disease and orthopaedic management of osteonecrosis are prominent reasons for hospitalization.

8.2.1 Infections

Infections account for 20–55% of all deaths in patients with SLE. Susceptibility to infections may be due to underlying immune deregulation and therapeutic factors, particularly high-dose glucocorticoids (GCs) and immunosuppressive drugs. A broad spectrum of infections has been reported in SLE (Navarra and Leynes, 2010). Risk factors are increased clinical and/or serological lupus activity (Jeong et al, 2009; Navarro-Zarza et al, 2010), major organ involvement, especially renal (Goldblatt et al, 2009) and lung involvement (Ruiz-Irastorza et al, 2009), persistent neutropenia ($<1000/\text{mm}^3$) (Dias et al, 2009), hypoalbuminaemia for severe CNS infections (Yang et al, 2007), high dose of glucocorticoids (Ruiz-Irastorza et al, 2009) and previous (within the past 6 months) use of cytotoxic drugs (Bosch et al, 2006; Zhou and Yang, 2009; Navarro-Zarza et al, 2010). Findings that favour the diagnosis of infection include rigors, leucocytosis and/or neutrophilia (especially in the absence of moderate/high dose glucocorticoid therapy), increased number of metamyelocytes on peripheral blood smear and concomitant immunosuppressive therapy. Diagnosis of SLE fever is more likely in the presence of leukopenia (not explained by cytotoxic therapy), normal or only slightly increased C-reactive

protein, low C3/C4 and raised anti-DNA antibodies. While awaiting microbiology results, antimicrobial therapy is recommended (Chen et al, 2008; Feng et al, 2010).

8.2.2 Atherosclerosis

Patients with SLE have an increased risk of developing coronary heart disease compared with age-matched controls. Aggressive treatment of dyslipidaemia (low-density lipoprotein-cholesterol <100 mg/dL, triglycerides <150 mg/dL) is recommended for patients with multiple risk factors, especially those with moderate/severe SLE, and with carotid thickening shown by ultrasound imaging.

8.2.3 Osteoporosis

In SLE patients, uncontrolled disease activity, premature menopause related to use of cyclophosphamide, relative vitamin D deficiency due to avoidance of sun exposure and the use of systemic glucocorticoids, all contribute to reduced bone mineral density and fragility fractures, in addition to those risk factors prevalent in the general population.

8.2.4 Malignancies

Haematological malignancies (particularly non-Hodgkin's lymphoma), lung, liver and thyroid cancer occur more commonly in SLE than in the general population (Tessier-Cloutier et al, 2014). Immunosuppressive therapy and intrinsic SLE-related mechanisms could account for this risk. Non-Hodgkin's lymphoma is associated with SLE (standardised incidence ratio: 4.4–5.7), with the most commonly identified histological subtype being diffuse large B cell lymphoma, which usually runs an aggressive course. Hodgkin's lymphoma is also more common in SLE. The risk for haematological malignancies may increase after exposure to immunosuppressive drugs, particularly in the 5 years after stopping treatment. Cervical dysplasia is increased in women with SLE owing to exposure to cytotoxic agents, particularly cyclophosphamide. Therefore, SLE should be regarded as a risk factor for HPV infection and cervical malignancy. Although the efficacy of HPV vaccine has not been investigated in patients with autoimmune diseases, the EULAR guidelines recommend that HPV vaccination should be considered for women with SLE as for the general population.

8.3 Prognosis of SLE in Europe

The 'Euro-Lupus Cohort' is composed of 1000 patients with SLE followed up prospectively since 1991 (Cervera et al, 1993; Cervera et al, 1999*; Cervera and Khamashta, 2006; Cervera et al, 2006; Cervera et al, 2009). Seventy-six of the 1000 patients (8%) developed the disease before the age of 14. Patients with childhood-onset SLE were more likely to have severe organ involvement, especially nephropathy, at presentation. Other major manifestations, such as neurological involvement, thrombocytopenia and haemolytic anaemia, were also common initial features in the childhood-onset group. However, during the disease evolution, the pattern

was quite similar in patients with childhood-onset disease and adult patients. Ninety patients (9%) developed the disease after the age of 50. Female predominance was not so pronounced in the older-onset group (5:1). The clinical picture in patients with older-onset disease best resembles that of patients with drug-induced SLE, primary Sjögren's syndrome or polymyalgia rheumatica. Typical SLE manifestations, such as malar rash, photosensitivity, arthritis or nephropathy, were less common than in younger patients, whereas sicca syndrome was common. A higher prevalence of serositis was found in male patients at presentation. In contrast, arthritis occurred less commonly in men. During disease evolution, a lower prevalence of arthritis was found in the male subjects. The prevalence of nephropathy, neurological involvement, thrombocytopenia, vasculitis and serositis was similar in both groups. No significant immunological differences were found between men and women. The frequencies of the main lupus manifestations during the initial 10 years of the 'Euro-Lupus Cohort' are slightly lower than those reported in large series from America and Asia. There was a lower frequency of most SLE manifestations during the last 5 years (1995–2000) (Cervera et al, 1999*), compared with the cumulative clinical manifestations during the initial 5 years of the study (1990–1995). In the Euro-Lupus Cohort, 10 years after entry into the study, survival was 92% (Cervera et al, 2001). The slightly higher survival in this cohort than in the American series may be due to the predominance of Caucasian patients (97%). There was a similar percentage of patients with active SLE (27%), thromboses (27%) and infections (25%) as the main causes of death. However, when the causes of death during the initial 5 years were compared with those during the ensuing 5 years, active SLE and infections (29%, each) appeared to be the most common causes during the initial 5 years, while thromboses (26%) became the most common cause of death during the last 5 years.

9 Patient-reported outcomes and socioeconomic impact

There are a number of patient-reported outcomes (PRO) that can be assessed with validated indexes in SLE patients. These include indexes for screening possible disease activity, organ damage, health-related quality of life (HRQoL), fatigue and work productivity (Holloway et al, 2014*).

The Systemic Lupus Activity Questionnaire (SLAQ) was developed for surveying disease activity in large groups of SLE patients in population studies and can be self-administered outside the clinical setting (Karlson et al, 2003; Yazdany et al, 2008; Chehab et al, 2015). For the same setting, organ damage can be estimated with the Brief Index of Lupus Damage (BILD) (Yazdany et al, 2011; Chehab et al, 2013) or the Lupus Damage Index Questionnaire (LDIQ) (Costenbader et al, 2010).

The self-perception of quality of life is significantly lower in SLE patients compared to the general population (Stoll et al, 1997). Impairment of HRQoL may result from a variety of intermingled factors, including disease activity, organ damage, comorbidities (such as fibromyalgia), adverse effects from medication and socioeconomic factors. This is an outcome of central importance from the patient's perspective and should be

taken in consideration in the clinical setting for facilitating shared decision on management goals (Mahieu et al, 2016). HRQoL measures are included in clinical trials and observational studies of SLE patients (Annapureddy et al, 2016). Both generic instruments, such as the Short form 36 (SF-36) (Stoll et al, 1997), and SLE-specific HRQoL tools are used. The lupus-specific tools include the Lupus Patient Reported Outcome (LupusPRO) (Jolly et al, 2012), LupusQoL (McElhone et al, 2007) and SLEQOL (Leong et al, 2005).

Compromise of HRQoL is an important component of the global burden of SLE. This intangible cost adds to high direct (healthcare) and indirect costs owing to loss of economic productivity associated with SLE (Carter et al, 2016*). Expensive new drugs are in development aiming to fulfil unmet needs for SLE treatment. However, outcomes of the SLE population are recognized to be greatly impacted by failure to extend benefits of current evidence-based management recommendations to many patients. Unfavourable disease outcomes are associated with poverty, low educational status, lack of access to appropriate healthcare, poor social support and treatment compliance issues (Alarcón et al, 2006; Carter et al, 2016*).

10 Evidence-based recommendations for the management of SLE

The EULAR has developed recommendations covering the most important aspects of the management of SLE (Bertsias et al, 2008*; Bertsias et al, 2010a*; Bertsias et al, 2012*; Andreoli et al, 2017*). These can be freely accessed at the EULAR site. Management and treatment of SLE is discussed in the next module.

11 Recommended textbooks

1. Dubois' Lupus Erythematosus and Related Syndromes. Eds. Wallace D, Hahn BHH. Saunders, 8th Edition, 2012.
2. Systemic lupus erythematosus. Ed. Lahita G. 5th edition. Elsevier, Amsterdam, 2011.

12 SLE: internet sites

<http://www.lupus.org>

<http://www.lupus.uk.com>

<http://www.mayoclinic.com/health/lupus/DS00115>

<http://www.lupus.org.uk>

<http://www.lupusresearchinstitute.org>

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SUMMARY POINTS

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterised by a broad spectrum of multisystemic manifestations.
- The pathogenesis of SLE is complex and includes genetic, hormonal and environmental factors.
- Peak onset is between the ages of 16 and 55. Women are affected up to twelve times more frequently than men.
- Age at onset, gender, ethnicity and immunological features influence the prevalence of clinical manifestations and disease evolution.
- Classification criteria were developed to ensure a consistent case definition of SLE for inclusion in clinical research and trials.
- There are no diagnostic criteria or pathognomonic features for the disease. The diagnosis is based on clinical and analytical features, while considering alternative causes for the clinical picture.
- Several validated activity indices are used to monitor disease activity in SLE patients. The SLICC/ACR criteria is a validated instrument to ascertain damage.
- There were significant improvements in long-term survival but patients with SLE still have higher morbidity and mortality than the general population.
- Factors contributing to mortality include high disease activity, damage accrual and low socioeconomic status. Infections, cardiovascular disease, malignancy and disease activity are major causes of death.

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module

EULAR on-line course on Rheumatic Diseases

Systemic lupus erythematosus:

Pathogenesis and clinical features

Marília Rodrigues, Luís Sousa Inês and Caroline Gordon

Previous versions were coauthored by Sofia Tosounidou, George Bertsias, Caroline Gordon, Dimitros T. Boumpas, Ricard Cervera, Gerard Espinosa, David D'Cruz

IN-DEPTH DISCUSSION I

Neuropsychiatric manifestations in SLE

Introduction

Neuropsychiatric (NP) manifestations in SLE include a wide range of neurologic and psychiatric features. Despite advances in the understanding of the pathogenic and clinical aspects of SLE, neuropsychiatric features remain a diagnostic and therapeutic challenge (Govoni *et al.*, 2016). Major difficulties include the selection of adequate diagnostic workup, correct attribution of neuropsychiatric manifestations to SLE or other causes and the appropriate management in view of the paucity of trial data (Hanly, 2014).

Epidemiology

The reported prevalence of NP in SLE ranges from 12% to 95% (Bertsias and Boumpas, 2010). This wide range owes to differences in research methodology, cohort characteristics, diagnostic workup and attribution of neuropsychiatric events to SLE. A key concept is that most of NP manifestations in SLE patients are not attributable to lupus disease activity (Hanly *et al.*, 2010). The American College of Rheumatology (ACR) Ad Hoc Committee on Neuropsychiatric Lupus has proposed a nomenclature for 19 NP syndromes known to occur in SLE patients (The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes, 1999). These standardized NP definitions are useful both in clinical practice and in research but do not imply any assumption of attribution to SLE. Mild NP syndromes such as headache or mood disorders are the most common: in a prospective international inception cohort study, the prevalence of headache was 58% after 10 years of follow-up (Hanly *et al.*, 2013); mood disorders occurred in 13% of the patients (Hanly *et al.*, 2015). Most of these NP syndromes were not associated with lupus disease activity and attributed to non-SLE causes. (Hanly *et al.*, 2013; Hanly *et al.*, 2015). Clinically severe NP involvement attributable to SLE is rare: in a prospective study of 360 patients from a Greek cohort over 3 years, the frequency of major central nervous system (CNS) events attributed to lupus was 4.3% (Kampylafka *et al.*, 2013). Due to the complex and interrelated aetiopathogenic mechanisms, NP events may occur in SLE patients at any time of the disease course.

Risk Factors

SLE-specific Risk Factors

Persistently positive, moderate-to-high titers of antiphospholipid antibodies (aPL) were associated to at least a fivefold increased risk of major NP events in SLE patients (Bertsias *et al.*, 2010). Positive aPL were associated with cerebrovascular disease (CVD), seizures, myelopathy, chorea and moderate to severe cognitive dysfunction (Sanna *et al.*, 2003). In a multicentre retrospective cohort study of 959 SLE patients, aPL emerged as the strongest risk factor for focal NP syndromes (Govoni *et al.*, 2012).

Previous or concurrent major NP syndromes, particularly stroke and seizures, were predictive of future NP events in several studies (Bujan *et al.*, 2003). Other consistent risk factor for NP manifestations is increased SLE activity and damage, with a robust association to seizure disorders and severe cognitive dysfunction. Indeed, increased systemic SLE disease activity was associated with concurrent NP events attributed to SLE, particularly for diffuse NP and CNS NP events (Morrison *et al.*, 2014). It is important to emphasise that although rare, the absence of overt SLE activity does not exclude that NP manifestations due to SLE. However, it implies a careful assessment of all the mimics (Rodrigues *et al.*, 2017).

SLE non-specific Risk Factors

Non-SLE related factors such as older age, hypertension, dyslipidaemia and other traditional risk factors were related to cognitive dysfunction, depression and CVD (Govoni *et al.*, 2016). Fibromyalgia and social impairment are increased in SLE patients and associated to depression, anxiety and mild memory and cognitive problems. Large studies correlated these factors to SLE duration and to the chronic burden of the disease rather than to SLE disease activity (Torrente-Segarra *et al.*, 2016). Other frequent risk factors in SLE patients, such as infection, metabolic disturbances and medication effects, especially glucocorticoids (GC), were associated to diverse NP syndromes (Bhangle *et al.*, 2013).

Pathogenesis

NP syndromes in SLE patients can result from lupus-specific mechanisms such as vascular abnormalities, autoantibodies and inflammatory mediators. These may interact in complex pathogenic mechanisms.

Vascular abnormalities

A vascular occlusive process is the most commonly reported. SLE-associated vasculopathy enhanced by endothelial activation and injury mediated by aPL is a plausible mechanism. The activation of the clotting cascade with hypercoagulable state increases the susceptibility to thrombotic phenomena both in large and small vessels (Belmont *et al.*, 1996). A true inflammatory process characterised by vasculitis with a transmural infiltrate and fibrinoid necrosis is rare (Rodrigues *et al.*, 2017).

Autoantibodies

A potential pathogenic role was proposed for anti-neuronal and anti-glutamate-receptor antibodies. The first was found to be elevated in the cerebrospinal fluid (CSF) of SLE patients with NP manifestations (Kang *et al.*, 2008). The latter was related in experimental studies to hippocampal apoptosis and cognitive dysfunction. Anti-ribosomal-P antibodies are found in up to 25% of patients with SLE. Their association with NP syndromes such as psychosis and depression were reported in some studies but remains controversial (Hanly *et al.*, 2011). In animal models, enhanced permeability of the blood-brain barrier is critical for the access of antibodies to

the cerebral parenchyma (Kowal *et al.*, 2004). Both SLE factors (immune complex or cytokines) and non-SLE factors (smoking or hypertension) may have a combined role on the barrier dysfunction that is a key factor for the pathogenesis of NP syndromes.

Inflammatory mediators

In experimental studies, neuronal and glial cells produce several cytokines in response to the presence of autoantibodies within the intrathecal space. Proinflammatory cytokines that may contribute to pathogenesis of NP manifestations include interferon- α , IL-2, IL-6, IL-8 and IL-10 (Trysberg *et al.*, 2000).

Classification of Neuropsychiatric manifestations in SLE

In the ACR nomenclature for neuropsychiatric syndromes in SLE, these are divided in two groups, depending whether there is central or peripheral nervous system involvement (Box 1). For each of these syndromes, a complete case definition, diagnostic criteria, and methods for ascertainment are proposed for use in clinical practice and research studies. This case definition provided a standardized description for each clinical NP syndrome. Conditions that act as confounders were identified for either exclusion (infection, neoplasia, nervous system primary disease) or recognition as association (hypertension, smoking, diabetes, GC), acknowledging that in some cases a definite attribution is not possible. The nomenclature also intends to expand the neurologic criteria (seizures, psychosis) included in the 1997 ACR classification for SLE. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) further included mononeuritis multiplex, myelitis, peripheral or cranial neuropathy and acute confusional state in the neurological criteria for SLE classification (Petri *et al.*, 2012). Both ACR and SLICC classification criteria require a confirmed attribution of the NP syndromes to SLE.

Although the ACR classification for NP syndromes standardizes reporting, its use does not replace clinical judgement, since its purpose is not diagnosis. Any of the ACR NP clinical syndromes in SLE patients can be directly caused by SLE or derived from other causes. Furthermore, a few NP syndromes observed in SLE were not included, such as neuromyelitis optica or posterior reversible encephalopathy syndrome (Barber *et al.*, 2011).

Box 1 Neuropsychiatric syndromes in systemic lupus erythematosus.**Central nervous system**

- Aseptic meningitis
- Cerebrovascular disease
- Demyelinating syndrome
- Headache (including migraine and benign intracranial hypertension)
- Movement disorder (chorea)
- Myelopathy
- Seizure disorder
- Acute confusional state
- Anxiety disorder
- Cognitive dysfunction
- Mood disorder
- Psychosis

Peripheral nervous system

- Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)
- Autonomic disorder
- Mononeuropathy, single/multiplex
- Myasthenia gravis
- Neuropathy, cranial
- Plexopathy
- Polyneuropathy

To request the complete Appendix with case-definition, exclusions and associations, contact:

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Diagnosis

The initial evaluation of patients with SLE presenting NP manifestations should aim to exclude the most important mimics before concluding for SLE-mediated CNS dysfunction (Figure 1). The differential diagnosis includes infection, neoplasia, metabolic disturbances, cardiovascular events, drug abuse and medication side effects. A complete medical history and physical examination focusing on past or recent signs of these conditions should be methodically performed.

Glucocorticoids assessment is also an important issue. Association with NP manifestations was reported considering different views: active disease with NP manifestations requiring glucocorticoids for its treatment or glucocorticoids side-effects. Regarding the side-effects, GC are associated with atherosclerosis in SLE, a

frequent mechanism for stroke and other NP syndromes (Doria *et al.*, 2003). Other well recognized side-effect are psychological and behavioural disorders. GC were linked with psychosis, cognitive dysfunction and other NP features. A GC dose-dependent effect was observed in most of these cases (Bhangle *et al.*, 2013)

Depending on the NP manifestations, the diagnostic workup might include biochemical and serological tests, echocardiography and ecodoppler (to exclude cardioembolic disease), lumbar puncture and CSF analysis (to exclude infectious, bleeding or malignant process), electroencephalography (to diagnose seizure disorder) and neuroimaging (to assess brain structure and function) (Table 1).

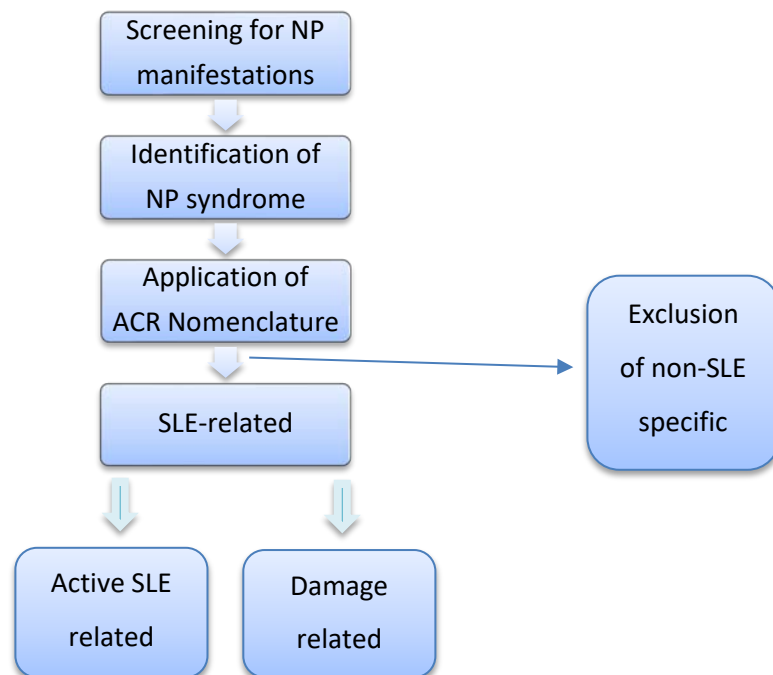


Figure 1 Management of NP manifestations in SLE.

Of all the autoantibodies and serum biomarkers tested, aPL have the greatest diagnostic utility in NP syndromes, especially in patients with focal symptoms or cognitive decline. The association between NP manifestations and other autoantibodies is less clear and careful interpretation should be made combining clinical and imaging data.

Lumbar puncture for CSF analysis is important to exclude non-SLE causes as infection, SNC bleeding or malignancy. The presence of high-risk features as severe or explosive headache onset, fever or concomitant infection, focal neurological signs, decreased level of consciousness, meningismus, overt SLE activity, aPL or antiphospholipid syndrome, use of immunosuppressants or anticoagulants support this diagnostic approach (Bertsias and Boumpas, 2010). Intrinsic immunological defects in SLE, especially in CD4 cells, may predispose SLE patients to opportunistic fungal infections, even without administration of immunosuppressive agents (Hung *et al.*, 2005). Therefore, bacterial (*Listeria monocytogenes*, *Staphylococcus aureus*, *Klebsiella*

pneumonia, Mycobacterium tuberculosis), opportunistic fungal infection (*Cryptococcus neoformans, Aspergillus fumigatus*), viral and parasitic infections need to be considered for the CSF analysis (Yang *et al.*, 2007).

MRI is the current gold standard for cerebral and spinal NP imaging (Bertsias *et al.*, 2010). It is a sensitive method to detect NP typical lesions and to exclude other causes (neoplasia, infection). The most specific pathological pattern in MRI are punctuate, T2-hyperintense lesions in the subcortical and periventricular white matter. However, these lesions are also found in SLE patients without neuropsychiatric manifestations (specificity 60–82%) (Sibbitt *et al.*, 2003). In cases with normal MRI or dissociation between MRI findings and clinical symptoms, quantitative MRI or radionuclide brain scanning may be considered.

Table 1 Clinical reporting, diagnosis and management of NP manifestations.

Clinical reporting		
Demographic	Age, Sex, Ethnicity	
	Highest schooling completed	
SLE Descriptors	Duration	
	Classification Criteria for SLE	
	Basic Laboratory Data	
	Current medications	
	Disease Activity and Damage	
NP Descriptors	Duration	
	Chronology (episodic, remittent, sustained, progressive)	
	Severity (mild, moderate, severe)	
	Isolated or with systemic SLE activity	
	Initial and final diagnosis or diagnoses	
Screening		
Complete Blood Count		
Serum biochemical test	Glycaemia, Uraemia, Na ⁺ , Ca ²⁺ , uraemia, vitamin deficiencies (B12), thyroid function tests	
Autoantibodies	aPL	
Cardiovascular Risk Factors	Dyslipidaemia, Hypertension, Cigarette smoking	
Exposures	Anticholinergics, Sedatives, Glucocorticoids, Drug abuse	
Investigations		
Lumbar Puncture	Infection	CSF biochemical analysis and culture
	Neoplasia	

Electroencephalography	Seizure Disorder	
Electrocardiography	Cerebrovascular Disease	Identification of rhythm and structural abnormalities.
Echocardiography		
Carotid Ecodoppler		Detection of atherosclerotic lesions.
Neuropsychological Tests	Cognitive Dysfunction	Diagnosis and Monitoring
Neuroimaging	Focal NPSLE	MRI
	Diffuse NPSLE with high-risk features after exclusion of non-SLE causes	(T1/T2-weighted, FLAIR, DWI, gadolinium-enhanced T1- sequences)
	Antiphospholipid Syndrome	
Management		
Symptomatic	Mood Disorder	Antidepressant
	Seizure	Anticonvulsant
	Psychosis	Antipsychotic
Immunosuppression	Immune or inflammatory aetiology	Glucocorticoids CYC, MMF, AZA Rituximab, IVIG
Anticoagulation	Vascular injury mediated by aPL	Acetylsalicylic acid Heparin Warfarin

Management

The identification and treatment of triggering or aggravating factors such as cardiovascular disorder, infection, metabolic abnormalities and drug adverse effects (GC and others) is important in all patients. Symptomatic therapy with anticonvulsants (seizure disorder), antidepressants (mood disorders) or antipsychotics (psychosis) should be considered when appropriate (Bertsias *et al.*, 2010). Therapy targeting immune or inflammatory activity is considered after exclusion of non-SLE related causes (Table 1). The selection of therapy upon the predominance of an inflammatory or thrombotic process is fundamental. The only trial of immunosuppressive therapy in NP syndromes in SLE found a significantly better response to combination therapy with intravenous cyclophosphamide than with intravenous methylprednisone alone (Barile-Fabris *et al.*, 2005). There is less evidence for efficacy of azathioprine (AZA) and mycophenolate mofetil (MMF). In some refractory NP syndromes, use of plasma exchange, intravenous immunoglobulin (IVIG) and rituximab (RTX) was reported with varying rates of success (Tokunaga *et al.*, 2007; Camara *et al.*, 2014; Kronbichler *et al.*, 2016). Antiplatelet therapy with or without anticoagulation is recommended when manifestations are related to aPL. Cohort studies suggest a role for antiplatelet agents in the primary prevention of aPL-associated

thrombotic CVD (Tektonidou *et al.*, 2009). Intensive treatment with anticoagulation may be considered for secondary prophylaxis of CVD. In the absence of controlled trials to guide the type, intensity and duration of anticoagulation a similar approach may be inferred from studies in patients with antiphospholipid syndrome (Pengo *et al.*, 2012).

Prognosis

Regardless of attribution, NP manifestations result in decreased quality of life, work disability and increased unemployment (Hanly *et al.*, 2010). The importance of NP involvement on damage accrual in patients with SLE is also reflected in the inclusion of five of the NP syndromes in the SLICC/ACR Damage Index for SLE (Gladman *et al.*, 1996).

Conclusion

NP involvement in SLE is associated with significant morbidity and poor functional outcomes. The diagnosis should rely in a careful clinical assessment and selection of appropriate workup. A complete and standardized characterization and correct attribution to SLE or non-SLE causes represent a crucial point in the effective management of NP manifestations. Further research on biomarkers and neuroimaging may provide better definition of pathogenic mechanisms, diagnostic and treatment strategy, and prognosis.

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module

EULAR on-line course on Rheumatic Diseases

Systemic lupus erythematosus: pathogenesis and clinical features

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IN-DEPTH DISCUSSION II

Shrinking lung syndrome

Introduction

Pleuropulmonary involvement may occur in about 60% of patients with SLE (Orens *et al* 1994). Subclinical involvement occurs even more frequently, with autopsy series reporting a prevalence of up to 93% (Ropes *et al* 1976). SLE may affect all the components of the respiratory system, including airways, lung parenchyma, pulmonary vasculature, pleura and respiratory muscles (Table 1). Pleuritis, with or without pleural effusion is by far the commonest pleuropulmonary manifestation of SLE. A less common but more serious entity is the shrinking lung syndrome (SLS) and this in-depth discussion reviews the clinical features, pathogenesis, investigations, management and outcome of SLS.

SLS was first reported by Hoffbrand *et al* in 1965 who described lupus patients with unexplained dyspnoea, small lung volumes, elevation of the diaphragm, and restrictive physiology. The overall prevalence of SLS in a large multi-ethnic cohort of lupus patients was 0.6%. Higher prevalence (6%) was reported among SLE patients with refractory disease (Bertoli *et al* 2007, Traynor *et al* 2005). SLS was also found in other rheumatic diseases including systemic sclerosis, rheumatoid arthritis and undifferentiated connective tissue disorder. SLS may complicate SLE at any stage with the mean time of SLS onset estimated at 4.3 years after diagnosis of lupus; rarely SLS can be the first manifestation of SLE.

Table 1: Respiratory involvement in SLE

a. Parenchymal involvement	I. Acute lupus pneumonitis
	II. Chronic interstitial lung disease
b. Pleural involvement	Pleurisy with or without effusion and fibrosis
c. Vascular involvement	<i>Non-thromboembolic disease</i>
	I. Diffuse alveolar haemorrhage
	II. Pulmonary arterial hypertension
	III. Acute reversible hypoxaemia
	<i>Thromboembolic disease</i>
d. Diaphragmatic involvement	Shrinking lung syndrome
e. Airways involvement	Bronchiolitis obliterans

Pathogenesis

The pathogenesis of SLS remains elusive. The most recent case report supports the hypothesis of pleural inflammation as the main mechanism of lung restriction in SLS. For the first time, authors implemented the use of dynamic contrast-enhanced lung MRI revealing marked pleural and pericardial enhancement (Nemec *et al* 2015). The wider use of this imaging technique may reproduce similar findings thus helping us to

understand the origin of this syndrome. Rarity of SLS and absence of pathologic data have led to a number of speculative aetiologies for SLS (summarised in Table 2).

SLS was initially thought to be related to alveolar micro-atelectasis and hyaline membrane formation resulting from pulmonary surfactant deficiency. Later, Gibson *et al* demonstrated diaphragmatic dysfunction evidenced by abnormal transdiaphragmatic pressures. It was thought that diaphragmatic weakness was a consequence of pleural adhesions, however later studies failed to confirm the link between the pleural adhesion and diaphragmatic weakness. The literature contains a single post-mortem study by Rubin and Urowitz who found no evidence of pleural adhesions and concluded that SLS was not due to primary lung disease or to diaphragmatic dysfunction related to pleural adhesions.

Marten *et al* supported the theory of weakness of both inspiratory and expiratory muscles caused by SLE. This notion was later rejected by Laroche *et al* who studied 12 patients with SLS using more reliable measures of respiratory muscle function and found that the reduction of vital capacity (VC) was due to abnormal chest wall expansion of uncertain aetiology. The theory of steroid induced diaphragmatic weakness was rejected because of improvement in lung function on increased immunosuppression. Wilcox *et al* who assessed phrenic nerve function in 9 patients with SLE with diaphragmatic weakness found no causative link.

Ishii *et al* proposed an association between SLS and anti- Ro antibodies based on 4 cases in the literature although they did not suggest a putative mechanism. Toya *et al* given the increased frequency of pleuritic chest pain suggested interaction between pleural inflammation and diaphragmatic dysfunction through pain-induced reflex inhibition of diaphragmatic activation.

Overall, the cause of SLS seems to be interplay between diaphragmatic dysfunction and pleural inflammation.

Table 2: Proposed aetiologies for pathogenesis of SLS

Author	Proposed aetiology
Hoffbrand and Beck, 1965	Alveolar micro atelectasis and hyaline membrane formation from surfactant deficiency
Gibson <i>et al</i> , 1977	Diaphragmatic dysfunction secondary to pleural adhesions
Marten <i>et al</i> , 1983	SLE induced inspiratory and expiratory myopathy
Laroche <i>et al</i> , 1989	Abnormal chest wall expansion of unknown aetiology
Hardy <i>et al</i> , 2001	Neurogenic origin through phrenic involvement
Wilcox <i>et al</i> , 1988	Evidence against phrenic nerve neuropathy
Toya <i>et al</i> , 2009	Pain-induced reflex inhibition of diaphragmatic activation
Ishii <i>et al</i> , 2000	Association with anti-Ro antibodies
Nemec <i>et al</i> , 2015	Pleural and pericardial inflammation

Clinical features

SLS typically presents with dyspnoea of variable severity progressing from exertional breathlessness to dyspnoea at rest. Dyspnoea is generally worse in the supine position with abdominal paradox commonly seen. Pleuritic chest pain is often reported, whereas dry cough and fever are rarely seen. Orthopnoea may occur because of diaphragmatic weakness. Past medical history may reveal pleurisy and, less commonly, pericarditis and/or myopathy. Poor chest expansion, rapid shallow breathing, and use of accessory muscles are found on clinical examination. Lung auscultation is usually normal although bibasal crepitations can be heard in the presence of basal atelectasis.

Diagnosis

Elevation of the diaphragm is a universal radiographic finding. Pleural effusions, pleural thickening or atelectasis are other infrequent findings. Chest CT and lung V/Q scan show no evidence of parenchymal involvement or thromboembolism. Bronchoscopy and bronchoalveolar lavage are unrevealing. Lung biopsy,

open or transbronchial, demonstrated normal lung tissue and a case report of an open pleural biopsy to investigate the area of pleural thickening on chest X-ray, showed fatty tissue.

Pulmonary function tests (PFTs) are consistent with a restrictive pattern and reduced total lung capacity (TLC). Carbon monoxide gas transfer capacity (DLCO) is reduced but the KCO (i.e. corrected for alveolar volume) is often normal.

The principal advantages of volitional tests are that they give an estimate of inspiratory or expiratory muscle strength, are simple to perform, and well tolerated. Maximal inspiratory pressure (MIP) generated at the mouth is a measure of global inspiratory muscle strength and it is usually reduced in SLS patients. Maximal expiratory pressure (MEP) at the mouth is not affected by diaphragmatic function, and a pattern of reduced MIP and normal MEP is consistent with diaphragmatic weakness. However, MIP and MEP may underestimate respiratory muscle strength due to incomplete activation of the muscles during the manoeuvre; hence a sniff technique measuring nasal pressures produces more reliable estimation of the inspiratory muscles. The disadvantage of mouth and nasal sniff pressures is that they don't discriminate weakness between the different respiratory muscles.

To increase diagnostic accuracy, we can measure relaxed VC in the supine and erect position alongside MIP/MEP and a sniff manoeuvre to look for diaphragmatic weakness. To evaluate the diaphragmatic movements, which are commonly reduced in SLS, ultrasound or fluoroscopy can be useful.

Finally, blood tests show typically normal creatinine kinase levels except for patients with myositis secondary to SLE.

Treatment

To date there is no universally agreed treatment approach for SLS, due to the absence of randomised controlled trials of treatment for SLS, uncertainty of its cause and different therapeutic strategies proposed by different investigators. Most reports describe the efficacy of oral corticosteroids (20mg/day to 1mg/kg/day of prednisolone) often preceded by pulses of intravenous methylprednisolone. Symptomatic improvement of patients receiving high doses of steroid starts within 48 hours, although major response usually takes several weeks to months. An increase in lung volumes is usually observed on high dose steroids, although the timing of improvement is variable. In severe cases, immunosuppressive agents, such as cyclophosphamide, azathioprine, mycophenolate mofetil and methotrexate in conjunction with corticosteroids were used with variable success (Duron et al, 2016; Borrel et al, 2016). There were several case reports in the literature supporting the use of B cell depleting therapy (e.g. Rituximab) in refractory cases of SLS (Toya *et al* 2009).

Other therapies that were tried, include theophylline and high-dose β agonists, mainly employing their effect of improving diaphragmatic strength (Van Veen *et al* 1993, Thompson *et al* 1985). A 31% improvement in lung

capacity was observed in SLS patients receiving theophylline, which can be tried alone or in combination with steroids. The use of β -agonists in SLS comes from case reports and a decrease of diaphragmatic fatigue is observed through their positive inotropic effect.

In a case report of SLS, implementation of nocturnal non-invasive positive pressure ventilation (NIPPV) alongside immunosuppressive therapy led to diaphragmatic improvement, demonstrated by improved PFTs parameters (Panchabhai *et al* 2016).

Prognosis

The overall prognosis of this syndrome is good. There is evidence from previous case reports and series that subjective improvement on initiation of treatment can be observed in almost 80% of patients (Duron *et al*, 2016; Borrel *et al* 2016). Objective improvement measured by either improved pulmonary function tests or respiratory pressures is observed up to 20% of patients. Death due to respiratory failure or associated complications is rare (Karim *et al* 2002).

Conclusion

SLS affects a small proportion of lupus patients causing significant morbidity. It should be considered a possible diagnosis in lupus patients presenting with dyspnoea. The underlying aetiology remains elusive. Given its rarity, randomized controlled trials are unavailable and controversies about its pathogenesis and therapy persist.

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Systemic lupus erythematosus: treatment

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LEARNING OBJECTIVES

- ➔ Select the best treatment for patients with simple and complex manifestations of systemic lupus erythematosus (SLE) including lupus nephritis (LN)
- ➔ Support your treatment decisions on the basis of evidence
- ➔ Appreciate the risks and side-effect profiles of commonly used medications for SLE
- ➔ Critically manage the risk factors for cardiovascular disease and other comorbidities
- ➔ Evaluate which drugs can be used during pregnancy and how to treat active SLE during pregnancy

Treatment of systemic lupus erythematosus (SLE) has several goals: (i) induction of a prompt response, aimed at controlling disease activity; (ii) maintenance therapy, aimed at maintaining the response and at preventing flares; and (iii) prevention and treatment of comorbidities (e. g. hypertension, diabetes mellitus, osteoporosis) and of drug-induced damage. The armamentarium of therapies for SLE include glucocorticoids, antimalarials, conventional synthetic immunosuppressive drugs as well as biologic therapies. During the last two decades, major improvements in the treatment of SLE can be mainly attributed to a better use of traditional immunosuppressive drugs. Although an array of new biological drugs has been developed and tested in the last decades and more are underway, only one new drug, belimumab, has been approved for the treatment of SLE.

The first part of this chapter is dedicated to review the scientific evidence for the use of different drugs; in the second part, we propose therapeutic protocols dealing with specific organ involvement; finally, comorbidities and non-adherence will be discussed. Specific treatment for the antiphospholipid syndrome is described in another chapter.

The reader is strongly encouraged to read the EULAR, EULAR/ERA-EDTA and ACR recommendations for the treatment of lupus and lupus nephritis (LN) (Bertsias, 2008; Bertsias, 2012; Hahn, 2012), and to integrate a treat-to-target approach in her/his daily practice (Mosca, 2012; van Vollenhoven, 2014).

1. THERAPEUTIC AGENTS

1.1 Glucocorticoids

Glucocorticoids (GCs) are the mainstay of treatment of SLE as induction therapy and to manage acute flares and have dramatically improved the prognosis of severe SLE. Thus, survival rates have increased from 50% at 3 years in the 1950s (Jessar, 1953) to 92% at 10 years in recent series (Cervera, 2003). GC regimens vary from low dose (0.1-0.2 mg prednisone/kg/day or equivalent) to moderate (0.2-0.5 mg/kg/day) or high (0.5-1 mg/kg/day) dose, according to the type of organ involvement, as discussed below. Of note, these dosages of GCs based on body weight and especially the high dose of 1mg/kg/day are not evidence-based. As much as the use of GCs has improved the outlook of SLE, limiting their use is of equal importance, since evidence is accumulating that GCs might contribute to irreversible damage (Al Sawah, 2015). Interestingly, the initial dose of prednisone in the first month of treatment is predictive of the prednisone doses over the following 11 months (Ruiz-Irastorza, 2016).

Intravenous (IV) pulse methylprednisolone therapy, mostly 500-1,000 mg daily for 1-3 days, was introduced in the 1970s (Cathcart, 1976) and is remarkably efficacious in critically ill patients (Isenberg, 1982), suffering renal impairment, central nervous system disease, severe arthritis, pleuropericarditis or thrombopenia, although the

jury is still out regarding the dose of IV methylprednisolone needed to achieve rapid control of activity (Franchin, 2006).

Tapering schedules are mainly based on physician's experience and clinical judgment. In the National Institute of Health (NIH) protocol for the treatment of lupus nephritis (LN), after three IV methylprednisolone pulses (1,000 mg/day for three days), patients were given oral prednisone 0.5 mg/kg/day for 4 weeks and the dose was further tapered by 5 mg every other day each week to a dose of 0.25 mg/kg every other day or the minimal dose required to control extra-renal disease (Austin, 1986; Boumpas, 1992; Gourley, 1996; Steinberg, 1991). In the Euro-Lupus Nephritis Trial, after three consecutive IV methylprednisolone daily pulses of 750 mg, patients were switched to oral prednisolone (mostly 0.5 mg/kg/day for 1 month; 1 mg/kg/day in severe cases) which was tapered by 2.5 mg/day every 2 weeks to reach a maintenance dose of 5-7.5 mg/day at 4-6 months (Houssiau, 2002). In a recent series of LN patients, induction therapy *without* oral steroids was given consisting of 2 pulses of IV methylprednisolone 500mg and 2 doses of 1 gram of rituximab given 2 weeks apart followed by mycophenolate mofetil. Although pioneering, this was not a randomized controlled trial and patients represented a population without much extra renal disease (Condon, 2013).

Many SLE patients are maintained for years on low dose GCs (between 2.5 and 7.5 mg prednisolone/day) (Badsha, 2002). Chronic use of high dose GCs is associated with increased risk of infection and metabolic (Cushingoid features, diabetes, cardiovascular events), musculoskeletal (myopathy, avascular osteonecrosis, osteoporosis) and other side-effects such as easy bruising and early cataract. Longitudinal cohort studies have confirmed that GCs contribute to damage accrual in SLE, as measured by the SLICC/ACR damage index (DI). The mean DI rose from 0.33 at baseline to 1.9 after 15 years of follow-up in an inception cohort and damage was considered as GC-related in 16% and 49% of the patients at baseline and last follow-up, respectively (Gladman, 2003). In another cohort, the accrual of organ damage was found to correlate with the mean daily prednisone dose, with the risk increasing for doses higher than 6 mg per day (Thamer, 2009). Finally, damage accrual was found to be associated with higher risk of mortality, every one point increase in DI being associated with a 1.32 times higher mortality during follow-up (Chambers, 2009). In these studies the possible confounding effect of disease activity itself should be noted (higher disease activity is associated with both higher dosages of prednisone and damage accrual) and despite statistical modelling remains difficult to completely correct for.

Taken together, while GC remain an inescapable therapy in severe acute SLE cases, many concerns are raised by patients and their physicians regarding their chronic use as maintenance therapy. As a consequence, patients should receive the lowest possible dose of GC for the shortest period of time. In this respect, other immunosuppressants, such as azathioprine or methotrexate can be efficacious GC-sparing agents, although robust data obtained from randomized trials are relatively scarce (Fortin, 2008). Recent data from the Belimumab trials suggest that belimumab can be a steroid-sparing agent in lupus patients, with more patients

who decreased oral GCs and less patients with increases in oral GCs in the belimumab groups (Van Vollenhoven, 2016). In patients requiring GC, adequate prevention of bone loss should be applied, keeping in mind that GC-induced osteoporosis is an early event. Patients must be immunized against influenza (every year) and *Streptococcus pneumoniae* (every 5 years) (Naveau, 2005).

1.2 Antimalarials

Antimalarials are widely prescribed to SLE patients. Hydroxychloroquine sulphate (HCQ) is the most frequently used, at doses ranging from 200 to 400 mg/day (maximum 6.5 mg/kg ideal body weight/day). Other antimalarials such as chloroquine (125-250 mg/day; maximum 4 mg/kg/day) and quinacrine (100 mg/day) are preferred for severe cutaneous cases (Okon, 2013). HCQ is an alkalinizing lysosomotropic drug that accumulates in lysosomes where it inhibits some important functions by increasing the pH. It can inhibit toll like receptor signalling, the accumulation of nucleic fragments in lysosomes, the autophagic degradation and it can inhibit the binding of beta-2-glycoprotein to phospholipids (Ponticelli, 2017). Of note, tobacco smoking reduces the efficacy of antimalarials (Ezra, 2012).

While mucocutaneous and articular manifestations are the original indications for the use of antimalarials in SLE, pivotal data have shown that these drugs are beneficial in a wider variety of disease manifestations. The Canadian Hydroxychloroquine Study Group placebo-controlled randomized study demonstrated that HCQ withdrawal in clinically stable SLE patients was associated with an increased flare rate (The Canadian Hydroxychloroquine Study, 1991; Tsakonas, 1998). In addition, uncontrolled data from the LUMINA cohort (LUpus in the MInorities, NAture versus nurture) indicated that therapy with HCQ independently reduces damage accrual (Fessler, 2005 ; Alarcon, 2007), including renal damage (Pons-Estel, 2009). Likewise, observational data from the Grupo Latino Americano de Estudio del Lupus suggested that HCQ improved survival rate (Shinjo, 2010), although critics have mentioned channelling bias as a limitation in these studies.

Besides better lupus disease control, antimalarials display many other interesting properties, such as lipid profile improvement (Tam, 2000), prevention of thrombotic events, influence on cardiovascular risk, and a beneficial effect on bone mineral density (Ruiz-Irastorza, 2006 and 2010; Espinola, 2002). A recent retrospective review of pregnancies in mothers with offspring affected by congenital heart block (CHB) suggests that HCQ use significantly reduces the recurrence of CHB (21.7% in non-HCQ users versus 7.5% in HCQ users) (Izmirly, 2012). Finally, HCQ whole blood measurements was recently found to be a reliable marker of adherence to therapy (Costedoat-Chalumeau, 2013). Conversely, low levels of HCQ suggesting poor adherence have been found to be predictive of flares (Costedoat-Chalumeau, 2007). Therefore, many experts currently advice to prescribe HCQ (minimum 200 mg/day) in all SLE patients, even in the absence of overt clinical manifestations (D'Cruz, 2001).

Antimalarials are considered safe and well tolerated and can be safely used during pregnancy. Side-effects include digestive intolerance (diarrhoea), skin rash, aquagenic pruritus, blue-grey or brown lower leg hyperpigmentation (Jallouli, 2013), cardiomyopathy, myopathy and retinopathy. Retinopathy can present with photophobia, blurred distance vision, missing or blacked out areas in the vision field (or while reading) and light flashes. Retinopathy is rare with HCQ at doses below 6.5mg/kg/day, and somewhat less exceptional with long-term chloroquine use. New data about the prevalence of retinopathy has led to a recent update of the American Guidelines of Ophthalmology for toxicity screening (Marmor, 2016). At the previously recommended doses of 6.5 mg/kg ideal weight/day the risk of retinal toxicity after 5 years is <1%, after 10 years <2%, but it appears to rise to almost 20% after 20 years. However, in patients with HCQ lower than or equal to 5 mg/kg, without signs of toxicity, the risk appeared much lower (Melles, 2014). Therefore, a maximum recommended dose of 5 mg/kg of observed (rather than ideal) body weight is proposed. In addition, a baseline fundoscopy and annual screening starting after 5 years, for patients on acceptable doses without major risk factors, is recommended. For patients on higher dosages or patients with risk factors more frequent examinations are recommended. Risk factors include age over 60 years, pre-existing macular degeneration, retinal dystrophy, obesity, liver disease and renal failure (Marmor, 2002; Mosca, 2009) and should be assessed regularly. Use of tamoxifen has been identified as an additional risk factor (Marmor, 2016). The rheumatology world has not yet adopted these new recommendations and some critical comments have been published.

In summary, antimalarials are safe and effective in treating musculoskeletal and mucocutaneous manifestations of SLE and reducing the risk of flares, and may have additional benefits in reducing organ damage in the long-term, allowing the reduction of GCs, and decreasing the risk for thromboses, atherosclerosis and osteoporosis.

1.3 Cyclophosphamide

Cyclophosphamide (CYC) was first used in SLE in the late 1970s at the Mayo Clinic as an oral drug to treat LN (Donadio, 1978). Sometimes oral CYC is still used for a limited time course (3 months; 1-2 mg/kg/day) as induction therapy (Mok, 2006; Ponticelli, 2010) but because of concerns regarding the side-effects of long-term exposure to oral CYC, such as alopecia, bladder cancer, haemorrhagic cystitis, bone marrow suppression, haematological malignancies, myelodysplasia and premature gonadal failure, most clinicians have moved to IV CYC.

The first IV CYC protocol was developed at the NIH and consisted of 6 monthly pulses of CYC (750-1,000 mg/m²) followed by quarterly pulses (at a similar dose) for 2 additional years, usually in combination with IV methylprednisolone pulse therapy and GCs (Austin, 1986; Boumpas, 1992; Gourley, 1996; Illei 2001). This protocol has been the standard of care for proliferative LN during two decades, as well as for severe non-renal lupus, despite the risk of severe infections linked to drug-induced neutropenia and other risks and side-effects.

The administration of anti-emetic drugs before pulse CYC reduces nausea and vomiting and IV hyper hydration and the use of 2-mercaptoethane sodium sulfonate (Mesna), which binds toxic metabolites, can be used to reduce the incidence of haemorrhagic cystitis. The use of MESNA is not strongly evidence-based, nor is the risk of bladder toxicity associated with IV CYC in rheumatic diseases as compared to the use in oncology, as elaborated in a review (Monach, 2010). The use can be considered on an individual basis, taking into account the dose and duration, oral versus IV CYC, other risk factors and the tolerability to hyper hydration. A major concern with this long-course IV CYC regimen is the risk of premature gonadal failure in female patients of child-bearing age, which is strongly dependent on cumulative dose but also on the age of the patient (Boumpas, 1993; Ioannidis, 2002; Katsifis, 2004). An increased incidence of cervical intraepithelial neoplasia in lupus women treated with high-dose IV CYC has also been reported (Ognenovski, 2004). This explains why a long-course of quarterly IV CYC pulses is not recommended anymore as maintenance therapy of LN (Bertsias, 2012; Hahn, 2012).

In order to reduce side-effects, a lower-dose IV CYC regimen (6 x 500 mg fixed dose every two weeks), followed by azathioprine (after 3 months), was developed at St-Thomas' Hospital in London (Houssiau, 1991; Haga, 1992) and further compared to a long-course IV CYC regimen in a controlled trial, the Euro-Lupus Nephritis Trial (Houssiau, 2002; Houssiau, 2004; Houssiau, 2010). Based on the positive results of this trial, the so-called "Euro-Lupus regimen" is now an accepted option for the treatment of proliferative LN (Bertsias, 2012; Hahn, 2012). While the original Euro-Lupus study represented mostly Caucasian patients with moderate LN, the Euro-Lupus regimen has also been shown effective in a population of more severe LN patients of more racially diverse background in a US-based study (ACCESS trial) (Wofsy, 2013, 2015). Of note, ethnicity might be of importance for the efficacy of IV CYC. Hispanic and black patients have shown lower response rates to IV CYC (in studies compared to MMF) (Isenberg, 2010). In Asian LN patients, the EURO-Lupus regime was evaluated against MMF without any observed differences (Rathi, 2016).

Finally, very high immunoablative doses of IV CYC have been tested in refractory lupus cases, with improvement in disease activity (Brodsky, 1998; Petri, 2003; Petri 2006).

1.4 Azathioprine

Azathioprine (AZA) is used in clinical practice as a GC-sparing agent in several autoimmune/inflammatory diseases, including SLE. The drug is transformed to 6-mercaptopurine (6-MP) and then to its active metabolites, thiosinic and thioguanilic acid (6 TGN), which incorporate into DNA, thereby causing DNA/protein crosslinks and interfering with nucleic acid structure. The daily dose of AZA is between 1 and 2.5 mg/kg. Gastrointestinal intolerance is the most common side-effect. Bone marrow suppression, increased risk of infections, hepatitis and hypersensitivity reaction are potentially severe but rare adverse events. Because allopurinol blocks xanthine oxidase (one of the enzymes that metabolizes 6-MP), these two drugs are generally

not combined. If both must be taken, the dose of AZA must be reduced by 50-75% to prevent bone marrow toxicity. In case of co-administration of AZA with warfarin, a higher dose of the anticoagulant may be required to maintain therapeutic INR levels (Ng, 2006).

Individuals who are completely deficient in thiopurine methyltransferase, the main enzyme responsible for metabolism of 6-MP (1/300) can develop severe pancytopenia on AZA. TPMT deficiency is not rare and some authorities recommend genotyping before starting AZA treatment ;the drug should not be prescribed in case of homozygous deficiency and the dose should be carefully titrated upwards in case of heterozygous mutations (Payne K, 2007). However, genotyping is not done routinely by many rheumatologists ; a frequent approach is to start and titrate therapy in steps from a low dosage (50mg) up to the desired dose and check tolerability and blood count after every increase, for example every two weeks.

AZA use has been best studied in LN, either as induction therapy (Grootscholten, 2006; Grootscholten, 2007) or as maintenance treatment (Houssiau, 2002; Houssiau, 2010b). Furthermore, it is effective as an immunosuppressive and steroid sparing agent in other manifestations of SLE. One of the advantages of AZA is its safety in pregnancy; the drug can be continued in pregnant LN patients who need long-term maintenance therapy, often as an alternative to mycophenolate mofetil (MMF) which must be stopped due to its teratogenicity (Perez-Aytes, 2008).

1.5 Methotrexate

Data on the use of methotrexate (MTX) in SLE derive from small cases series, uncontrolled studies and a few controlled trials (Fortin, 2008). MTX, at doses up to 15–25 mg/week, seems efficacious not only in the treatment of articular manifestations refractory to low-dose steroids and antimalarials, but also in the treatment of serositis, cutaneous manifestations, and other features of moderately severe systemic lupus. A systematic review on 3 RCTs and 6 cohort studies showed that MTX was associated with lower SLEDAI scores when compared to controls and significant reductions in corticosteroid use (Sakthiswary, 2014). Small case series suggest MTX may also work for lupus vasculitis and some haematological manifestations, and in a small number of cases it has been given intrathecal for central nervous system lupus (Winzer, 2010).

The safety profile of MTX in SLE patients is similar compared to rheumatoid arthritis (RA) patients. However, because disease-related renal impairment is more frequent in SLE, MTX dose reduction may be required in LN patients with renal failure. Although MTX is generally well tolerated, it can cause dyspepsia, headache, general malaise, increase in serum liver enzyme levels and bone marrow toxicity, the two latter side-effects requiring regular blood monitoring. Rarely, a dry non-productive cough can be the symptom of MTX-induced interstitial lung disease.

1.6 Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a reversible inhibitor of inosine monophosphate dehydrogenase (IMP-DH) and has lymphocyte-selective cytostatic effects, inhibiting T and B lymphocyte proliferation. The drug, used at a dose between 1 and 3 g/day, was gradually introduced into the therapeutic armamentarium for SLE since the end of the 1990s (Glicklich, 1998; Gaubitz, 1999) and subsequently studied in several large randomized controlled trials (RCTs) in LN. These trials showed that MMF is efficacious as induction (Chan, 2000; Ginzler 2005; Ong, 2005; Appel, 2009) and maintenance therapy (Contreras, 2004; Dooley 2011; Houssiau, 2010b). MMF was further tested in open series of patients suffering from renal or non-renal disease (Karim, 2002; Bijl, 2003; Pisoni 2005). A recent cohort study showed its efficacy in refractory to standard of care non-renal manifestations and reduction of corticosteroid use (Tselios, 2016).

MMF side effects are generally moderate and rarely lead to treatment discontinuation. They mainly consist of gastrointestinal manifestations (diarrhoea, nausea, vomiting), hepatitis and anaemia, the latter mainly observed in patients with renal impairment. Other side effects such as pancreatitis and febrile pancytopenia have been observed rarely. The drug is strictly contraindicated in pregnancy (at least during the first trimester) because of proven teratogenicity, with peculiar involvement of the face (Perez-Aytes, 2008).

Recently, a new drug containing mycophenolic acid, the active metabolite of MMF, became available. One gram of mycophenolate mofetil corresponds to 720 mg of mycophenolate sodium. This new formulation may have better gastrointestinal tolerability (Budde, 2004) and was tested in LN (Zeher, 2011).

1.7 Calcineurin inhibitors

Calcineurin inhibitors (CNI) display two modes of action. First, they inhibit T-cell mediated responses, such as cytokine production (e. g. of IL-2), leading to reduced immune activation and glomerular immune complex deposition. Second, they stabilize the podocyte actin cytoskeleton thereby contributing to maintenance of the integrity of the filtration barrier and explaining their potent antiproteinuric effect in LN patients (Faul, 2008).

Cyclosporine A (CSA) has been used to treat a variety of clinical manifestations, as reviewed elsewhere (Griffiths, 2001; Morton, 2000) but has been best studied in LN, including membranous nephropathy. At an initial dose of 4-5 mg/kg/day, CSA was found as efficacious as IV CYC in a randomized trial performed in patients with proliferative LN (Zavada, 2010). The drug was also compared against AZA for maintenance therapy of LN (Moroni, 2006). It is not always well tolerated: transient increase in serum creatinine, hypertension, hypertrichosis, gum hypertrophy, tremor and seizures may occur (Conti, 2000).

Tacrolimus (TAC) is a macrolide compound isolated from a soil fungus found in Northern Japan and is now widely prescribed in transplantation. It has been tested in proliferative and membranous LN in Asian populations (Mok, 2005; Szeto, 2008; Miyasaka, 2009) and was found to have similar efficacy as MMF in a

randomized trial (Mok, 2016), although a trend towards more renal flares and functional decline was observed in the follow-up. Multi-target therapy, combining TAC, MMF and GC, was shown to induce a higher rate of early renal remission compared to IV CYC (Bao, 2008; Liu, 2015), with a note of caution regarding possible rebound proteinuria when TAC is withdrawn. A positive note is that TAC has no known negative effects on fertility and pregnancy. A new CNI, voclosporine, is currently being tested in LN in combination with MMF.

Current practice is not to use CNI as first therapy in LN due to their potential toxicity. They can be useful in selected cases with persistent proteinuria despite standard immunosuppression.

1.8 Thalidomide

Thalidomide (THA), formerly marketed as Softenon, was developed as an antiemetic drug to relieve morning sickness of pregnant women and as a sleeping pill. In the early 1960s, it was found to be dramatically teratogenic (phocomelia) and was withdrawn. Further studies have shown its efficacy in the treatment of leprosy and multiple myeloma. The mechanism of action of the drug is poorly understood, but it appears to display antiangiogenic effects. THA has been used in SLE since the early 1980s (usually 50 mg/day at night) and many studies have demonstrated its efficacy (Pelle, 2003; Coelho, 2005; Cuadrado, 2005). THA is mostly prescribed for severe chronic discoid lupus resistant to antimalarials, with usually very impressive results. Toxicity is the major limiting factor. Thus, polyneuropathy is frequent (at least 20% of patients), can be disabling and is mostly irreversible (Briani, 2004). Patients on THA require regular neurological assessments and electromyography. In some countries, a monthly negative pregnancy test is required before the drug can be prescribed and obtained. Relapses after discontinuation are frequent and may justify the use of a lower maintenance dose such as 50 mg three times weekly.

Immunomodulatory analogues of THA have been developed, such as pomalidomide and lenalidomide, which are purported to be more potent and less toxic than THA. Lenalidomide was recently studied in refractory cases of cutaneous lupus (Cortes-Hernandes, 2012).

1.9 Dapsone

Dapsone, (DAP), 4,4 – diaminodiphenylsulfone, is used in the treatment of dermatitis herpetiformis and as antimycobacterial drug in leprosy. The efficacy of the drug in SLE was suggested in case reports and small series (Fenton, 1986; Neri, 1999; Chang, 2011). DAP seems efficacious in treating bullous LE, subacute cutaneous lupus and mucosal ulcers. It is suggested to start with 100 mg daily and then to taper to the minimally efficacious dose in 2-3 months. DAP can cause nausea and dyspepsia. Major side effects include haemolysis, especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and polyneuropathy. Methaemoglobinaemia is the rule in patients treated with DAP but is not, per se, a reason to withdraw therapy, except if it induces a decrease in haemoglobin.

1.10 Leflunomide

Leflunomide (LEF) is a synthetic isoxazole derivative of low molecular weight, with immunomodulatory and anti-inflammatory effects. Its efficacy in the treatment of rheumatoid arthritis and psoriatic arthritis is well established, and some data have been published on its efficacy in SLE (Remer, 2001; Tam, 2004) and even LN (Tam, 2006). In the absence of proper controlled trial its use should be limited to selected cases. Its pros and cons have been described by Wu, 2013.

1.11 Intravenous immunoglobulin

Intravenous immunoglobulins (IVIG) are used as rescue therapy in many refractory autoimmune diseases and some reports suggest its efficacy as treatment of difficult SLE cases (Sherer, 2006). It may be given at 1-2 g/kg/day for 2 consecutive days or 0.4 g/kg/day for 5 consecutive days, and can be repeated monthly as maintenance therapy. Treatment duration in reported series has varied from a few months to years. Except for a clear role in the treatment of SLE-related thrombocytopenia and/or haemolytic anaemia, no other clinical indications for IVIG are supported by strong evidence. IVIG has been used in the management of critically-ill SLE patients (Engel, 1999), but also as a treatment for mild to moderate SLE, in LN (RCT, Boletis, 1999), and for the prevention of recurrent pregnancy losses. Treatment with IVIG is associated with a small risk for thromboembolism but has otherwise surprisingly few side-effects. In contrast to conventional immunosuppressants, IVIG therapy does not increase the infection risk and may therefore be considered proposed in selected cases when concomitant infection cannot be ruled out. Also, IVIG are safe to use in pregnancy. Treatment cost and lack of evidence-based recommendations clearly limit their use.

1.12 Plasma exchange

Plasma exchange (PE) has an established role in the treatment of several autoimmune diseases and syndromes, such as Goodpasture syndrome and microangiopathic haemolytic anaemia. PE has been used to treat various manifestations of SLE over the past 35 years (Pagnoux, 2005), and case reports have suggested effectiveness in controlling severe disease activity, such as alveolar haemorrhage, catastrophic anti-phospholipid syndrome (Bortolati, 2009), neurological involvement (Bartolucci, 2007), haematological manifestations, pericarditis, myocarditis, nephritis, and vasculitis and severe SLE in pregnant patients with or without the anti-phospholipid syndrome (Zandman, 20015). However, a controlled trial comparing the efficacy of PE as treatment of LN in addition to IV CYC failed to show any benefit (Lewis, 1992). Moreover, in uncontrolled series PE in combination with IV CYC in SLE was associated with more severe infections and deaths compared to IV CYC alone (Aringer, 1998). Therefore, PE should probably only be considered as an adjunctive therapy in conjunction with high dose GCs and IV CYC in severely ill patients with SLE where specific pathophysiological mechanisms are activated, such as microangiopathy or catastrophic anti-phospholipid syndrome.

1.13 Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (HSCT) is a high-risk procedure involving a conditioning regimen to eliminate autoreactive lymphocytes, followed by infusion of previously harvested autologous haematopoietic stem cells, with the aim of reconstructing the immune system. HSCT is becoming a therapeutic option in severe systemic sclerosis and has been used in severe refractory SLE (Alchi B, 2013). Procedure-related mortality is currently too high to propose HSCT, except within the frame of investigational protocols. Basically, only patients with very severe uncontrolled disease and at risk for permanent organ damage or death should be considered for this procedure.

1.14 Mesenchymal stem cell therapy

Several open studies suggest that allogeneic mesenchymal stem cell (MSC) therapy might be useful as adjunct therapy of lupus or LN (Liang, 2010; Sun, 2009; Sun, 2010). It should be stressed, however, that none of these trials were controlled and that the fate of MSC in vivo and their mechanism of actions are far from unravelled (Tyndall, 2010).

1.15 Targeted therapies

New insights in the pathophysiology of SLE and advances in biotechnology have led to a large number of targeted therapies that have been tested in SLE. So far, only the monoclonal anti-BLyS antibody belimumab has been approved for lupus by the EMA and the FDA. The anti-CD20 monoclonal rituximab has been used as an off-label drug, sometimes with apparent success in individual patients, but failed to demonstrate efficacy in randomized controlled trials. The design and choice of outcome measures in trials for a heterogeneous disease such as lupus is a challenge and may have contributed to negative results in the past. The use of some biologics was associated with a high rate of infectious side effects in SLE, such as the anti-CD20 monoclonal ocrelizumab and the anti-BLyS/APRIL receptor construct atacicept. Many targeted therapies are still under investigation in Phase II/III clinical trials. Table Ia lists the main clinical trials performed with biologics in SLE. Table Ib lists the trials that are still ongoing.

Table 1a: Targeted therapies in SLE – Trials in bold met their primary endpoint

Target	Molecule	Acronym First author, year	L/LN	Phase	N	Results
CD20	Rituximab	EXPLORER Merrill, 2010	L	II/III	257	No proven benefit vs SOC
		LUNAR Rovin, 2012	LN	III	144	11% more responders but not statistically significant
CD20	Ocrelizumab	BELONG Mysler, 2013	LN	III	381	Early termination – Infections (combo with MMF)
CD22	Epratuzumab	ALLEVIATE 1/2 Wallace, 2013	L	II	90	Early termination – No drug supply
		EMBLEM Wallace, 2014	L	IIb	227	More BICLA responders
		EMBODY 1	L	III	786	No benefit vs SOC
		EMBODY 2	L	III	788	No benefit vs SOC
BLyS	Belimumab	BLISS-52 Navarra, 2011	L	III	865	More SRI responders
		BLISS-76 Furie, 2011	L	III	826	More SRI responders
		BLISS-SC Stohl, 2017	L	III	836	More SRI responders
	Atacicept	Ginzler, 2012 Isenberg, 2015 APRIL-SLE (75mg arm)	LN	II/III	6 461	Early termination – Infections Results of 75mg arm, no effect on flare rate, 2 deaths in 150mg arm
	Tabalumab	ILLUMINATE-1 Isenberg, 2016	L	III	1164	No more SRI-5 responders
		ILLUMINATE-2 Merrill, 2016	L	III	1124	More SRI-5 responders in Q2W arm
IFNa	Sifalimumab	Merrill, 2011	L	I	33	Safe profile, inhibition type 1 IFN signature
	Sifalimumab	Kamashta, 2016	L	IIb	431	More SRI responders all dosages
	Rontalizumab	ROSE Mc Bride, 2012	L	II	238	More SRI responders in ≥10 mg pred
	IFNKinoid	Lauwerys, 2013b	L	I/II	28	Down-regulation of IFN signature
IFN receptor	Anifrolumab	Furie, 2017	L	IIb	305	More SRI-4/GC taper responders
IL6	Sirukuma	Rovin, 2016	LN	II	24	No more renal response
TWEAK	BIIB023	ATLAS	LN	II		Early termination - Inefficacy
CD28	Abatacept	Merrill, 2010	L	IIb	175	No less BILAG A/B flares
		Furie, 2014	LN	II/III	298	No more renal responses
		Wofsy, 2013a				Alternative analysis: pos result
		ACCESS	LN	II	134	No benefit vs SOC (GC+EL IV CYC)
		Wofsy, 2013b				
CD40L	BG9588	Boumpas, 2003	L			Early termination – Thrombosis
	IDEC131	Davis, 2001	L	II	85	No benefit vs SOC

L: SLE; LN: lupus nephritis; N: number of patients included; SOC: standard of care; NS: not significant; MMF: mycophenolate mofetil; BICLA: British Isles Combined Lupus Assessment; SRI: Systemic lupus erythematosus Responder Index; IFN: interferon; BILAG: Bursitis Isles Lupus Assessment Group index; GC: glucocorticoids; EL: Euro-Lupus; IV: intravenous; CYC: cyclophosphamide.

Table 1b: Targeted therapies in SLE – ongoing trials

Target	Molecule	Acronym	L/LN	Phase	Description
CD20	Rituximab	RITUXILUP	LN	III	RTX + IV MP + MMF vs GC + IV MP + MMF induction (NCT01773616)
		RING	LN	III	RTX for persistent proteinuria despite 6 months of standard immunosuppression (NCT01673295)
	RTX/BEL	CALIBRATE	LN	II	RTX + CYL vs RTX + CYC + BEL safety (NCT02260934)
BLyS	Belimumab	EMBRACE	L	III	BEL in SLE black race (NCT01632241)
	Belimumab	BLISS-LN	LN	III	BEL + CYC or MMF induction vs placebo. BEL + AZA or MMF maintenance vs placebo (NCT01639339)
	Atacicept	ADDRESS II	L		NCT01972568)
IFN receptor	Blisibimod*	CHABLIS-SC I	L	II	Sc BL in addition to SOC (NCT01395745, NCT02074020)
		CHABLIS-SC II	LN	II	
	Anifrolumab		L	III	ANF + MMF vs placebo + MMF (NCT02446899)
CD28	Abatacept	IM101-330	L	I/II	ABA vs placebo in SLE arthritis (NCT02429934)
			LN	III	ABA vs placebo on background MMF + GC (NCT01714817)
	Abatacept		LN	III	ABA vs placebo on background MMF + GC (NCT01714817)

L: SLE; LN: lupus nephritis; SOC: standard of care; RTX: rituximab; IV MP: intravenous methylprednisolone; GC: glucocorticoids oral; MMF: mycophenolate mofetil; BEL: belimumab; BL: blisibimod; CYC: cyclophosphamide; ANF: anifrolumab; ABA: abatacept; Sc: subcutaneous.

**Press release Nov 2016 : CHABLIS-SCI has failed to reach the primary outcome*

1.15.1 Anti-B-cell therapies

Rituximab (RTX) is an anti-CD20 chimeric mouse/human B-cell depleting monoclonal antibody widely used for treatment of B-cell lymphoma, rheumatoid arthritis and granulomatosis with polyangiitis (formerly called Wegener's disease). CD20-negative plasmacytes and long-lived plasma cells are not affected by RTX treatment, thereby explaining why serum immunoglobulin titres rarely drop and why specific immune protection (e. g. against tetanus toxoid) is maintained. RTX was first tested by several expert groups as rescue therapy for

lupus and LN patients refractory to standard immunosuppression (Looney, 2004; Anolik, 2004; Leandro, 2002; Gunnarsson, 2007; Tokunaga, 2007; Jonsdottir, 2008; Diaz-Lagares, 2012). Two regimens have been used, the so-called lymphoma regimen (375mg/m² of BSA every week for four consecutive weeks, together with IV CYC) or the rheumatoid arthritis regimen (1 gm, twice, two weeks apart, without IV CYC). These small series suggested that RTX can be very efficacious in refractory lupus, with an effect on serological parameters, clinical outcomes, and renal biopsy. Rituximab has an acceptable safety profile, although a concern has been raised based on two cases of progressive multifocal leukoencephalopathy (Molloy, 2012). However, since that initial report no further cases have been published. B-cell depletion usually occurs within 2 weeks after the first infusion and B-cell repopulation after 3 to 40 months. Flares of disease activity have been reported in about 40% of treated patients, mostly concomitant with B-cell reconstitution. Retreatment with RTX was found to be efficacious and safe (Turner-Stokes, 2011). However, it is not clear whether patients should be pre-emptively re-treated at the time of reconstitution of B-cells. Based on this experience two randomized clinical trials were done: EXPLORER in general lupus (Merrill, 2010a) and LUNAR in LN (Rovin, 2012). Both studies, in which RTX was used as an add-on therapy, failed to show superiority of RTX over standard of care. These negative results, although they may well indicate that RTX is not truly effective in SLE, have been attributed to a number of limitations in study design, such as the selection of inadequate outcome measures and co-medications that may have masked the real benefit of RTX. Two studies are in the pipeline to further define the role of RTX in the treatment of LN. One, entitled RING, is testing the hypothesis that RTX is efficacious in LN patients who failed to achieve a sufficient renal response after at least 6 months of standard immunosuppression. The other, entitled RITUXILUP, is based on the results of an open series of 50 LN patients treated with an oral GC-free regimen, i. e. two pulses of 500 mg IV methylprednisolone and two doses of 1 g RTX, both given two weeks apart, followed by MMF. Renal response rate in these patients, who did not receive oral GCs, was similar to that reported in trials using standard GC therapy (Condon, 2013). The currently recruiting RITUXILUP randomized trial is aimed at testing the non-inferiority of RTX over oral GCs in LN patients treated with two pulses of 500 mg IV methylprednisolone and MMF.

Ocrelizumab (OCR), a humanized anti-CD20 monoclonal antibody, was tested in the BELONG LN trial, as an add-on induction therapy superimposed to GCs and MMF or GCs and Euro-Lupus IV CYC. The trial was terminated early due to a high rate of serious infections in the MMF/OCR group (Mysler, 2013).

Epratuzumab (EPR) is an anti-CD22 monoclonal antibody that acts as a CD22/BCR modulator. More specifically, binding of EPR to CD22 favours the co-localization of CD22 with the BCR, thereby promoting the inhibitory effect of CD22 on BCR signalling (raised threshold). B-cell depletion is much less stringent with EPR compared to RTX. EPR was first tested in ALLEVIATE-1 and ALLEVIATE-2, which were prematurely stopped due to drug supply issues but showed some efficacy (Wallace, 2013). In ENBLEM, a Phase IIb placebo-controlled dose-ranging randomized short-term (12 weeks) trial using a composite endpoint as primary outcome

measure, the BILAG-based Combined Lupus Assessment (BICLA), a beneficial effect was observed in patients given a cumulative dose of 2,400 mg (Wallace, 2014). However, EPR failed in the two pivotal phase III EMBODY studies.

1.15.2 Anti-cytokine therapies

Belimumab (BEL) is a fully humanized monoclonal antibody that binds BLyS (B cell activating factor), a cytokine that stimulates B-cell survival, development and differentiation into plasma cells. Increased levels of BLyS are observed in lupus prone mice as well as in SLE patients. After a promising Phase II dose-ranging trial (Wallace, 2009), two multinational pivotal Phase III trials (BLISS-52 and BLISS-76) demonstrated a statistically significant benefit for the addition of BEL to standard of care in terms of reducing disease activity, flare rates and GC sparing (Navarra 2011; Furie 2011). Both BLISS trials used as primary endpoint a new composite index named the Systemic Lupus Erythematosus Responder Index (SRI) that combines the SELENA-SLEDAI with the British Isles Lupus Assessment Group (BILAG) and the Physician's Global Assessment. Patients with severe active LN and CNS disease were excluded from both trials. Despite a high response rate induced by standard of care, both trials reached their primary endpoints, as did the BLISS-SC trial in which subcutaneous belimumab was tested (Stohl, 2017). Post-hoc analyses indicated that BEL was more efficacious in patients with higher disease activity, anti-dsDNA positivity, low complement or GC treatment at baseline (van Vollenhoven, 2012). Another post-hoc analysis showed that BEL was most effective in musculoskeletal and mucocutaneous domains (Manzi, 2012). While BEL was EMA-approved in 2011 for the treatment of lupus patients with clinically and serologically active disease and inadequate response to standard therapies, the optimal place of BEL remains to be further tuned (Hahn, 2013). Reassuring long-term safety data are now available (Ginzler, 2014) and a LN trial and a trial in patients of black ethnicity is currently in the pipeline. In serologically active anti-dsDNA positive patients with persistent disease manifestations despite low-dose GCs, HCQ and another immunosuppressant, a course of BEL is warranted with re-evaluation after 6 months. Of note, 1 case of progressive multifocal leukoencephalopathy has been reported in a belimumab-treated patient (Fredericks, 2014).

Other BLyS blocking agents are currently being tested, such as atacicept, a receptor construct that inhibits BLyS and APRIL (Ginzler, 2012) or blisibimod (anti-BLyS peptibody). Development of tabalumab (a monoclonal antibody targeting soluble and membrane-bound BLyS) was halted based on the fact that only one of the two pivotal Phase 3 trials met its primary outcome (Merrill, 2016; Isenberg, 2016).

Type I interferons (IFN) play a pivotal role in the pathogenesis of SLE (Rönnblom, 2006). Several molecules were currently developed to block this pathway (Lauwerys, 2013a). A RCT with the anti-IFN monoclonal rontalizumab failed to demonstrate clinical efficacy (McBride, 2012), but small studies with sifalimumab (anti-IFN α) looked promising (Merrill, 2011; Petri, 2013) and a large phase II trial achieved its primary endpoint

(Khamashta, 2016). The IFN α kinoid (a biomolecule designed to induce natural immunity against the cytokine) did not show clinical efficacy in a very small trial (Lauwerys, 2013b). The anti-IFN receptor monoclonal anifrolumab raises many hopes, based on positive Phase II results across several outcome measures. Two dosages (300mg and 1000mg) were tested against placebo in moderate- to severe lupus in addition to standard therapy. The primary endpoint, an SRI response with sustained reduction of steroids <10 mg/day occurred more frequently with both doses and achieved statistical significance with the 300 mg dose, and several secondary outcomes were also met (Furie, 2017). A prespecified secondary analysis in the type 1 interferon “high” population (those with higher IFN-related gene transcripts in peripheral blood leukocytes) showed even stronger results. Herpes zoster and influenza infections were reported more frequently in the anifrolumab groups. A phase III trial is ongoing.

Anti-IL6 sirukumab (Szepietowski, 2013), anti-IL6 receptor tocilizumab (Illei, 2010) and anti-TWEAK BIIB023 were all tested in very small trials but are unlikely to be developed further in SLE. Anti-TNF therapies have never been properly evaluated in SLE, but some experiences with infliximab in a few refractory cases suggested unacceptable safety risks (Aringer, 2009).

1.15.3 Inhibition of co-stimulatory molecules

Activation of (autoimmune) B cells and production of (auto)antibodies depend on optimal co-stimulation through several pairs of transmembrane proteins, such as CD40/CD40L and CD80-86/CD28. Inhibition of these pathways has therefore been tested in SLE.

Two different humanized monoclonal antibodies targeting CD40L have been developed: BG9588 and IDEC 131. A study of the BG9588 monoclonal anti-CD40L antibody in SLE patients with diffuse proliferative glomerulonephritis was terminated early because of thrombotic events, despite an observed reduction of proteinuria, haematuria and anti-dsDNA antibodies (Boumpas, 2003). The anti-CD40L monoclonal IDEC 131 was safe in a Phase I trial (Davis, 2001) but not superior to placebo in a Phase II study (Kalunian, 2002).

Abatacept (ABA) is a CTLA4-Ig fusion protein that binds to CD80/86, thereby preventing its interaction with CD28 on T-cells. The drug is approved for RA. A RCT with abatacept in non-renal SLE failed (Merrill, 2010). ABA was not superior to placebo in LN patients on a background of MMF and GCs for the induction of a complete renal response at 12 months (Furie, 2014). However, using other definitions of renal response, differences in favour of ABA were seen (Wofsy, 2013a), but in a subsequent trial ABA was again not superior to placebo (when given on a Euro-Lupus IV CYC/AZA background) (Wofsy, 2013b).

1.15.4 Other new therapies

Laquinimod (LAQ) is an antigen-presenting cell modulator that skews T cells towards an anti-inflammatory phenotype characterized by increased production of IL-10 and down-regulation of proinflammatory cytokines.

In a small randomized controlled trial, LAQ was found to induce more renal remission compared to placebo, but the difference was not statistically significant (Jayne, 2013).

Lupuzor (LUP) is a peptide (also known as P140) originating from the small nuclear ribonucleoprotein U1-70K. It was shown to display tolerogenic and immunomodulatory effects in preclinical lupus models, i. e. inhibition of T-cell reactivity against self-peptides. It was recently tested in SLE patients and found to induce significantly more SRI responses compared to placebo (Zimmer, 2013).

1.16 Hormonal contraception and hormonal replacement therapy

The use of oestrogens in SLE patients raises safety concerns due to the theoretical risks of disease flares and thromboembolic complications. Two randomized controlled trials, performed in patients with inactive or stable disease without a history of thrombosis, suggest that the use of combined oral contraceptives, containing 30-35 mcg of ethynyl oestradiol, does not increase the incidence of flares, nor the rate of thrombotic events (Petri, 2005; Sanchez-Guerrero, 2005). In patients with the antiphospholipid syndrome (excluded in the study by Petri et al., but not in the trial performed by Sanchez-Guerrero et al.) and/or a history of thrombosis, preference must however be given to other forms of contraception (Culwell, 2009). For patients with SLE in need of chronic anticoagulation a progestin-releasing intrauterine device is likely the ideal contraceptive method.

Prior to the unexpected early termination of the Women's Health Initiative (WHI) trial of continuous conjugated equine oestrogens (CEE) and medroxyprogesterone acetate (MPA), the prevailing view was that hormone replacement therapy (HRT) was a low-risk intervention. Studies in SLE patients, questioning the safety of hormone replacement therapy (HRT) mainly stem from that era. Nowadays, risks (including breast cancer) and potential benefits of HRT need to be carefully weighed on the basis of individual patient characteristics. In SLE, in the HRT-SELENA trial, 0.625 mg of conjugated oestrogen daily plus 5 mg of medroxyprogesterone for 12 days per month was compared to placebo. Severe flares were not more frequent in the treated group but there were significantly more mild and moderate flares (relative risk: 1.34). Moreover, as in the general population, thromboembolic events were more common, although the difference was not statistically significant (Buyon, 2005). Of note, the trial excluded patients with high-titre anticardiolipin antibodies, lupus anticoagulant, or a previous history of thrombosis, who should not be given HRT. This said, HRT studies in SLE have been performed with oral oestrogens, and it is not known what the effect is of currently available regimens.

2. THERAPEUTIC PROTOCOLS FOR SPECIFIC ORGAN INVOLVEMENT

The therapy of SLE must be chosen based on the complexity of the disease and individual patient characteristics. International organizations such as the European League Against Rheumatism EULAR and the American College of Rheumatology ACR have issued treatment recommendations which may be helpful to the clinician and ensure uniform standards of care (Bertsias, 2008; Bertsias, 2012; Hahn, 2012). Treatment of SLE is guided by the type and the severity of each disease manifestation. Unless biomarkers become available that will allow us to predict to which drug a given SLE patient will respond, we mostly use a “trial and error” approach, of course with full knowledge of available data. Thus, systemic treatment of mild SLE, such as mild mucocutaneous or musculoskeletal involvement, is based on the administration of a short-course of low-dose GCs (0.1-0.2 mg/kg/day) and longer-term antimalarial drugs (mainly HCQ 200-400 mg/day). As already discussed, withdrawal of GCs is a priority and antimalarials are therefore often prescribed long-term irrespective of disease severity. Moderately severe SLE (e. g. more severe mucocutaneous and musculoskeletal disease or serositis) is generally treated with a short-course of medium dose GCs (0.2-0.5 mg/kg/day), promptly tapered to lower dose. In patients who are GC-dependent (i. e. whose disease tends to relapse as soon as the dose of GCs is decreased), it is advised to start a steroid-sparing immunosuppressant, the choice of which depends on the type of organ involvement. In case of arthritis, MTX (or LEF) may be preferred; in case of haematological disease or serositis, AZA might be a good candidate, as well as BEL in selected cases. Severe lupus (e. g. proliferative lupus nephritis, CNS involvement or severe thrombocytopenia) is best treated by a combination of pulse IV methylprednisolone followed by oral GCs (0.5 mg/kg/d) and MMF or IV CYC to induce a prompt response. When this goal is achieved, maintenance therapy with the less toxic immunosuppressant (AZA, MMF) is mandatory, given the high relapse rate. Refractory lupus needs special attention and is likely best managed in expert centres. For such patients, RTX and other biologic therapies are additional options. The following paragraphs specifically deal with certain organ involvements and summarize our best knowledge. They should not be applied “à la lettre” but should serve as a guide for optimal care. Of note, treatment of the antiphospholipid syndrome associated with SLE is discussed in another chapter.

2.1 Renal involvement

When untreated, LN may lead to renal failure with a major impact on survival and quality of life. Renal damage is a predictor of mortality in SLE and recurrent flares are associated with worse long-term outcomes (Bruce, 2015). In most cases a renal biopsy is pivotal to guide therapy. Glomerular lesions are graded according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification criteria (Table II) (Weening, 2004). Importantly, not all LN patients need to be treated aggressively, and renal pathology may avoid both under- and overtreatment. Thus, patients with Class I or II LN should be treated by optimal renal protection (ACEI/ARB) and HCQ and do not need immunosuppression, in contrast to patients

with proliferative disease (Class III and IV). Pure membranous LN (Class V) raises some specific treatment issues.

Table II: Implication of histology grading for the therapy of LN

ISN/RPS	Pathology	Signs	Risk for ESRD	Treatment
I	No hypercellularity Mesangial ID	Low proteinuria	Very low	ACEI/ARB HCQ
II	Mesangial hypercellularity Mesangial ID	Low proteinuria	Very low	ACEI/ARB HCQ
III/IV	Endo/extra capillary hypercellularity Subendothelial ID	Proteinuria Renal impairment	10-20% with treatment; high risk without treatment	ACEI/ARB HCQ GC and other IS
V	Widening of BM Spikes Sub-epithelial ID	Proteinuria Renal impairment	<10%	ACEI/ARB HCQ GC and other IS (selected cases)

ISN/RPS: International Society of Nephrology/Renal Pathology Society; ESRD: end-stage renal disease; ID: immune deposits; ACEI: angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blockers; HCQ: hydroxychloroquine; GC: glucocorticoids; IS: immunosuppressant; BM: basement membrane.

The main treatment goal in LN is to achieve a prompt response because absence of an early response (6 months) is a poor long-term prognostic factor (Houssiau, 2004; Tamirou, 2016). It was recently demonstrated in two studies that achievement of proteinuria < 0.7-0.8 g/day at 12 months was the best predictor of long-term renal outcome (Dall'Era, 2015; Tamirou, 2015). The current paradigm is to induce a response with an intensive approach using potentially toxic drugs for a short period of time and to maintain the response with a less aggressive immunosuppressant for the long-term. This said, complete renal response rates after 6 months of induction therapy remain low with current therapies (in most studies below 30%), which means that there is room for improvement. Similarly, relapses occur in more than 20-40% of patients (according to length of follow-up) despite maintenance therapy, indicating that further research is needed. Prognostic factors include non-white race, poor socioeconomic status, uncontrolled hypertension, high activity and chronicity on biopsy, renal impairment at baseline and poor initial response to therapy (Austin, 1995). Existing guidelines for the treatment of lupus nephritis include the ACR and EULAR/ERA-EDTA recommendations (Bertsias 2013, Hahn 2012). A comprehensive overview of LN treatment was recently published (Zampeli, 2017).

2.1.1 Induction treatment

Three different immunosuppressive regimens can be proposed for patients with Class III/IV LN, namely

- i) NIH IV CYC (0.75-1g/m² monthly x 6) combined with IV methylprednisolone and oral GCs (Austin, 1986; Boumpas, 1992; Gourley, 1996; Illei, 2001);
- ii) Euro-Lupus IV CYC (500 mg every two weeks x 6) combined with pulse IV methylprednisolone (3 daily pulses of 750 mg) and oral GCs (prednisolone 0.5 mg/kg/d) (Houssiau, 2002) or
- iii) MMF (2-3 g/day) (Chan, 2000; Ginzler, 2005; Ong, 2005; Appel, 2009).

The Euro-Lupus Trial showed similar efficacy between option i and ii, although the patients were mostly of Caucasian descent and with moderate nephritis (Houssiau, 2002). Another aspect in the original trial was the start of maintenance therapy with AZA, which started after 3 months in the low dose CYC group and after 12 months in the high dose CYC group where 2 extra quarterly pulses of CYC were given. Results after 10 years' follow-up have been published and are comparable (Houssiau, 2010). Finally, it should be stressed that the Euro-Lupus regime is also efficacious in LN patients presenting with more severe disease at baseline and in a more racially diverse LN population, as recently demonstrated in the US-based ACCESS trial (Wofsy, 2013).

All RCTs comparing NIH IV CYC to MMF concluded that the two regimens are equally toxic and efficacious, at least in the short and medium term, even for severe LN patients (Tang, 2008; Rovin, 2013; Appel 2009; Ginzler 2005). This was also the conclusion of a Cochrane systematic review (Henderson, 2012) comparing MMF to CYC as induction (and also MMF vs AZA as maintenance). A recent Bayesian network analysis even showed higher remission rates and more favourable safety profile with MMF (Lee, 2015). That said, MMF is more patient-friendly, does not interfere with fertility and can be readily monitored by measurements of mycophenolic acid serum titers. Lower response rates to IV CYC (compared to MMF) have been reported in Hispanics and Blacks (Isenberg, 2010). This does not mean that IV CYC should be withdrawn from the armamentarium of LN. Very long-term data (at least 10 years) are only available so far for LN patients treated with IV CYC. Importantly, IV CYC treatment ensures optimal adherence, especially the Euro-Lupus IV CYC regime because patients are seen every fortnight in the clinic. The Euro-Lupus regime was also tested against MMF in an Asian LN population and no differences could be observed (Rathi, 2016).

AZA induction therapy has been compared to NIH IV CYC. While no more cases of ESRD were observed in the AZA group, there were more renal relapses and more chronic changes on repeat renal biopsies in the AZA group (Grootscholten, 2006; Grootscholten, 2007; Arends, 2012). Except in selected cases (e. g. for toxicity concerns regarding IV CYC and MMF or because of onset of LN during pregnancy), AZA is not recommended as induction therapy (Bertsias, 2012).

Tacrolimus has been studied against MMF in Chinese patients with AZA maintenance and appeared non-inferior, although a trend towards more renal flares and renal function decline with tacrolimus was observed during the follow-up 5 years (Mok, 2016). The combination of MMF and TAC was superior tot IV CYC for achieving a complete renal remission in another Asian study (Liu, 2015).

2.1.2 Maintenance treatment

Two drugs are mainly used for maintenance therapy in LN: AZA (ideally 2-2.5 mg/kg/day) and MMF (usually 2 g/day). The long-term quarterly high-dose IV CYC NIH maintenance regime cannot be recommended anymore, given an unacceptable rate of premature gonadal failure (Boumpas, 1993). AZA and MMF have a very reasonable toxicity profile for long-term use and have been compared in two RCTs : MAINTAIN (Houssiau, 2010b; Tamirou 2016) and ALMS (Dooley, 2011). While in the latter, a multi-ethnic study, MMF was shown superior to AZA to prevent renal relapses, this was not the case in the former, an European-based trial with mainly Caucasian patients. The design of these two trials are different and their results should therefore not be compared head-to-head. Rather, we would suggest, as recommended by the EULAR (Bertsias, 2012) and the ACR (Hahn, 2012), that the two drugs can be used as maintenance therapy of LN, an opportunity since not all patients will respond to the same drug. Patients planning pregnancy should not use MMF which is absolutely contraindicated, at least during the first 3 months. Calcineurin inhibitors are an alternative to AZA or MMF in selected cases. Their stringent antiproteinuric effect, through their effect on podocytes is of interest, as well as the possibility to use them during pregnancy. Nevertheless, their toxicity profile (hypertension, renal impairment, effects on lipid profile, tremor, hirsutism, gum hyperplasia, etc.) and the rebound of proteinuria after their withdrawal explain why we do not propose them as first line maintenance drugs in LN.

An understudied topic is when to stop immunosuppression, as very few studies have addressed this pivotal question (Moroni, 2006). In the absence of data it seems prudent to maintain AZA or MMF for at least several years after remission, or at least very good disease control, is achieved. Of course, each patient's individual situation must be considered. Most experts feel that GCs can be discontinued relatively soon after a full response has been achieved, but this will also depend on the presence of extra-renal manifestations.

2.1.3 Membranous LN

Membranous lupus glomerulonephritis (ISN/RPS Class V LN) is characterized by sub epithelial immune deposits. It can exist in isolation or be associated with proliferative Class III/IV disease. In the latter cases, most physicians consider that the presence of proliferative lesions guides therapy. Moreover, patients treated for proliferative disease sometimes switch to membranous LN, discovered on repeat kidney biopsy performed because of persisting proteinuria.

Treatment of pure membranous LN does probably not differ from that of idiopathic membranous nephropathy. Based on the nephrology experience, for patients with mild proteinuria a “watchful waiting” approach with optimal blockade of the angiotensin renin aldosterone system is usually appropriate. In patients with severe proteinuria, immunosuppressants are usually added, combining GCs with either MMF, AZA or CNI. In a controlled trial performed at the NIH, patients with pure membranous LN received (A) CSA

and alternate-day GCs; or (B) alternate-month IV CYC for 6 doses and alternate-day GCs; or (C) alternate-day GCs alone. Regimes (A) and (B) were both found superior to (C) at one year, but, interestingly, while the effect was prompter with CSA, relapses were more frequent than in the IV CYC group (Austin, 2009). A subset analysis performed in the 84 pure membranous LN cases randomized in two large recent randomized LN trials comparing MMF and IV CY (Ginzler, 2005; Appel, 2009) revealed that both drugs were equally effective at 24 weeks (Radhakrishnan, 2010). Subcutaneous heparin is used in the prevention of thrombosis in patients with nephrotic syndrome and low serum albumin (< 2 g/dL).

2.1.4 Biologics in LN

As already alluded to, none of the biological therapies tested so far has demonstrated effectiveness in LN as add-on therapy, superimposed to standard of care. The future of targeted therapy in LN may therefore well be elsewhere, e. g. as a GC-sparing agent or for the treatment of refractory cases not responding to at least 6 months of standard immunosuppression, as currently tested in the RING study.

2.1.5 Optimal care for LN patients

The principles of optimal care for LN are summarized in Table III

Table III: Optimal care for LN patients

Early detection and complete baseline evaluation, including renal biopsy
Education on the long-term risks and the treatment goals
Follow-up in specialized Lupus Clinics
Identification of non-adherence to therapy
Minimize glucocorticoids
Early treatment switch in case of insufficient response after 6 months
Optimal renal protection (BP: $\leq 120/80$ mm Hg; antiproteinuric therapy)
Prevention of cardiovascular disease (smoking cessation, weight control, BP control, lipids)
Prevention of GC-induced bone loss
Immunization (HPV, influenza, <i>Streptococcus pneumoniae</i>)

2.1.6 Renal replacement therapy

Between 10 and 20% of LN patients will require renal replacement therapy (RRT), the lower figures being observed in RCTs and the higher in the real world. It is of critical importance to look for these data in the very long-term, since LN usually starts in young patients. In some very refractory cases, it may be wiser to step down immunosuppression, when the battle is lost anyway, in order to avoid further toxicity. Haemodialysis is preferred by certain expert nephrologists based on a higher rate of infectious events in LN patients treated by peritoneal dialysis, but this view is not unanimously shared (Rietveld, 2008). Most LN patients with ESRD are suitable candidates for renal transplantation (RT) (Nossent, 1991). Some recommend waiting to transplant to

allow for quiescence of the SLE-related immune activity. Other data suggest that longer waiting times to transplant may be associated with equivalent or worse, not better, graft outcomes among LN-ESRD patients (Plantinga, 2015). More studies are needed to clarify the potential confounding effect of lupus disease activity on the observed associations. When feasible, the ideal setting is pre-emptive grafting (before ESRD is reached) with a living donor (Lochhead, 1996; Ward, 2000). Recurrence of LN in the graft is possible but rare (1-4%) (Moroni, 2005; Stone, 1997). On the whole, graft survival has been reported to be similar compared to other ESRD groups and lower than in other glomerular diseases. The factors associated with a poor outcome of RT are listed in Table IV.

Table IV: Poor prognostic factors in renal transplantation for SLE

Cadaveric transplantation	Living donor RT is associated with better graft survival
Ethnicity	Black patients have a poorer graft survival
Anti-phospholipid positivity	Thrombotic events are much more frequent in RT recipients with APL antibodies
Disease activity after RT	Persistent lupus disease activity requires further immunosuppression but is associated with more infectious events
Clinical status at the time of RT	Poor general medical condition deleteriously impacts graft and patient survival after RT
Dialysis duration	Long-term dialysis risk factor for graft failure? (unclear)

2.2 Central nervous system involvement

Neuropsychiatric involvement in SLE (NPSLE) is characterized by a variety of clinical manifestations and its pathogenesis and assessment are complex and debated. As a consequence, designing controlled trials is extremely difficult and treatment of NPSLE strongly relies on the treating physician's clinical experience (Hanly, 2005). Treatment of NPSLE can be symptomatic, based on experience with, for example, anticonvulsants, antipsychotic or antidepressant drugs and/or aimed at controlling pathogenetic mechanisms, such as inflammation and thrombosis. EULAR recommendations have been published to guide in this process (Bertsias, 2010).

Faced with a patient with possible NPSLE, two issues are critical. First, is it really related to lupus? Many clinical manifestations are vague and can be best explained by alternative hypotheses, such as infection (viral, opportunistic, bacterial, TB), drug toxicity and even fatigue or depression. CNS imaging, cerebrospinal fluid examination and cognitive tests are not always helpful, thereby making the picture even more complicated. Other demyelinating diseases, such as multiple sclerosis, need to be ruled out (Magro Checa, 2013). The second dilemma deals with the mechanism involved: is it inflammation or thrombosis mediated by anti-phospholipid antibodies? Or do both play a role? While this question might look trivial in theory, the answer is always difficult at the bedside. Yet, treatment is very different!

The data currently available, albeit scarce, support the use of IV methylprednisolone and IV CYC pulse therapy as first choice treatment in severe NPSLE, after exclusion of manifestations which could be attributed to the presence of anti-phospholipid antibodies (Trevisani, 2006, Cochrane review). In a retrospective analysis, CYC was found efficacious in treating patients with organic brain disease (55% of the patients in that study), stroke (35%), neuropathies (10%), persistent headache (10%), seizures (9%), psychiatric manifestations (26%), transverse myelitis (16%) and cranial neuropathies (13%). Improvement was observed in 61% of the patients, stabilisation in 29% and deterioration in 10% (Neuwelt, 1995). Only 1 non-blinded randomized controlled trial compared the efficacy of pulse IV methylprednisolone versus IV CYC in treating NPSLE. CYC was administered as monthly pulses (0.75 g/m²) for 6 months and then every 3 months for one year. CYC was significantly more effective in the treatment of NPSLE than pulse IV MP, particularly in treating patients with seizures, optic neuritis, peripheral neuropathy, and brainstem disease (Barile-Fabris, 2005). In acute severe NPSLE, such as transverse myelitis, prompt installation of combined therapy with pulse IV methylprednisolone and IV CYC should be considered strongly.

In refractory NPSLE cases, other treatments can be tried, without strong evidence base. Case reports suggest that PE (Neuwelt, 2003; Bartolucci, 2007), IVIG (Sanna, 2008), RTX (Narvaez, 2011) and even intrathecal dexamethasone and MTX (Zhou, 2008) can be useful.

In patients with SLE and the anti-phospholipid syndrome, the approach should clearly be different, with oral anticoagulation strongly advised to maintain an INR value around 2.5-3 (Ruiz-Irastorza, 2005). The possible role of anti-platelet agents in these patients is under discussion, as is the intensity of anticoagulation (INR) and the duration of therapy. Given the effects of antimalarials on platelet aggregation, HCQ should be considered as well. In Table V, a tentative treatment scheme for NPSLE is proposed.

Table V: Management of NPSLE

Inflammatory mechanisms *	
Induction	Pulse IV MP and IV CYC Symptomatic therapy Plasma exchange in refractory cases Rituximab in refractory cases
Maintenance	GC tapering Steroid-sparing immunosuppressant: AZA, MMF(?) Symptomatic therapy
Thrombotic mechanisms *	
Induction	Oral anticoagulation (target INR 2.5-3.0) Symptomatic therapy
Maintenance	Oral anticoagulant (target INR 2.5-3.0) Symptomatic therapy Low-dose aspirin

** beware that both mechanisms can play a role at the same time*

2.3 Mucocutaneous involvement

Expertise is needed to make a proper distinction between acute, subacute and chronic cutaneous lupus erythematosus (CLE), not to mention lupus profundus, chilblain lupus and lupus tumidus (Okon, 2013). The differential diagnosis is broad: some more common conditions, such as rosacea, need to be ruled out. In patients with cutaneous involvement, photo protection is very important and strict sunscreen adherence and adequate clothing must be emphasised and/or application of a sun protection factor ≥ 50 spf about 20 minutes before sun exposure (Kuhn, 2011a). Topical GCs, topical tacrolimus and antimalarials are first-line therapies. Topical GCs must be prescribed and preference must be given to the potent fluorinated derivatives (instead of hydrocortisone) (Jessop, 2009). They should however be used with “holiday” periods (e. g. two weeks on and one week off) to avoid skin atrophy and telangiectasias. Topical CNIs have been introduced more recently with excellent results reported for tacrolimus ointment (Tzung, 2007; Kuhn, 2011b). Antimalarials are the standard systemic therapy of CLE. HCQ is most frequently used, but in more severe cases of chronic CLE, better results have been reported with chloroquine, quinacrine and with combinations of different antimalarials (Meinao, 1996; Toubi, 2000). When antimalarials fail, MTX has been shown effective in a few RCTs and case series, and AZA, THA and dapsone can be efficacious in difficult to treat cases (Kuhn, 2016). Belimumab showed efficacy in a subgroup analysis of the BLISS trials for mucocutaneous parameters (Manzi, 2012). THA deserves special attention given its impressive effects in refractory chronic CLE (Cortez-Hernandes, 2012), with the caveats already mentioned before. There is one case report of the successful use of tocilizumab (anti-IL 6) in a case of refractory SLE with lupus tumidus and urticarial vasculitis (Makol, 2012). The type I IFN system has also become a potential target in cutaneous disease, since skin lesions are characterized by a strong expression of IFN-regulated proinflammatory cytokines. Anifrolumab showed significant improvement of disease activity including skin lesions, suggesting efficacy in cutaneous lupus (Furie, 2015).

2.4 Musculoskeletal involvement

Non-erosive polyarthritis, affecting predominantly finger joints, wrists and knees, occurs in the vast majority of SLE patients (about 90% of cases) and is one of the earliest disease manifestations. Low-dose GCs and antimalarials are the first choice treatment for polyarthritis, together with NSAIDs in the absence of contraindications. In more severe GC-dependent cases, MTX can be prescribed based on several trials and case series (Gansauge, 1997; Carneiro 1999; Islam, 2012; Rahman 1998; Winzer, 2010), as well as LEF (Remer, 2001; Wu, 2013), AZA or belimumab (BLISS trial). Less frequently, SLE patients develop a deforming arthropathy, called Jaccoud’s arthropathy, which mostly appears insidiously and induces much disability in daily life activities. While the classical acute polyarthritis is usually promptly responsive to therapy, few interventions (including rehabilitation procedures) are helpful in Jaccoud’s arthropathy.

Osteoporosis has long been neglected in SLE, based on the wrong assumption that young women were protected against GC-induced bone loss by their female hormones. SLE patients, however, have an increased risk of osteoporotic fractures (1.2-4.7 fold) compared to the general population and the risk is further increased by a longer disease duration, GC use in the previous 6 months, and previous osteoporotic fractures (Bultink, 2014). Another cohort study detected prevalent vertebral fractures in 18-50% of SLE patients and revealed low 25-hydroxyvitamin D serum levels, low body mass index and baseline use of antimalarials as associated with bone loss in SLE (Bultink, 2016). Smoking, renal and ovarian failure, and reduced exercise are traditional risk factors often encountered in SLE patients. These data show that this comorbidity cannot be neglected and risk factors should be actively assessed and if possible treated, for example by vitamin D3 and calcium supplementation, exercise and smoking cessation. The use of anti-osteoporosis medication in premenopausal women has unfortunately remained poorly studied despite the clear need for data in patients with severe SLE starting at younger ages.

Avascular osteonecrosis (AON) is frequent in SLE, mainly in patients treated with high-dose GCs (Houssiau, 1998) and is a major contributor to musculoskeletal damage, as assessed by the SLICC-DI. The best prevention is to avoid high doses of GCs as much as possible.

2.5 Haematological involvement

Mild leukopenia is frequent when SLE is active and does not require treatment per se. Anaemia is also common in SLE and might be unrelated (iron deficiency being common in women of childbearing age) or linked to the disease, either through chronic inflammation (active SLE commonly induces erythroblastopenia), renal impairment, or haemolysis (much rarer). In case of erythroblastopenia, treatment of lupus usually corrects the anaemia. Active haemolysis (low haptoglobin, elevated LDH, high reticulocyte count) usually requires high dose GCs, promptly tapered, together with a GC-sparing agent, such as AZA or MMF. In relapsing or refractory cases, RTX and recently belimumab have been shown useful. Mild thrombocytopenia, as for example often seen in the presence of antiphospholipid antibodies, does not require specific therapy. Severe thrombocytopenia can be life-threatening and requires high dose GC treatment (pulse IV methylprednisolone and oral prednisolone) and/or IVIG. Again, steroid-sparing agents should be prescribed if remission cannot be maintained with low dose GCs. RTX and splenectomy can be considered in refractory/relapsing cases.

When thrombotic thrombocytopenic purpura (or thrombotic thrombocytopenic microangiopathy) occurs in the setting of pre-existing SLE the syndrome is typically associated with the presence of antiphospholipid antibodies. This diagnosis should always be excluded in a lupus patient with pancytopenia, mainly acute thrombocytopenia, haemolysis, an excess of schistocytes on blood smears, renal failure and other micro-thrombotic manifestations (e. g. skin necrotic lesions). This microangiopathy, sometimes present within the

frame of the so-called “catastrophic antiphospholipid syndrome” requires aggressive therapy combining plasma exchanges, anticoagulants and GCs.

The macrophage-activation haemophagocytic syndrome (Rosado, 2013) is a potentially fatal complication of SLE, mainly in children (Parodi, 2009; Bennet, 2012), and should always be excluded in critically ill patients with fever, pancytopenia, elevated liver enzymes, coagulopathy (hypofibrinogenaemia), elevated ferritinaemia and high triglyceride levels. Bone marrow aspiration shows the typical picture of macrophages phagocytosing haematopoietic cells. The syndrome is a cytokine storm due to unabated macrophage activation. Prompt intervention is required with IV methylprednisolone and oral GC. In severe cases, IV CYC, CYA and cytostatic drugs such as etoposide may be useful adjunct therapies.

2.6 Serositis

The treatment of SLE-related serositis is mostly based on the usual treatment for active SLE. Medium doses of GCs are usually needed. Other immunosuppressants have been used successfully, such as AZA or MTX. Pleuro-pericardiocentesis may be required in case of large effusions or to rule out other diagnoses in difficult cases.

3. COMORBIDITIES

3.1 Cardiovascular disease

In 1976, Urowitz et al. first described a “bimodal mortality pattern” in SLE, with a first peak due to the disease itself and a second wave related to cardiovascular disease (CVD) (Urowitz, 1976). This pivotal observation was largely confirmed by many expert groups and it is now clearly established that SLE patients are at high risk of CVD (Manzi, 1997; Roman, 2003). While traditional factors (smoking, hypertension, diabetes, hyperlipidaemia, etc.) play an obvious role and must be reviewed (Table VI), they do not fully explain the risk, thereby lending support to the possibility that unabated lupus-induced inflammation per se is a risk factor. In this respect, one should expect that GC use would be associated with improved cardiovascular prognosis but the data prove exactly the contrary: prednisone doses of more than 10 mg/day increase the cardiovascular risk two fold and doses of more than 20 mg/day fivefold (Magder, 2012), probably due to the well-known metabolic effects of GCs. Taken together, disease control is essential but this goal should be achieved with the lowest possible cumulative dose of GCs. Antimalarials contribute to a more favourable lipid (Rahman, 1999) and glucose (Petri, 1994) profile and display some antithrombotic activity (Ruiz-Irastorza, 2006), by reducing the binding of antiphospholipid anti-beta2-glycoprotein I complexes to phospholipid bilayers (Rand, 2008). Finally, primary prevention with aspirin and statins should also be considered. In vitro and in vivo studies suggest that statins have direct anti-inflammatory, antithrombotic and plaque-stabilizing effects via a number of mechanisms, besides their well-known lipid-lowering effect. However, a well-designed randomized controlled trial (the LAPS trial) with atorvastatin failed to demonstrate prevention of progression of coronary artery calcium

content and carotid intima thickness in adult SLE patients (Petri, 2011), and therefore it is at present unclear if the use of statins can be advised in the absence of hypercholesterolemia.

Table VI: Cardiovascular risk factors and targets in SLE.

Risk factor	Target	Interventions
Blood pressure	<120 mmHg syst; <80 mmHg diast	ACEI/ARB as first choice
LDL cholesterol	<100 mg/dl or <130 mg/dl	Statins - HCQ
Diabetes mellitus	Fasting blood glucose <7.0 mmol/l	Weight loss – Metformin – HCQ
Smoking	Stop smoking	Nicotine replacement – Bupropion – Varenicline
Obesity	Body mass index <25 kg/m ²	Diet – Aerobic exercise
Homocysteine	<85 µg/dl	Folic acid supplements

3.2 Other comorbidities

Relevant comorbidities and the main preventative measures are shown in Table VII.

Table VII: Comorbidities in SLE.

Comorbidity	Interventions
Cardiovascular disease	See. Table VI
Osteoporosis	Less GCs Calcium salts and D3 supplementation Bisphosphonates in selected cases Exercise Smoking cessation
Infections	Less GCs Anti-influenza immunization (yearly) Anti-pneumococcal immunization (q5 years) Anti-HPV
Vitamin D3 deficiency	D3 supplementation (25-OHD3 ≥25 ng/ml)
Fatigue	Exercise
Malignancy	PAP smears (yearly)
Secondary fibromyalgia	Exercise Pain clinic

Prevention of infections deserves special attention as it is one of the leading causes of death in SLE (Cervera, 2003). Not only opportunistic infections but also common pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, contribute to mortality. SLE patients must be vaccinated against relevant pathogens (but note that the use of live vaccines may be contraindicated if they take GCs and/or other immunosuppressants). Current data suggest that vaccination of SLE patient is safe and efficacious (Kuruma, 2007; Battafarano, 1998), although serum antibody titers may be lower, but sufficiently protective; older concerns that vaccination could trigger lupus flares have not been born out in carefully designed studies.

4. ADHERENCE TO THERAPY

Not surprisingly, many young lupus patients do not take the many pills we prescribe to treat their L or LN, as recently demonstrated by HCQ blood titers measurements. Some patients take their medications only for a few days before the visit the clinic, a common phenomenon in chronic diseases known as “white coat compliance”. Thus, a hypertensive patient who wants to please his physician will take a few blood pressure-lowering pills for a short period of time preceding the visit and will be declared compliant since his/her blood pressure levels measured the day of the visit will be deemed satisfactory. In contrast, patients taking HCQ once in a while will be unmasked by whole blood HCQ measurements. In a retrospective analysis, more lupus flares were observed in patients who were less compliant (Costedoat-Chalumeau, 2007). Non-adherence can be addressed in clinical practice by repeated explanations given to lupus patients and their relatives on the reasons why each drug is prescribed, and by sketching the global treatment plan as soon as the treatment is started, so that patients understand that many of the drugs will be progressively withdrawn or their dose tapered, even if some will be prescribed for several years. In this respect, the help of a nurse practitioner in our busy lupus clinics can be most valuable.

SUMMARY POINTS

- Glucocorticoids are responsible for some of the damage observed in SLE. Their use should be limited to the shortest possible period of time. Intravenous pulse methylprednisolone therapy is useful for acute life-threatening cases and may allow reduction of peak oral GC dose.
- Antimalarials should be considered for all SLE patients, even in the absence of overt active clinical manifestations. Their benefits include flare prevention, amelioration of some SLE symptoms, and beneficial effects on lipid and glucose profile. They are also believed to have antithrombotic properties and may reduce cardiovascular risk. Antimalarials are safe in pregnancy and need not be discontinued.
- In lupus nephritis, intravenous pulse cyclophosphamide (either the low-dose Euro-Lupus regimen or the higher-dose NIH regime) and mycophenolate mofetil are equivalent induction therapies. Azathioprine and mycophenolate mofetil can both be used for long-term maintenance treatment. Yet, further improvement is eagerly awaited since complete renal remission rate is only 30% after induction therapy and since up to 40% of patients suffer from renal relapse.
- Belimumab is the first biologic approved for the treatment of lupus. It was shown superior to standard of care in two pivotal trials. Yet, its precise place in daily practice needs to be further defined. Other biologic therapies are currently being tested, with promising results for the type-1 interferon inhibitor anifrolumab.
- Despite two negative randomized trials, rituximab deserves further investigation, based on many reports suggesting efficacy in severe refractory cases of lupus nephritis and of some other lupus manifestations. Several trials are currently ongoing under the umbrella of the Lupus Nephritis Trials Network (www.lupusnephritis.org).
- Kidney transplantation is an important option for patients with end-stage renal disease. Recurrence of lupus nephritis after renal transplantation is rare and graft survival is by and large comparable to a control population.
- Patients with SLE are at increased cardiovascular risk. Traditional risk factors should therefore be monitored and controlled by lifestyle modification (*e. g.* diet, weight control, smoking avoidance) and by specific treatments (*e. g.* statins, antihypertensive).
- Patients with SLE, especially those treated with GC and other immunosuppressants, are at high risk of infections. Immunization against influenza and *Streptococcus pneumoniae* is strongly recommended. Osteoporosis is another major comorbidity to evaluate and manage if necessary.
- Lack of adherence to therapy may contribute to treatment failure.

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EULAR on-line course on Rheumatic Diseases

Systemic lupus erythematosus: treatment

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IN-DEPTH DISCUSSION I

**Treatment of systemic lupus erythematosus during
pregnancy**

1. Morbidity and risk factors in lupus pregnancy

Lupus patients run high-risk pregnancies for themselves and their baby, as illustrated by the data gathered in a meta-analysis performed on 37 studies, totalizing 2,751 pregnancies in 1,842 lupus patients (Smyth, 2010). They are summarized in Table I.

Table I: Foetal and maternal morbidity in SLE pregnancy*

Foetal complications (%)		Maternal complications (%)	
Unsuccessful pregnancy	23.4	Lupus flare	25.6
Premature birth <37/40	39.4	Hypertension	16.3
Still birth	3.6	Nephritis	16.1
Neonatal death	2.5	Pre-eclampsia	7.6
Foetal growth retardation	12.7	Eclampsia, stroke and death	<1.0

*: After Smyth, 2010

Several risk factors of poor foetal and maternal outcome have been repeatedly identified (Bramham, 2011; Chakravarty, 2005; Kwok, 2011). They include active maternal disease at the start of pregnancy (and obviously during pregnancy), past history of renal disease, past history of thrombosis, uncontrolled hypertension, smoking and antiphospholipid antibody positivity. Regarding the latter, it was hypothesized that placental thrombosis was the major mechanism leading to foetal loss but this assumption is not confirmed by histological examination of lupus placentas, where thrombosis is rare. Rather, the current view is that antiphospholipid antibodies, actually anti- β 2-glycoprotein 1 antibodies, crosslink β 2-glycoprotein 1 molecules massively anchored to phosphatidylserine flipped to the outer layer of trophoblasts when these cells fuse during syncytium formation. This compromises their proliferation and differentiation and leads to defective placentation (Moroni, 2011). Heparin most likely interferes with this process by inhibiting binding of β 2-glycoprotein 1 to phosphatidylserine.

2. General management of lupus pregnancy

Preconception evaluation is pivotal. It may discourage pregnancy in the few patients with end-stage organ failure, such as a GFR below 30 ml/min/1.73m², pulmonary hypertension, heart or lung failure, etc. More frequently, it will help delaying pregnancy for several months until the disease is fully under control, in order to optimize the success rate. Last, but not least, the medication chart will be discussed in depth in order to decide which drugs should be withheld (and when) and which ones should be continued or introduced.

Pregnant lupus patients should be followed by an experienced multidisciplinary team, ideally within the frame of a Lupus-in-Pregnancy Clinic, where obsessional medical and obstetrical follow-up can be provided. Besides standard clinical examination, the rheumatologist will check the following on monthly interval: serum

creatinine, full blood count, liver tests, urinalysis, proteinuria, serum complement and anti-DNA antibody titres. Of note, not all symptoms presented by lupus pregnant patients should be attributed to lupus! Thus, fatigue, facial blush, hair loss, anaemia, gingivorrhagias, dyspnoea and headaches are all very common in normal pregnancies and should not mislead the clinician. Thyroid tests should be performed at baseline given the high prevalence of autoimmune thyroid disease in SLE. Needless to say, immunization status against several pathogens needs to be checked, like in the normal pregnant population.

Pregnant lupus patients should see an obstetrician as soon as pregnancy is diagnosed in order to determine the age of pregnancy as accurately as possible. Then, monthly visits will be scheduled until week 20, every fortnight until week 28 and weekly thereafter. Between week 16 and 24, special attention will be given to the foetal heart rate in anti-SSA/Ro and/or anti-SSB/La patients (vide infra). Uterine, umbilical and cerebral artery Doppler studies will be performed on a regular basis as foetal surveillance tests. Placentation is best evaluated by uterine Doppler. Thus, the persistence of a protodiastolic Notch after week 26 reflects poor placentation and predicts poor outcome (prematurity, growth retardation). Umbilical Doppler evaluates placental resistance: an absence of end diastolic flow (a fortiori a reverse diastolic flow) after week 24 indicates increased placental resistance and correlates with poor outcome. At last, cerebral artery Doppler evaluates brain vessels vasodilation due to foetal hypoxia (the so-called brain sparing effect): a resistance index below the 10th percentile after week 24 also predicts bad outcome. Serial measurements are of the utmost importance because they help define a prognostic trend and contribute to the decision of elective premature delivery, based on the risk/benefit balance, after having induced foetal lung maturation with fluorinated glucocorticoids that cross the placental barrier.

The differential diagnosis between a renal lupus flare and preeclampsia is always difficult since both conditions cause proteinuria. Arguments in favour of each diagnosis, all relative, are described in Table II. Serum C3 levels are of special interest in this setting (Buyon, 1986). Elevated uric acid levels have been associated with pre-eclampsia rather than lupus (Bellomo, 2012).

Table II: Differential diagnosis between a lupus flare and preeclampsia

	Preeclampsia	Lupus flare
Extra-renal signs	-	+
Haematuria	-	+
Elevated liver tests	+	-
Low platelets	+	±
Microangiopathy	+	-
Elevated serum uric acid	+	-
Low serum complement	-	+
Elevated anti-DNA antibodies	-	+
Response to glucocorticoids	-	+
Response to delivery	+	-

3. Lupus medications

The most important rule is to control the mother's disease. In this respect, patients should be warned against abrupt withdrawal of all therapies, as they could be tempted to do without adequate preconception counselling. Lupus flares need to be adequately treated by non-fluorinated glucocorticoids (GC), which are not harmful to the foetus, as they are likely inactivated in the placenta. While GC, which can also be administered in IV pulse therapy, might be life-saving in critically-ill pregnant SLE patients, a note of caution must be made regarding the use of high doses of oral GC which have been associated with hypertension, diabetes and premature rupture of the membranes (Ostensen, 2006). The only immunosuppressants on the black list in pregnant SLE patients are cyclophosphamide, methotrexate and mycophenolate mofetil, because of their well-known teratogenicity. In very severe and selected cases, they could, however, be prescribed after the first trimester, when most of the organogenesis is done. NSAIDs are clearly contra-indicated, mainly after week 32 (premature closure of ductus arteriosus). Cyclosporine A, hydroxychloroquine and azathioprine (AZA) do not harm the foetus. A recent report indicated that offspring born from mothers treated with AZA run a higher risk of late development delays (Marder, 2013), but these data require confirmation in a larger prospective study.

4. Management of hypertension

Hypertension is common in SLE patients, especially in those suffering from lupus nephritis. Recommendations regarding blood pressure lowering drugs parallel those for the general pregnant population. Thus, ACEI/ARBs must be withdrawn from the second trimester onwards because they can cause ACEI foetopathy (oligohydramnios, renal failure, hypotension and bone malformations). β -blockers may induce foetal bradycardia and intra-uterine growth retardation. Diuretics are not advisable given their effect on placental perfusion related to maternal volume depletion. Treatment of hypertension therefore relies on the use of α -methyldopa, calcium channel blockers, labetalol and hydralazine.

5. Management of the antiphospholipid syndrome in lupus pregnancy

Table III is aimed at guiding physician's choice according to different clinical sketches. Two proposals are evidence-based. First, patients with a history of thrombosis treated with vitamin K antagonist, whether they have – or not – antiphospholipid antibodies (APL Ab), must be switched as soon as possible to full dose heparin or full dose low-molecular weight heparin (LMWH) (sketch #1). Second, patients with antiphospholipid antibodies (APL Ab) and at least one episode of late foetal loss (after week 10) or early eclampsia or severe intrauterine growth retardation, the combination of low-dose aspirin and prophylactic doses of heparin (or likely LMWH) must be prescribed as it was shown to improve foetal outcome (Empson, 2005; Mak, 2010) (sketch #4). The jury is still out whether low-dose aspirin alone is sufficient for patients with recurrent early

foetal losses, with some physicians advising combination therapy upfront, while others will reserve it for low-dose aspirin failures (sketch #3). Whether asymptomatic APL Ab-positive patients should be given low-dose aspirin is also a matter of debate (sketch #1).

Table III: Management of the antiphospholipid syndrome in pregnancy

Sketch	APL Ab	History of			Proposal
		Thrombosis	Recurrent early ($\leq 10/40$) foetal losses	Late foetal loss ($>10/40$) Early preeclampsia	
#1	+/-	+	0	0	LMWH full dose
#2	+	0	0	0	No treatment or low-dose aspirin
#3	+	0	+	0	Low-dose aspirin Combined with LMWH prophylactic in case of aspirin failure
#4	+	0	0	+	Combination of low-dose aspirin and LMWH prophylactic

6. Management of the neonatal lupus syndromes

Neonatal lupus (NNL) is a rare syndrome observed in a very small percentage (2%) of offspring born from mothers with anti-Ro/SSA and/or anti-La/SSB antibodies, who suffer from SLE, Sjögren's syndrome or are asymptomatic antibody carriers (Brucato, 2002). The autoantibodies cross the placenta and may harm the foetus until they disappear from the circulation. The most dire clinical manifestation is a complete congenital heart block (CHB), that usually appears between week 16 and 24 of pregnancy and is fatal in 15 to 30% of cases, with many survivors requiring permanent pacing. Abrupt onset is classical but, in some cases, the complete block is preceded by a lesser degree block. Myocarditis and pericarditis may be associated. The skin might be involved, typically with subacute lesions that disappear after a few weeks or months, very much in contrast to the CHB, which is permanent. Other manifestations of NNL include hepatosplenomegaly, hepatitis, haemolysis and thrombocytopenia. The risk of recurrence (in another child) is high (20%). The only recommendation is to perform serial echocardiograms and obstetric sonograms, at least every 2 weeks starting from week 16 onwards, in mothers with anti-Ro/SSA and or anti-La/SSB antibodies. The goal is to detect early foetal heart abnormalities (*e. g.* premature atrial contractions, signs of congestive heart failure or pericardial effusion), that sometimes precede complete atrioventricular block and may justify therapy with fluorinated GC, that cross the placenta. Routine prophylactic therapy with fluorinated steroids is not recommended even in women who previously gave birth to a child with NN. The hope that IV Ig maternal therapy would lower the risk of recurrence of CHB was turned down by a recent prospective study (Friedman,

2010). By contrast, a retrospective study suggests that HCQ use significantly reduces the recurrence of CHB (21.7% in non-HCQ users *versus* 7.5% in HCQ users) (Izmirly, 2012).

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module

EULAR on-line course on Rheumatic Diseases

Systemic lupus erythematosus: treatment

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IN-DEPTH DISCUSSION II

**How to translate treatment recommendations into daily
practice**

In the main text of this module, various treatment options and their indications in SLE are discussed. Despite heterogeneity of SLE and the limited number of controlled trials in certain areas, treatment recommendations have been published for lupus (Bertsias, 2008) and lupus nephritis (Bertsias, 2012; Hahn, 2012). The aim of this in-depth discussion is to facilitate the transfer of general treatment recommendations to each individual lupus patient. Treatment should be based on regular assessments of *i*) disease activity, *ii*) damage, *iii*) quality of life (and other patient reported outcomes), *iv*) co-morbidities, and *v*) drug toxicity.

Disease activity assessment should always support treatment decisions at the bedside. Several activity scores (SLEDAI, SLAM, ECLAM, BILAG) have been validated which can be used in clinical practice. Probably the most complex (but also the most comprehensive) instrument is the BILAG index, in which the scoring is based on the principle of physician's intention to treat in 8 organ domains

(<http://etheses.bham.ac.uk/149/1/Yee08PhD.pdf>). Grade A and B flares, which are defined by the requirement for potent immunosuppression, are now used as inclusion criteria in many clinical trials, and the definitions used to characterize these flares, in the 8 organ domains, comprise most of the reasons for intervention in active lupus patients. Therefore, if appropriate teaching is provided, the BILAG scoring system captures a very clear picture of active, controlled or uninvolved organs. While full control of disease activity should be the ultimate goal of immunosuppressive therapy in SLE, persistent complete remission is rarely achieved in the real world (Urowitz, 2005) and tight control of disease activity is only a very recent approach in SLE, very much in contrast to what is already applied for many years in rheumatoid arthritis. A potential risk could be to over-treat lupus patients thus exposing them to unnecessary drug-related side effects. The aim of the recently described treat-to-target approach in SLE is to achieve minimum disease activity over prolonged periods of time without drug-induced morbidity, with the hope to reduce damage accrual (Mosca, 2012), as assessed by the SLICC damage index (Gladman, 2000).

Besides regular evaluations of disease activity and damage, more attention should be paid to quality of life (QoL). This outcome measure is obviously the most important from a lupus patient's perspective and is becoming increasingly relevant, thanks to improved survival rates and due to the growing need for more clinically- and scientifically-based arguments to justify the reimbursement of expensive drugs, such as biologics. Patients with SLE generally perceive their health as being suboptimal, with 35–50% of patients rating their health as 'fair/not so good' or 'poor' (Zink, 2004; Fischer-Betz, 2005; Yelin, 2007; Katz, 2009). All subscales of the SF-36, a universal instrument to evaluate QoL, are impaired in comparison to healthy controls (Barta, 2010). The level of health-related QoL is only partially explained by disease activity and damage. Across all studies, the most commonly implicated factors impairing the QoL of SLE patients are older age, fatigue and the coexistence of neurological or psychiatric disorders (especially depression and anxiety) (Schmeding, 2013). Fatigue is clearly a major issue, even in patients with fully controlled disease. Reasons for fatigue are manifold: anaemia, decreased vitamin D levels, disease activity, secondary fibromyalgia, depression, sleep disturbance,

lack of aerobic fitness and, most frequently, combination of all those. Lupus patients, like patients with other chronic illnesses, experience a vicious circle starting with disability, pain and fatigue caused by active disease, which is accompanied by depression and leads to inactivity. As a consequence, patients further limit their physical activities, thereby further reducing their aerobic capacity and further increasing their fatigue and disability. In addition to its direct effect on QoL, reduced physical activity favours premature atheroma and its cardiovascular consequences. Taken together, QoL should be in the focus of every visit. When disease activity is under control, patients should be advised to perform supervised exercises. There is only limited evidence that exercise improves fatigue in lupus patients but the data available so far at least document that physical training is safe in patients with mild disease activity and that many patients experience QoL improvement. This said, a direct start with exercise may be too high a hurdle for some heavily fatigued patients who will feel even more exhausted after training. For them, and also for those with overt depression, a psycho-educative training may be indicated as first approach (Haupt, 2005). It is of critical importance that patients switch from a passive to a more active coping strategy. In special cases, antidepressants may be indicated.

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Pregnancy related problems in rheumatic diseases, including the antiphospholipid syndrome

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Part I: pregnancy and rheumatic disease

LEARNING OBJECTIVES

- Recognise and evaluate specific maternal and foetal problems arising in different rheumatic diseases during pregnancy
- Recognise periods during and after pregnancy prone to a disease flare
- Perform a risk assessment in each woman planning a pregnancy
- Use an algorithm for treatment in patients planning a pregnancy
- Monitor and follow-up pregnant patients
- Explain the importance of an interdisciplinary approach in the follow-up of pregnant patients
- Counsel women with rheumatic disease desiring children

1. Introduction

Rheumatic diseases occur preferentially in women, often during child-bearing age. Most women with rheumatic disease wish to have children even when functional disability is present. Pregnancies in these women are now common. The interaction of pregnancy and the rheumatic diseases is varied, ranging from spontaneous improvement to aggravation of disease symptoms. Likewise, rheumatic diseases differ in the occurrence of complications during pregnancy and pregnancy outcome (table 1). This chapter describes the maternal course of several common and some rare rheumatic diseases during pregnancy, foetal outcome and treatment during pregnancy and post-partum. The antiphospholipid syndrome (APS) is described in part 2 of this chapter.

Table 1 Influence of pregnancy on the course of several rheumatic diseases and on foetal/neonatal outcome

Disease	Risk of major organ involvement during pregnancy	Increased risk of foetal/neonatal complications	Prevailing response of disease to pregnancy
Rheumatoid arthritis	Rare	Prematurity and IUGR increased in presence of active RA NLS	Improvement in about half of the patients
Ankylosing spondylitis	No	Prematurity	Active/aggravated
Juvenile idiopathic arthritis	No	No	Improvement
Connective tissue diseases†	Organ involvement not more frequent than outside pregnancy	Prematurity, IUGR, NLS	No major influence or variable
Systemic lupus erythematosus	Possible, especially renal involvement	Pregnancy loss, IUGR, prematurity, NLS	Active/aggravated
Antiphospholipid syndrome	No	Pregnancy loss, IUGR, prematurity	Higher risk of thrombosis especially in the peripartum period
Vasculitis	Respiratory tract, kidney	Foetal loss, prematurity, IUGR	Too few data to discern a major effect

†Sjögren's syndrome, systemic sclerosis, dermatomyositis/polymyositis.

NLS, neonatal lupus syndrome; RA, rheumatoid arthritis; IUGR : intrauterine growth restriction.

2. Specific terminology in pregnancy

2.1 Pre-eclampsia

According to the American College of Obstetrics and Gynaecology guidelines, the diagnosis of pre-eclampsia no longer requires the detection of proteinuria. Pre-eclampsia can be defined by the association of (1) persistent high blood pressure that develops during pregnancy or during the postpartum period (blood pressure >140 mm Hg systolic and/or >90 mm Hg diastolic in two separate readings taken at least 6 h apart), and (2) one of the following: proteinuria, low platelets, kidney or liver involvement, fluid in the lungs, seizures and/or visual disturbances.

2.2 HELLP syndrome

The diagnostic criteria used for the Haemolysis, Elevated Liver, Low Platelets (HELLP) syndrome are variable and inconsistent. Haemolysis defined as the presence of microangiopathic haemolytic anaemia, is the hallmark of the triad of HELLP syndrome. The classic findings of microangiopathic haemolysis include abnormal peripheral smear (schistocytes), raised indirect bilirubin, low haptoglobin levels, raised lactate dehydrogenase levels (threshold of 180–600 U/L) and significant drop in haemoglobin levels (Sibai, 2004).

2.3 Intrauterine growth restriction

Small gestational age (SGA) fetuses are those who are smaller than normal for gestational age. SGA can be associated with intrauterine growth restriction (IUGR) and occurs when the unborn baby is at or below the 10th weight centile for his or her gestational age because of pathological conditions.

2.4 Foetal loss in APS

In APS, foetal losses after 10 weeks of gestation are called foetal deaths, whereas in obstetrics, these foetal losses are still called miscarriages (early, or late when they occur after the first trimester).

3. Physiological changes during pregnancy

Multiple adaptations occur during normal pregnancy to allow for tolerance of an immunogenic allograft (the foetus). These adaptations include hormonal and cytokines changes during pregnancy. This is developed in the subsection 1.4 .

Pregnancy-induced hypercoagulability is also a physiological adaptive mechanism resulting in a higher risk of thrombosis, in particular during the third trimester and the six postpartum weeks. Concentrations of coagulation factors II, V, VII, VIII, X and von Willebrand factor rise significantly, accompanied by an increase in the concentration of plasma fibrinogen. Total protein S and activated protein C sensitivity decrease during gestation, whereas protein C levels are unaffected.

White blood cells, mainly neutrophils, erythrocyte sedimentation rate, D-dimers, C3 and C4 levels and CH50 activity physiologically increase during gestation.

Plasma and blood volumes slowly increase by 40–50% over the course of the pregnancy. Consequently, the haematocrit and haemoglobin levels decrease.

Heart rate and cardiac output also increase with a decrease in blood pressure. The glomerular filtration rate commonly increases by 50% with a fall in serum creatinine and urea levels. Proteinuria is increased owing to increased excretion, and levels of up to 300 mg/24 h are considered within the normal range in pregnancy (Germain and Nelson-Piercy, 2006).

4. Immunology of pregnancy

Conception induces a variety of hormonal changes in the maternal body which are necessary for the support of pregnancy and foetal survival. With advancing gestation a complex interplay between the maternal neuroendocrine system, the placenta and the foetus occurs. Circulating plasma levels of bound and unbound cortisol and sex hormones (oestrogens and progesterone) rise progressively during pregnancy. In addition to hormones, immunoregulatory factors are secreted by the placenta that suppress T cell proliferation and

induce tolerance or hyporesponsiveness in maternal T cells. The total number of T and B cells in the maternal circulation remains stable throughout pregnancy, though the composition of T cell subsets changes, especially regulatory T cells, which are a unique subset of suppressive CD4 T helper cells indispensable for immune tolerance to self-antigens and foreign antigens. They also are involved in the maintenance of tolerance and prevent the immunological rejection of the foetus during pregnancy. It has been reported that murine and human pregnancy is associated with an expansion of peripheral blood Treg cell pool compared with a non-pregnant woman, spiking in the second trimester. Thereafter the Treg number decreases to slightly above normal levels at delivery, which provides a partial explanation for the flares following birth.

Pregnancy does not result in a general state of impaired immunity. The maternal defence mechanisms remain intact with normal responses to active and passive immunisation but hyporesponsiveness or tolerance to foetal antigens.

4.1 Cytokines and the Th1/Th2 immune response

Successful pregnancy requires appropriate temporal expression of cytokine and cytokine receptor genes in the decidua and in the maternal circulation. Early studies in mice showed a shift of a Th1 to a Th2 immune response, where it also became evident that successful pregnancy was largely dependent on a Th2 cytokine profile whereas spontaneous abortion showed a Th1 cytokine pattern. Evidence for this shift of the Th response is strongest at the maternal–foetal interface. However, extended studies in animals and humans showed that a modulation adapted to the stage of pregnancy takes place, not a persistent domination of a Th2 cytokine pattern throughout pregnancy. Studies of maternal serum levels of cytokines and their receptors have shown an increase of anti-inflammatory cytokines which can induce tolerance. The increase of regulatory T cells during pregnancy suppresses the proliferation of interferon γ and interleukin 12 (IL-12)-producing effector T cells, and promotes the secretion of IL-10, IL-4 and transforming growth factor β .

4.2 Cellular communication between mother and foetus

Human leucocyte antigen (HLA) incompatibility between mother and child may be an advantage in pregnancy. Foetal cells and cell-free DNA routinely traffic into the maternal circulation during normal pregnancy. The concentration of foetal DNA increases over the course of pregnancy and decreases rapidly after parturition. Studies investigating the response of maternal peripheral blood mononuclear cells to trophoblast or paternal HLA antigens showed that paternal antigens stimulated the production of IL-4 thereby promoting a Th2 response.

4.3 Postpartum period

After delivery, the body readjusts to the non-pregnant state. At the same time, lactation creates a unique hormonal milieu. Thus, the postpartum period is not simply a reversal to the state before conception, but is a

state of its own. Some gestational changes, such as levels of glucocorticoids, reverse quickly, while others, such as lymphocyte subsets and their responses, readjust over weeks and months. As a consequence of decreasing cortisol, catecholamines and other factors, secretion of proinflammatory cytokines increases after delivery. Immunological rebound effects occur as shown by more vigorous B cell responses post-partum. Overall, post-partum is a vulnerable period with a risk of first onset or relapse of autoimmune disease.

5. Fertility

Rheumatic diseases can impair fertility (ability to have a child) and, more often, fecundity (time to achieving pregnancy) in several ways. Pain and stiffness in joints and muscles or involvement of connective tissue of the genital tract, as in systemic sclerosis (SSc), can make sexual intercourse difficult and reduce its frequency. In addition, fatigue, depression and some drugs such as methotrexate may decrease libido. Some patients do not wish to become pregnant out of fear of genetic transmission of their disease. Several autoantibodies can inhibit fertilization or implantation as in the APS. Some connective tissue diseases, like systemic lupus erythematosus (SLE) and APS, can be associated with increased pregnancy loss, which could reduce family size. In addition, chronic disease often disturbs the hypothalamic–gonadal axis and the hormonal balance, resulting in periods of hypogonadism. Thus, complex interactions exist between disease, sexual functioning and fertility. Few drugs are gonadotoxic like the alkylating agents, but treatment with potentially foetotoxic drugs can exclude pregnancy and thereby induce, at least temporarily, infertility. Non-steroidal anti-inflammatory drugs (NSAIDs) can delay or inhibit ovulation due to the inhibition of prostaglandins (Edelman et al, 2013). Recent studies on animal models have suggested that the effect of COX-2 inhibition on the ovary may be strong enough to inhibit ovulation, going as far as to test its potential usefulness as an emergency contraceptive. In one study, the rate of ovulation decreased to 25% in women treated with NSAIDs around the time of ovulation. In another study, ovulation was delayed by a mean of 5 days in women treated with NSAIDs (Bata et al, 2006). This should be kept in mind when attempts to become pregnant fail in a patient receiving treatment.

5.1 Fertility in different rheumatic diseases

In a population-based study, a lower number of births and a reduced period of reproduction were found in women with rheumatic disease compared with healthy controls. The interval between pregnancies was longer and the proportion of women achieving a subsequent pregnancy was reduced in rheumatic disease. Lower birth rates have been reported in women with rheumatoid arthritis (RA), and reflect, at least in part, the choice of these women to limit their family size. This may be due to the experience of parenting disability, particularly in patients with a postpartum flare of RA.

A large retrospective study of reproductive performance in Caucasian patients with ankylosing spondylitis (AS) found on average 2.4 children per woman, which is no different from the fertility rate in the healthy population. A population-based study of women aged 40–42 years found normal fertility but diminished

fecundity in women with AS. Diminished fecundity was also reported in women with juvenile spondyloarthritis, and fertility was found to be reduced compared with the national average. Reduced family size in spite of normal fertility and fecundity can be a result of pregnancy loss due either to miscarriage or stillbirth, or to perinatal deaths but not only this: pregnancy usually has to be planned during periods of disease control, especially in SLE. So, these women have their first child later and fewer children. Pregnancy loss is particularly obvious in patients with APS, and to a lesser degree in women with SLE. An increased rate of pregnancy loss is also seen in patients with familial Mediterranean fever (FMF), active vasculitis or inflammatory myopathies.

6. Rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis

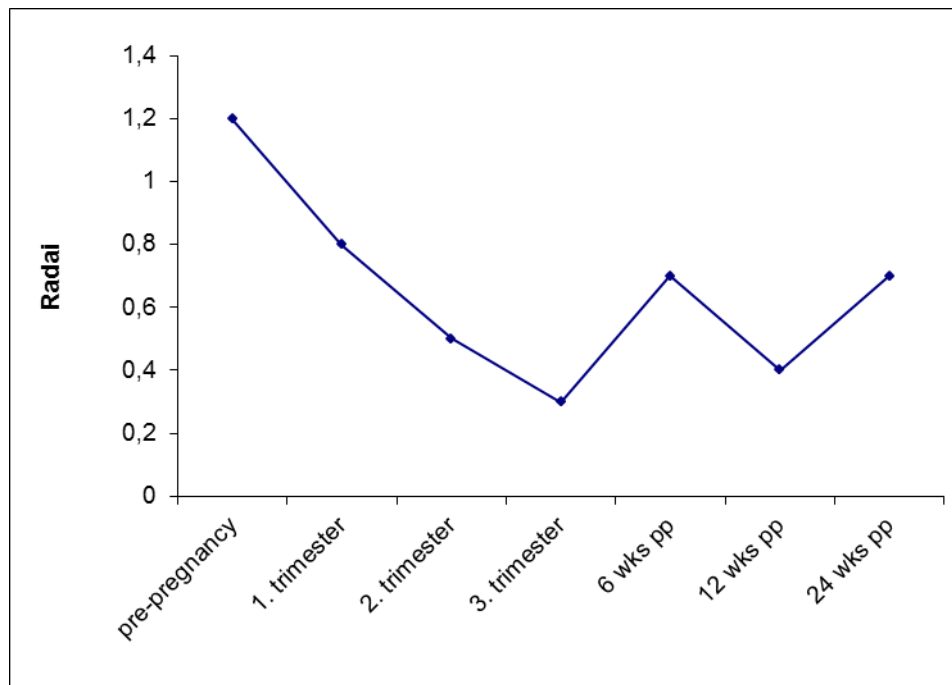
6.1 Effect of pregnancy on disease activity in women with RA

Among the rheumatic diseases, the interaction between pregnancy and RA is the most thoroughly studied.

Retrospective studies between 1940 and 1980, comprising a total of 345 pregnancies, indicated that about 75% (range 54–86%) of patients experienced improvement of symptoms and signs of RA during pregnancy (Ostensen *et al*, 2011*). Five detailed prospective studies comprising 128 pregnancies found improvement or remission of RA in about two-thirds. However, the two largest prospective studies found improvement in 65% and 48%, respectively, and complete remission limited to a small proportion of pregnant patients with RA. The difference in gestational improvement is due to the design of early studies, which were mostly retrospective, and lack of appropriate disease activity measurements. The influence of pregnancy on the activity of RA was often judged by global statements of patients. In contrast, more recent studies were preferentially prospective, and used validated instruments to measure disease activity (Ostensen *et al*, 2004; Gromnica-Ihle *et al*, 2006; de Man *et al*, 2008*) (figure 1). In addition, the self-assessment of patients has changed during the past 50 years. In the 1940s only aspirin and gold therapy were available for the treatment of arthritis. Therefore, a beneficial effect of pregnancy was felt as being much more impressive than during a time where highly efficient treatments for RA keep most patients at a low or moderate level of disease activity. Patients who enter pregnancy in a state of low disease activity notice fewer of the beneficial effects of pregnancy, but remain mostly stable. Patients with high disease activity at conception benefit the most from pregnancy. Interestingly, patients negative for both rheumatoid factor (RF) and cyclic citrullinated autoantibodies (CCP) were more likely to improve during pregnancy. In a prospective study of 118 patients, 75% of patients negative for RF and CCP antibodies improved compared with only 39% of those positive for RF and CCP antibodies (de Man *et al*, 2010). In addition, disease severity in early pregnancy is predictive of preterm delivery and SGA (Bharti *et al*, 2015). Most studies agree that if a woman with RA improves during one pregnancy she is likely to do so also in subsequent pregnancies. However, a prospective study reported that RA disease course in following pregnancies could not be predicted based upon previous pregnancies (Ince-Askan *et al*, 2016). Only

15 % of patients had a comparable disease activity course in subsequent pregnancies. In contrast, a flare post-partum seems to predict flares after subsequent pregnancies.

Figure 1 The Rheumatoid Arthritis Disease Activity Index (RADAI) in patients with rheumatoid arthritis with improvement studied prospectively before, during and after pregnancy. pp, post-partum. (Reproduced with permission from Gromnica-Ihle and Østensen, *Z Rheumatol* 2006;65:209–12.)



6.2 Effect of RA on pregnancy outcome

Women with rheumatic diseases in general have been found to have higher risks of adverse outcomes like pre-eclampsia, preterm delivery, caesarean section, foetal death and IUGR or SGA babies. A Norwegian population-based study found the rate of preterm delivery and infants SGA higher for first born children in mothers with RA than in healthy women. Two prospective studies of 285 pregnancies in women with RA found birth weight within normal range, but lower than in healthy women, and even lower in infants of RA mothers with high disease activity or those treated with prednisone.

6.3 Maternal disease activity post-partum

According to retrospective and prospective studies, most patients had recurrent disease within 3–4 months of delivery (Østensen *et al*, 2012*). Prospective studies from the past two decades found that RA relapsed in 49–62% of patients within the first 6 months after delivery requiring an increase in drug treatment. A prospective study showed that entering pregnancy with low disease activity was a relevant factor for stable low disease activity during gestation and even for a reduced risk for a post-partum flare. One study reported a correlation between lactation and increased disease activity post-partum in women with RA, who were breast feeding for

the first time. However, earlier studies reported no correlation between a disease flare and breast feeding. A prospective study evaluating women with a 12-year follow-up found no significant influence of pregnancy on long-term RA outcome, but found a trend for patients with multiple pregnancies to have less radiographic joint damage and a better functional level.

6.4 Pregnancy-induced amelioration and postpartum relapse of RA

A number of different factors have been considered in the pregnancy-induced amelioration of RA. Most of the candidate factors studied, such as increased serum cortisol concentrations, raised levels of sex hormones and pregnancy-associated α_2 globulin, did not explain the improvement of RA during pregnancy. Others, such as reversal of abnormalities in the percentage of IgG immunoglobulins lacking the terminal galactose, have been described in association with amelioration of RA during pregnancy. It has been proposed that prolactin plays a role in the postpartum relapse (Ostensen and Villiger, 2002).

In studies of mother–child pairs for whom the mother experienced RA improvement during pregnancy compared with those who did not, foetal–maternal disparity in the HLA class II molecules HLA-DR and DQ was seen significantly more often in the former than in the latter. One subsequent study confirmed this observation, while another report came to a different conclusion. A study investigating dynamic changes in levels of foetal DNA in serum from women with RA and inflammatory arthritis, during and after pregnancy, found an inverse relationship between serum foetal DNA levels and disease activity. The uptake and cross-presentation of soluble foetal paternally inherited HLA peptides by maternal antigen-presenting cells might well affect autoimmunity in patients with RA, though the nature of this modulation has as yet not been elucidated. Alternatively, or additionally, regulatory T cells might be contributory, increasing during pregnancy and suppressing maternal autoimmune responses. These possibilities are not exclusive and it is likely that the explanation for disease amelioration in RA is multifactorial (Ostensen *et al*, 2012*).

6.5 Juvenile idiopathic arthritis

Some 150 pregnancies have been studied retrospectively in women with a history of juvenile idiopathic arthritis (JIA). Taken together these studies showed a beneficial effect of pregnancy on the activity of oligoarticular and polyarticular JIA, whereas women with juvenile spondyloarthritis most often experienced an aggravation. Most importantly, inactive JIA before conception was not reactivated during pregnancy.

The limited experience from the literature indicates no increase in the rate of miscarriage, pre-eclampsia or premature delivery in women with JIA except in a recent Australian study of two large population health datasets that found a higher rates of pre-eclampsia (that might be related to the use of steroids), postpartum haemorrhage and severe maternal morbidity in women with JIA (Chen *et al*, 2013). Most patients, particularly those with inactive JIA in adulthood, will have uneventful pregnancies and deliver healthy children of normal

birth weight. Compared with other infants, the Australian database showed increased risk of prematurity in children with mothers with JIA but no others adverse neonatal outcomes (Chen *et al*, 2013). A postpartum flare has been described in 52–90% of JIA pregnancies within the year after delivery. Flares are more frequent in women who had active disease before pregnancy and in women who are breast feeding (Ostensen, 1992*).

6.6 Special problems

Problems at delivery may arise in women with early-onset JIA due to growth disturbances. If the maternal bone alteration has affected the pelvis, cephalopelvic dystocia can preclude normal vaginal delivery and require caesarean section. Bilateral hip involvement with marked reduction of mobility may also prevent vaginal delivery. Some patients have received hip replacement in adolescence because of severe arthritis in the hip joints. Unilateral or bilateral hip joint prosthesis allows vaginal delivery provided that the range of motion is normal or only slightly reduced. In one study, an increased rate of surgical delivery was found in patients with JIA, mostly in women with hip prostheses. General anaesthesia with intubation may be difficult in patients with temporomandibular or crico-arythenoid joint involvement or in those with subluxation in the cervical spine. Regional anaesthesia is the preferable method in these cases.

6.7 Psoriatic arthritis

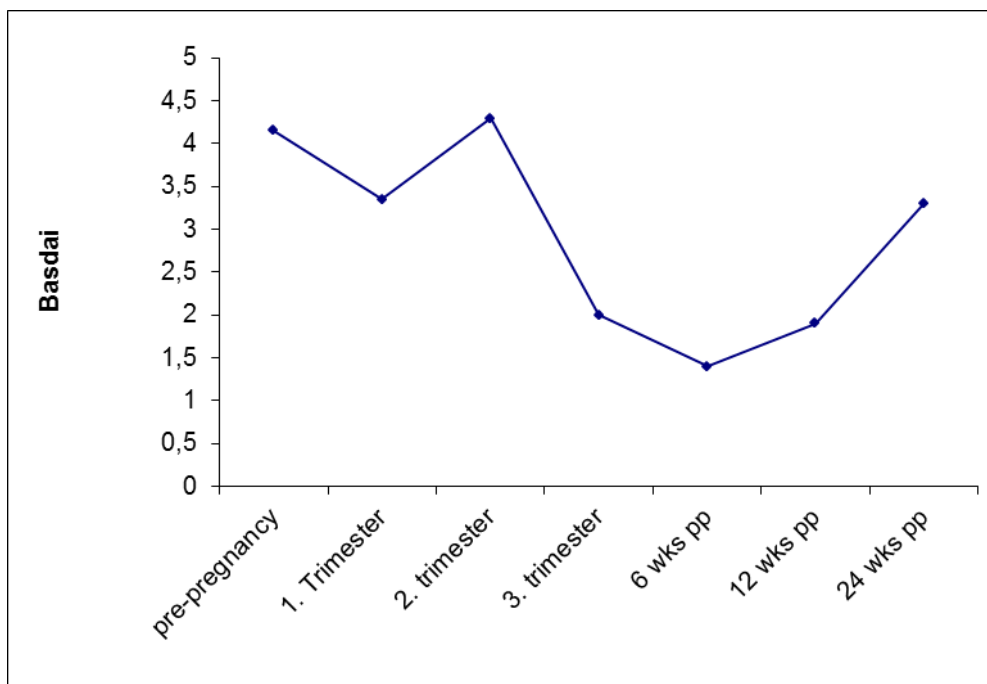
The few reports on the interaction between pregnancy and psoriatic arthritis (PsA) comprise 25 pregnancies; 85% of the pregnant patients with oligo- or polyarticular PsA improved during pregnancy. Pregnancy had little effect on skin disease. A postpartum relapse occurred 2–12 weeks after delivery in 60–80% of patients. Except for one stillbirth, no spontaneous abortion or premature delivery occurred in this limited number of PsA pregnancies (Ostensen, 1992*).

7. Ankylosing spondylitis

Both retrospective and prospective studies have investigated the effect of pregnancy on the course and severity of AS. In contrast to RA, pregnancy does not improve the symptoms of AS. In the majority of patients, disease activity is not substantially altered during pregnancy (Lui *et al*, 2011). Two prospective studies involving 32 patients with AS assessed the disease course of AS during and after pregnancy, in detail, by clinical and laboratory measurements. The typical pattern was active disease during the first and early second trimester, sometimes accompanied by a flare around week 20 of pregnancy (figure 2). Active AS produced increased pain and stiffness of the spine, intensified nocturnal pain and occasionally, acute arthritis in the peripheral joints. Pregnancy modifies posture and spinal mobility (by production of relaxin and other hormonal changes during gestation, which cause ligament relaxation). In some patients, pain at the attachment sites of ligaments or tendons and a feeling of tightness in the chest created additional problems. Anterior uveitis could become active during this period. A need for NSAIDs and analgesics was present in about 70% of the patients.

For the group as a whole, disease activity decreased again in the third trimester, but complete subsidence of symptoms was not seen (Ostensen et al, 2012*). Within a population-based case-control study, offspring of women with AS were more often preterm (9.0% vs 4.9%)(Jakobsson et al, 2016). Cases with more extensive antirheumatic therapy exposures tended to have a higher risk for elective caesarean section and being SGA.

Figure 2 The Bath Ankylosing Spondylitis Activity Index (BASDAI) in patients with ankylosing spondylitis studied prospectively before, during and after pregnancy. pp, post-partum. (Reproduced with permission from Gromnica-Ihle and Ostensen, Z Rheumatol 2006;65:209–12.)



Some 20% of patients with AS have improved spinal and extraspinal symptoms during pregnancy. These patients most often have a history of arthritis in joints other than the spine, or psoriasis or inflammatory bowel disease associated with their AS. In patients studied during multiple pregnancies, the intensity of disease symptoms varied from one pregnancy to the other. No uniform pattern of improvement or aggravation emerged. However, complete remission of symptoms never occurred in any patient with pure spinal disease.

7.1 Maternal disease activity post-partum

Fifty percent to 80% of patients with AS experience aggravation of symptoms 4–12 weeks after delivery. Episodes of acute peripheral arthritis or anterior uveitis occur 1.5–3 times more often after delivery than during pregnancy. Disease activity returns as a rule to the pattern before pregnancy during the year following delivery.

7.2 Course of pregnancy and delivery

The rate of miscarriage, foetal death, prematurity and infants SGA is within the limits of the rate for healthy women. As a rule, pregnancies conclude at term with the delivery of live, healthy children of normal birth

weight. Compared with healthy women, Caesarean section is more often performed in patients with AS. Inflammation or ankylosis of the sacroiliac joints is not a mechanical hindrance to the progression of parturition. Also, hip disease or total hip replacements resulting from early-onset AS does not preclude normal delivery.

7.3 Special problems

Anaesthesiologists often fear that neuraxial anaesthesia is difficult to establish in patients with AS because of ankylosis in the lumbar spine. However, ankylosis of the lumbar spine is rare in female patients with AS and occurs only after disease duration of three to four decades. These concerns can be overcome by documenting the absence or presence of ankylosis by carrying out an X-ray examination of the lumbar spine before a planned pregnancy.

8. Systemic lupus erythematosus

Pregnancy in women with SLE is associated with higher maternal and foetal risk than in healthy women. Even if pregnancies are now frequent in women with SLE, they are still associated with higher foetal and maternal morbidity and mortality. The main complications are SLE flares, adverse obstetric outcomes (sometimes due to the associated APS) and neonatal lupus syndrome.

Optimal management requires detailed planning of the pregnancy in a preconceptional consultation, and multidisciplinary care with close collaboration between internist/rheumatologist, obstetrician and anaesthetist (see online in-depth discussion I).

8.1 The effect of disease activity

Active disease during the 6 months before conception and a history of lupus nephritis significantly increase the risk of flares during pregnancy. Flare rates vary between 25% and 65% in the oldest studies (when hydroxychloroquine was stopped). Most of the flares in pregnancy are mild to moderate. They occur as frequently in each trimester, including in the postpartum period (Clowse *et al*, 2005*).

Whereas articular manifestations are less frequent during pregnancy, renal and haematological manifestations are more frequent and more severe during this period. The risk of flares (especially renal) and of maternal and foetal complications (increased rates of perinatal mortality, preterm delivery and foetal growth restriction) depends on lupus activity before conception and on whether kidney damage has occurred (Clowse *et al*, 2005*; Bramham *et al*, 2011). Impairment of renal function may be increased by pregnancy in women with pre-existing kidney disease, especially if there is chronic renal insufficiency, proteinuria, low complement level or hypertension (Bramham *et al*, 2011). Chronic renal insufficiency is associated with higher rates of foetal

loss, foetal growth restriction (Gladman *et al*, 2010) and prematurity (Bramham *et al*, 2011)**Erreur ! Source du renvoi introuvable.**

The PROMISSE study (Predictors of Pregnancy Outcome: Biomarkers in APS and SLE) included pregnant patients with inactive or stable mild/moderate SLE (Buyon *et al*, 2015*). Within these pregnancies, severe flares occurred in less than 5 % of pregnancies. Adverse pregnancy outcomes (APOs) occurred in 19 % of all pregnancies. Baseline predictors of APOs included presence of lupus anticoagulant, antihypertensive use low platelet counts and higher disease activity whereas non-Hispanic white race was protective. Among women without baseline risk factors, the APO rate was 7.8%. For those who either were LAC-positive or were LAC-negative but non-white or Hispanic and using antihypertensives, the APO rate was 58.0% and foetal or neonatal mortality was 22.0%.

8.2. Pregnancy in patients with Lupus nephritis

SLE patients with nephritis are at higher risk for adverse pregnancy outcomes, including premature delivery, low birth weight and intra-uterine growth restriction. According to the EULAR recommendations, pregnancy may be planned in patients with inactive lupus nephritis and UPCR <50 mg/mmol for the preceding 6 months, with GFR that should preferably be >50 ml/min (Bertsias GK *et al*, 2012*). Stable renal disease is treated with the same drugs that are recommended as acceptable during prepregnancy counselling (hydroxychloroquine, prednisone, azathioprine or calcineurin inhibitors). Replacing mycophenolate mofetil with azathioprine in patients with stable lupus and quiescent lupus nephritis for pregnancy planning rarely leads to renal flares (Fischer-Betz R *et al*, 2013*). Low dose Aspirin (LDA) should be started within early pregnancy to reduce the risk for preeclampsia. Patients with nephrotic-range proteinuria during pregnancy are candidates for anticoagulation.

Hypertensive disorders of pregnancy are among the leading preventable contributors of maternal and foetal adverse outcomes, including maternal and foetal death. New onset of hypertension in pregnancy may be a first sign of emerging pre-eclampsia or of renal flare. Arterial hypertension is defined as a blood pressure equal to or higher than 140/90 mmHg in 2 measurements with a time interval of at least 4-6 hours between both. The four types of hypertension during pregnancy are: (1) gestational hypertension, (2) preeclampsia-eclampsia, (3) chronic hypertension, and (4) chronic hypertension with superimposed preeclampsia.

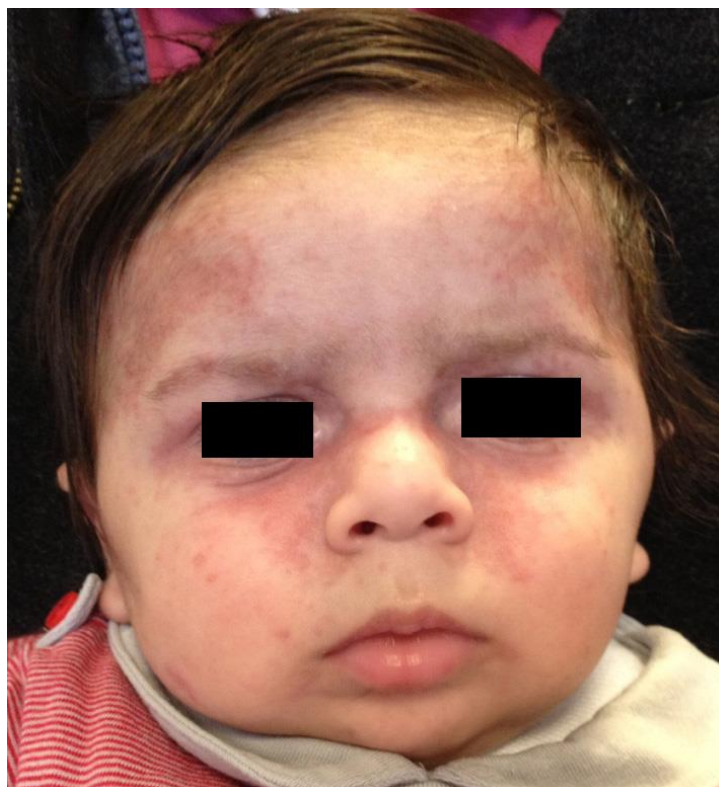
In pregnancy, blood pressure higher than 160/110 mmHg requires immediate treatment. There is no strict definition of a definitive blood pressure goal. Due to the danger of foetal growth restriction with too low blood pressure counts, diastolic blood pressure should not be lower than 90-100 mmHg, or 80-90 mmHg respectively, if the mother has hypertensive end-stage organ damage or other risk factors. Angiotensin-converting enzyme (ACE) inhibitors should be stopped before conception or at the latest in the first trimester. If necessary, an alternative antihypertensive compatible with pregnancy should be given (like Methyldopa,

Labetalol, Metoprolol, Nifedipine). For monitoring, any fall in serum C3/C4 is significant given than levels usually rise during pregnancy. Additional investigations may be needed to rule out pre-eclampsia before diagnosing exacerbation of renal disease.

8.3 Presence of anti-SSA/Ro and/or anti-SSB/La antibodies and risk of neonatal lupus syndrome

Occurrence of neonatal lupus syndrome is related to the presence of anti-SSA/Ro and anti-SSB/La antibodies in mothers with different rheumatic diseases (Sjögren's syndrome, SLE or more rarely, RA), but it also occurs in mothers without any connective tissue disease. These maternal antibodies cross the placental barrier and can cause neonatal lupus in the foetus or newborn, by a passively acquired autoimmunity model, manifesting mainly as cardiac manifestations that are usually permanent or transient cutaneous (figure 3), haematological and/or hepatic manifestations.

Figure 3: Cutaneous lesions of neonatal lupus syndrome on the periorbital region in a 3 month-old child.



Atrioventricular block (AVB) is the most common manifestation of cardiac neonatal lupus. The risk of AVB increases from 1% to 2% in the absence of any history of previous AVB (whereas the estimated incidence of AVB in the population is 0.005%) to around 17% when siblings are born with neonatal lupus (Costedoat-Chalumeau *et al*, 2004*). AVB is most often discovered between 20 and 24 weeks of gestation. The probability of survival to the age of 10 years is 86% in live born children, and pacemakers are required in 70% of them (Izmirly *et al*, 2011*).

Late-onset cardiomyopathy has also been described in children from mothers with anti-SSA antibodies despite early pacing (Moak *et al*, 2001), justifying close follow-up of children with any cardiac manifestation. Cardiomyopathy could be a sequelae of endocardial fibro elastosis, another manifestation of heart toxicity of these antibodies, which can be seen on foetal echocardiography as hyperechogenic heart areas (Nield *et al*, 2002; Guettrot-Imbert *et al*, 2011).

Curative treatment of AVB is based on fluorinated glucocorticoids (betamethasone or, if not available, dexamethasone) that cross the placental barrier, unlike prednisone and methylprednisolone but the value of this treatment is controversial. Complete AV block, once established, seems not to be reversible. No prophylactic treatment is indicated for women with anti-SSA antibodies and an unremarkable history. Hydroxychloroquine seems to reduce the risk of recurrence in another child (Izmirly *et al*, 2012), but further prospective studies are needed to confirm these findings. Hypothyroidism in mothers with anti-Ro/SSA and/or anti-La/SSB antibodies increases by nine fold the risk of delivering a child with congenital heart block compared with women with these same antibodies who have normal thyroid function.

8.4 Effect of antiphospholipid antibodies or APS

See online in-depth discussion II.

8.5 Treatment of SLE during pregnancy

Treatment of lupus during pregnancy usually includes maintenance of the previous treatment, especially hydroxychloroquine. Discontinuation of hydroxychloroquine is related to an increased risk for SLE exacerbations during pregnancy (Andreoli *et al*, 2017). Exposure to prednisone should be limited to <10 mg/day (in the absence of flare). If an immunosuppressive agent is required, azathioprine is preferably used. Uncontrolled studies also suggest an acceptable benefit/risk ratio of calcineurin inhibitors (cyclosporine A, tacrolimus) in controlling SLE activity during pregnancy. Low-dose aspirin is indicated at least in patients with antiphospholipid antibodies, nephritis or a previous adverse obstetrical outcome, and some physicians prescribe this treatment to all patients with SLE to prevent pre-eclampsia (Schramm *et al*, 2014). All pregnant women with SLE, especially those receiving glucocorticoids and heparin, should receive calcium and vitamin D until the end of lactation. Multidisciplinary monitoring includes regular clinical, laboratory and ultrasound evaluations. Delivery may be scheduled at around 38 weeks, but this remains empirical and should be evaluated.

9. Primary Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is 10 times more common in women than in men, with a peak incidence at or near menopause. Most patients with pSS have completed their families before disease onset. Therefore few studies have investigated pregnancy outcome in pSS.

9.1 pSS during pregnancy and pregnancy outcome

Only one study has examined the effect of pregnancy on the symptoms of SS and found no major changes. Thus patients with SS should not expect improvement of sicca symptoms during pregnancy. In previous retrospective studies of patients with pSS the foetal loss rate has varied from 7% to 24%, with a significantly increased risk documented in two studies. In addition to the risk of AVB, a recent case–control study (34 pregnancies) showed a statistically significant increase of the rate of spontaneous abortions, preterm deliveries, low birth weight infants and caesarean section (De Carolis *et al*, 2014). By contrast, two previous studies, involving 172 pregnancies in women with pSS, found neither increase in prematurity or growth restriction nor any influence of anti-SSA and anti-SSB antibodies on the outcome of pregnancy.

9.2 Conclusion

The few reported pregnancies after disease onset do not permit a conclusion to be drawn about the possible influence of established pSS on pregnancy outcome. The most important, though small (1–2%), risk associated with pSS is the development of chronic heart block in children of anti-SSA- or anti-SSB-positive mothers.

10. Systemic sclerosis

SSc has a female preponderance of about 8–10:1 in the reproductive years; the mean age at onset of symptoms is in the early 40s, leaving the possibility of becoming pregnant after onset of the disease. Because of similarity to chronic graft-versus-host disease, the role of transfer of foetal cells during pregnancy and microchimerism was intensively studied in SSc. Microchimeric cells have been demonstrated in the peripheral blood and affected skin of patients with SSc; however, there is no evidence that pregnancy has a decisive role in the aetiology of SSc.

10.1 SSc during pregnancy and pregnancy outcome

Early case reports and small series described adverse, sometimes fatal, maternal outcomes in pregnant patients with scleroderma. Large retrospective case–control studies, and the only prospective study by Steen (2007*), showed that pregnancy does not profoundly alter the disease. In a study of 133 pregnancies in 69 patients, no change in disease-related symptoms was found in 88%, improvement occurred in 5%, and aggravation in 7% of pregnancies. Cutaneous disease did not change much and progression of skin disease was uncommon during pregnancy or post-partum in any of the studies. Usually, Raynaud's phenomenon improved and arthralgias and reflux worsened during pregnancy, whereas cardiopulmonary problems essentially remained unchanged in women with SSc.

Serious organ manifestations of SSc can threaten the outcome of pregnancy (Steen, 2007*). The renal manifestations of SSc, including hypertension, progressive renal failure or proteinuria, can appear at any stage

of pregnancy and usually present as hypertension. A fourfold increase of hypertensive disorders including pre-eclampsia was found in a retrospective study of 504 pregnancies in women with SSc. Risk factors for renal crisis are early diffuse SSc and rapidly progressing skin disease. Treatment with high-dose prednisolone may be an additional risk factor (Steen, 2007*). Case–control studies have shown that renal crisis does not occur more often in pregnant than in non-pregnant patients with SSc, and has a frequency varying between 2% and 11%. Successful pregnancy after the occurrence of a renal crisis has been described in patients continuing angiotensin-converting enzyme (ACE) inhibitors throughout pregnancy in spite of the foetal risk associated with these drugs.

Another serious complication is pulmonary hypertension, with a survival rate of about 2.8 years and a 30–50% risk of maternal mortality in cases of pregnancy. Fortunately, a multidisciplinary team approach has now improved pregnancy outcome in these high-risk pregnancies.

Retrospective and prospective studies have shown an increased frequency of prematurity in SSc. A retrospective study of 109 SSc pregnancies found preterm deliveries (25% vs 12%) and severe preterm deliveries (<34 weeks) (10% vs 5%), IUGR (6% vs 1%) and very-low-birth-weight babies (5% vs 1%) significantly more common in women with SSc than in healthy women. This may be attributable to disorders of placental perfusion secondary to the fibrosing process and to the vasculopathy associated with scleroderma. In a large retrospective study no general increase in miscarriages was found in patients with SSc, except for women with longstanding diffuse scleroderma.

10.2 Special problems

In case, Raynaud's syndrome remains severe during pregnancy vasodilators such as nifedipine can be used. Gastro-oesophageal reflux often becomes aggravated in late pregnancy. It can be managed with anti-reflux measures such as frequent small food intake, avoidance of a prone position after dinner and H2 blockers. All proton pump inhibitors, except for rabeprazole, can also be used if necessary. Although ACE inhibitors are contraindicated during late pregnancy, should renal crisis occur, their use may be life saving for the mother.

10.3 Conclusion

Patients with SSc can have successful pregnancies. The risk of an adverse pregnancy outcome is greater in patients with the diffuse form than with the limited form of SSc. Women with early diffuse and rapidly progressing disease should wait until their SSc is less active. Patients with severe organ involvement, such as cardiomyopathy, severe restrictive lung disease, pulmonary hypertension, malabsorption or severe renal insufficiency, should probably be discouraged from becoming pregnant.

11. Polymyositis and dermatomyositis

Only 14% of female patients present with idiopathic inflammatory myopathies (IIM) during childbearing years. Therefore, the pregnancy experience for women with polymyositis (PM) or dermatomyositis (DM) is limited.

11.1 PM and DM during pregnancy and pregnancy outcome

To date, 62 pregnancies in 52 patients with PM/DM have been described in case reports or small retrospective series: 49% of the patients had disease onset before pregnancy, 36% manifested IIM during pregnancy and in 15% of the patients the disease started post-partum. Pregnancy outcome in mothers with IIM varied with disease severity (Silva *et al*, 2003*; Doria *et al*, 2004*). In patients with active disease during pregnancy, 43% ended with foetal or neonatal death and 33% of infants showed IUGR. By contrast, patients with inactive IIM during pregnancy delivered healthy babies of normal birth weight in more than 85% of the cases. In patients who were diagnosed with IIM during pregnancy, the percentage of foetal survival was 48%. Sixty-three per cent of cases diagnosed in the first trimester resulted in pregnancy loss or neonatal death or foetal growth restriction, whereas most patients diagnosed in the second and third trimester had live infants (77%), despite a high frequency of premature births (23%) (Silva *et al*, 2003*). Raised levels of creatine kinase have occasionally been detected in neonates of mothers with PM or DM. No sign of IIM developed in any of the children.

The course of inflammatory myopathies does not appear to be influenced by pregnancy, even though muscle impairment may be increased by weight gain during pregnancy (Silva *et al*, 2003*).

11.2 Special problems

When PM/DM is active during pregnancy, high-dose prednisone 1 mg/kg/day should be started and maintained until the serum creatine kinase levels have returned to normal. If the response to prednisone is insufficient, cyclosporine A or azathioprine can be added. In anecdotal cases, IIM refractory to high-dose glucocorticoid treatment has responded to treatment with intravenous immunoglobulin during pregnancy.

11.3 Conclusion

The data from case reports and small series indicate that most women with PM/DM with inactive disease at conception have normal pregnancies with a good outcome. Relapses at a quiescent stage seem rather uncommon during pregnancy. In contrast, women with active disease at conception or disease onset during pregnancy are at high risk of an adverse pregnancy outcome.

12. Familial Mediterranean fever

12.1 FMF during pregnancy and pregnancy outcome

The course of FMF during pregnancy is variable. Both complete remission and unchanged or aggravated disease with frequent attacks have been reported. Early studies found an increased rate of miscarriage of up to 25% in women with untreated FMF (Ben-Chetrit *et al*, 2010). An increase in recurrent abortion was also found in a population-based study that compared the outcome of 239 pregnancies in patients with FMF with the outcome of pregnancies in healthy subjects. An increased rate of preterm birth was found in patients with FMF. Perinatal outcome did not differ between children born to patients with FMF or to healthy mothers.

12.2 Special problems

Continuous treatment with 1–2 mg/day of colchicine suppresses acute attacks of FMF and reduces the occurrence of amyloidosis. Patients refusing colchicine treatment or treated with inadequate doses may enter pregnancy with renal amyloidosis. A deterioration of renal function during or shortly after pregnancy may occur in these patients with high serum creatinine and proteinuria >2 g/24 h.

Treatment with colchicine during pregnancy has raised concern owing to its transplacental passage and its ability to inhibit mitosis. However, several retrospective studies, comprising a total of 881 pregnancies, showed no increase in congenital malformations or chromosomal aberrations in offspring exposed at conception or during pregnancy. In one study, amniocentesis was performed to detect chromosomal aberrations in colchicine-exposed pregnancies; no increase was found compared with the number expected for maternal age distribution (Ben-Chetrit *et al*, 2010).

12.3 Conclusion

Attacks of serositis and fever may lead to early uterine contractions, resulting in miscarriage or preterm delivery (Ben-Chetrit *et al*, 2010). In addition, untreated FMF increases the risk of developing amyloidosis. Therefore, continuation of colchicine before a planned pregnancy and throughout pregnancy is recommended.

13. Vasculitides and pregnancy

The most common primary types of vasculitides are Takayasu arteritis (TA), polyarteritis nodosa, granulomatosis with polyangiitis (GPA, formerly called Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly called Churg–Strauss syndrome). There is limited information on pregnancy outcome in these diseases because most of the primary vasculitides occur in older people and are more common in men.

Of the large- and medium-vessel vasculitides, only TA is presented (table 2). The risk of TA associated with pregnancy is mainly due to arterial hypertension and/or pre-eclampsia with a greater risk in more severe and extensive cases of the large-vessel arteritis.

Table 2 Interaction of pregnancy and vasculitis

Disease	No. of pregnancies reported	Effect of pregnancy on disease	Risk of maternal complications in pregnancy	Risk of pregnancy complications	Risk of foetus/neonate
<i>Takayasu arteritis</i>	160	Unchanged in 72% Improvement in 20%	Dependent on type of involvement. Progression of renal insufficiency, congestive heart failure	Hypertension in 30–44% Pre-eclampsia in 12–16%	Mostly favourable outcome, intrauterine growth restriction, low birth weight if severe maternal disease
<i>Granulomatosis with Polyangiitis</i>	62	Relapse in 40% during pregnancy, also when in remission at conception	Onset during pregnancy; risk of severe maternal disease	Pre-eclampsia in 22%, prematurity in 40%	Abortion, intrauterine growth restriction, low birth weight
<i>Eosinophilic Granulomatosis with Polyangiitis</i>	23	No major effect on disease activity	Asthma, aggravation of cardiac disease, skin rash	No increased risk	Rare, mostly favourable outcome
Microscopic polyangiitis	20	No major effect on disease activity	Renal disease, pulmonary haemorrhage	Prematurity	Transfer of MPO-ANCA to foetus and pulmonary–renal syndrome in neonate rarely occurs

ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase.

GPA, EGPA and microscopic polyangiitis (MPA) are small-vessel, necrotising vasculitides associated with the presence of antineutrophil cytoplasmic antibodies (ANCA). The most common manifestations of these diseases are in the respiratory tract and the kidneys. Reports on pregnancy in GPA, EGPA, and MPA are extremely rare owing to the infrequent occurrence of these diseases in women of childbearing age (Sangle *et al*, 2015). The literature consists nearly exclusively of case reports published over a period of decades with variance in patient characteristics and management. Old reports tend to describe more adverse pregnancy outcomes than recent ones, owing to less developed obstetric medicine and fewer treatment modalities at that time. A

retrospective study of 22 pregnancies in women with ANCA-positive vasculitis (13 GPA and 1 MPA) in remission and with main disease manifestations in ear, nose, throat and kidney found rather good pregnancy outcomes. Only two children were premature, and a relapse occurred in one pregnancy only (Tuin *et al*, 2011).

A recent retrospective study of 51 pregnancies reported a lower median gestational age but a similar median birth weight in these pregnancies (Sangle *et al*, 2015). Outcomes are poorer if pregnancies occur during active vasculitis with higher risk of pregnancy loss or induced abortion, prematurity or even the mother's death. Pregnancy does not seem to have a major impact on vasculitis activity. Life-threatening manifestations can occur, especially in patients with vasculitis-related cardiac or renal damage (Pagnoux *et al*, 2011*).

13.1 Treatment of active vasculitis during pregnancy

Active vasculitis in patients with TA, GPA, EGPA and MPA during pregnancy requires prompt and aggressive immunosuppressive therapy. Prednisone is the main option, with doses adjusted to the type and severity of organ manifestations. Systemic manifestations may require treatment with high-dose oral prednisone (0.5–1.5 mg/kg/day), or intravenous pulse methylprednisolone (0.5–1 g daily for three consecutive days). As soon as the disease is controlled, prednisone can be tapered to the lowest effective dose. In refractory cases azathioprine can be added. At life-threatening aggravation during the second and third trimester cyclophosphamide or Rituximab may be required. If GPA is limited to the upper airways, local treatment, antibiotics and, if necessary, low-dose oral prednisone may be sufficient. In patients with EGPA, special care should be taken in monitoring bronchospasm during pregnancy and post-partum. Some patients refractory to glucocorticoids respond to the addition of intravenous immunoglobulin therapy.

13.2 Conclusion

Conception in a stage of quiescent or well-controlled disease is essential for good maternal and foetal outcome in all forms of vasculitis. Conception during active disease should be discouraged. Maternal and foetal outcome has been satisfactory in most patients with TA, GPA and EGPA when the disease activity was well controlled. However, disease onset may occur during pregnancy as well as post-partum. Patients with active disease at conception or disease onset during pregnancy are at increased risk of adverse pregnancy outcomes since options for effective treatment are limited. The severity of the initial manifestations of vasculitis does not predict the activity of the disease during pregnancy. A disease flare during pregnancy or post-partum is possible even when the vasculitis was quiescent at conception. Frequent controls during pregnancy and post-partum are therefore mandatory.

14. Behçet disease

Behçet disease (BD) affects both genders at 15–45 years of age, therefore pregnancy in patients with BD is not rare. The interaction of pregnancy and BD has been recorded in case reports and several retrospective series. No prospective study has been conducted.

14.1 BD during pregnancy and pregnancy outcome

Four retrospective series, comprising 222 pregnancies in women with BD, showed improvement or even remission in 53–80%. A relapse was reported in 16–35.5%, respectively, consisting of oral or genital ulcers, arthritis and eye inflammation. The proportion of BD flares tended to be lower in patients treated with colchicine (Noel *et al*, 2013). Serious maternal complications were rare, with one Budd–Chiari syndrome occurring post-partum, one deep vein thrombosis and one pulmonary embolism. Decidual vasculitis and intervillous inflammation have been described in full-term and first trimester placentas of patients with BD.

A case–control study comparing 77 pregnancies in patients with BD and 288 pregnancies in healthy controls showed a significantly higher rate of adverse outcome in patients with BD than in the control group (26% vs 2%). Miscarriage occurred in 21% of patients with BD compared with 5.2% in healthy women. Surgical delivery was more common in women with BD (15% vs 5%). Hypertension and gestational diabetes mellitus occurred more often in pregnant patients with BD. No difference was found in neonatal health or birth weight. An association between history of deep vein thrombosis and the risk of obstetric complications has been described in one of these reports (Noel *et al*, 2013).

Transient neonatal BD has been recorded in six case reports. Clinical symptoms were oral and genital ulcers, skin lesions, bloody diarrhoea, stridor and neurological involvement developing within 1 week after birth and resolving by 6–16 weeks after birth. Symptoms subsided in five cases spontaneously or after receiving treatment with prednisone. One infant died of generalised seizures. The pathogenesis of neonatal BD is unclear, but transplacental passage of maternal immunoglobulins is suspected.

14.2 Special problems

BD is associated with an increased risk for thrombosis. In spite of this, no recommendation for routine use of low-dose aspirin or anticoagulation with heparin during pregnancy has been identified in the literature or among experts. Patients with BD with previous thromboembolic events should receive heparin during pregnancy. For mucocutaneous, ocular and articular manifestations of BD, glucocorticoids, colchicine, azathioprine and cyclosporine have been shown to be effective. Severe uveitis may respond to infliximab.

14.3 Conclusion

Available data suggest that pregnancy does not aggravate maternal disease, though a relapse may occur in about 20% of BD pregnancies. The flares concern predominantly the skin, the mucosa and the articulations, and occur mainly during the first trimester. There does not seem to be any increase in obstetric complications, but the available data are sparse and prospective data are needed (Noel *et al*, 2013). Serious maternal complications or neonatal BD are rare, but because they are unpredictable careful monitoring during pregnancy and post-partum is required.

15. Drug treatment during pregnancy and lactation

Recommendations from a EULAR task force on antirheumatic drugs and pregnancy have been published in 2016 (Götestam Skorpen *et al*, 2016*) (Table 3). An adjustment of treatment is necessary for patients wishing to become pregnant or for those already pregnant. Treatment must be tailored to the individual patient according to disease activity and secure effective maternal disease control, as well as safety of the foetus. Drugs excluded for pregnant patients are combination treatments that include methotrexate, which is foetotoxic, or new drugs not studied or which have not been used in pregnant patients. Tables 4–7 summarise information on the safety of antirheumatic drugs during pregnancy and lactation. An algorithm for a treatment strategy of patients with rheumatic disease at different stages of pregnancy is presented in figure 4. A detailed and comprehensive overview of antirheumatic drugs during pregnancy and lactation is given in several surveys.

Table 3 Points to consider for the use of antirheumatic drugs before and during pregnancy (Götestam Skorpen et al, 2016*)

Points to consider for use of antirheumatic drugs during pregnancy		Grade of recommendation
1	Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare.	B
2	csDMARDs methotrexate (MTX), MMF and cyclophosphamide are teratogenic and should be withdrawn before pregnancy.	B
3	Non-selective cyclooxygenase (COX) inhibitors (non-steroidal anti-inflammatory drugs, [NSAIDs]) and prednisone should be considered for use in pregnancy if needed to control active disease symptoms. NSAIDs should be restricted to the first and second trimesters.	B
4	In severe, refractory maternal disease during pregnancy methylprednisolone pulses, intravenous immunoglobulin or even second or third trimester use of cyclophosphamide should be considered.	D
5	csDMARDs, targeted synthetic DMARDs (tsDMARDs) and anti-inflammatory drugs with insufficient documentation concerning use in pregnancy should be avoided until further evidence is available. This applies to leflunomide, mepacrine, tofacitinib and selective COX II inhibitors.	B–D
6	Among biological DMARDs (bDMARDs), continuation of anti-TNFs during the first part of pregnancy should be considered. Etanercept and Certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.	B
7	bDMARDs rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.	D

Table 4 Antirheumatic drugs and biological agents not to be continued during pregnancy (Reproduced with permission from Østensen and Forger, Curr Opin Pharmacol 2013;13:470–5*)

Drug	Developmental toxicity reported		Recommendation
	In animals	In humans	
Methotrexate	In animals and humans		Discontinue 3 months before pregnancy*
Mycophenolate mofetil	In animals and humans		Discontinue 6 weeks before trying conception
Cyclophosphamide	In animals and humans		Withdraw before pregnancy
Leflunomide	In animals	No increase in adverse outcomes in 109 pregnancies	Stop and washout† before pregnancy
Abatacept	Toxicity in animals	Case series: no increase in adverse outcomes	Discontinue 3 months before pregnancy

Tocilizumab	Not in pharmacological doses	Register data, case series: no increase in adverse outcomes	Discontinue 3 months before pregnancy
Belimumab	Limited data		Discontinue 5 half-life before pregnancy [‡]
Anakinra			
Ustekinumab			
Tofacitinib			
Rituximab	B cell depletion in the foetus of animals and humans when given in 2nd or 3rd trimester		Discontinue 6–12 months before pregnancy
Infliximab, Adalimumab, Golimumab	No toxicity in animals	Sporadic cases, cause–effect relationship not conclusive	Discontinue at missed period or after a positive pregnancy test. For active disease refractory to other treatment, TNF inhibitors may be given during pregnancy. Monoclonal antibodies must be stopped between gestational weeks 20 and 30.
Etanercept	No toxicity in animals	Little transplacental passage	Etanercept and certolizumab can be given throughout pregnancy.
Certolizumab	No toxicity in animals	No increase in adverse outcomes in 139 pregnancies. Little transplacental passage	
Bisphosphonates	Toxicity in animals	Insufficient data on human pregnancy	Discontinue at conception

**In France, conception is allowed the day after stopping methotrexate because of its short half-life (3–4 h). Of course, folic acid is essential in these women.*

†Because of the very long half-life (18 months) of leflunomide, a washout should be done with cholestyramine 8 g three times a day or powdered activated carbon 50 g four times a day during 11 days for both. Leflunomide concentration must be monitored to allow pregnancy.

‡They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.

TNF, tumour necrosis factor.

Table 5 Treatment of a flare with drugs compatible with pregnancy

Type of flare	Drugs compatible with pregnancy	Precaution
Acute arthritis in one or several joints; pain, stiffness	Intra-articular glucocorticoids, NSAID: diclofenac, ibuprofen, ketoprofen, mefenamic acid, naproxen, piroxicam Colchicine	NSAID must be discontinued at week 24 or 32 of gestation depending on country's recommendations
Pain	Paracetamol	1–4 g/day can be given throughout pregnancy
Systemic flare	Oral glucocorticoids	Keep at ≤ 10 mg/day in first trimester
	Methylprednisolone pulses	Shorter possible period
	Chloroquine HCQ	HCQ preferable because of less tissue distribution
	Azathioprine	Keep at 2 mg/kg/day
	Cyclosporine	Control maternal blood pressure
	Sulfasalazine	Requires folate substitution
	Tacrolimus	Be aware of higher risk of cytomegalovirus infection
	IVIg	Same cautions than in non-pregnant patient

HCQ, hydroxychloroquine; NSAID, non-steroidal anti-inflammatory drug. IVIg: intravenous immunoglobulins.

Table 6 Non-steroidal anti-inflammatory and immunosuppressive drugs during lactation

Drug	Excreted into breast milk	Adverse effect on nursing child	Recommendations
NSAID	Yes	None reported	Nursing possible: prioritize agents with short half life
Celecoxib	Yes but very low	None reported	Nursing possible
Prednisone	Yes	None reported	Nursing possible. Consider a 4h delay before breastfeeding after prednisolone if dose > 50mg/day
Chloroquine, hydroxychloroquine	Yes	None reported	Nursing possible
Colchicine	Yes	Diarrhoea: reconsider breastfeeding	Be aware of macrolide prescription in breastfed infants
IVIg	Heterogenous results	Rare	Nursing possible
Sulfasalazine	Yes	Rare	Nursing possible. Caution in premature children, G6PD deficiency and hyperbilirubinaemia
Leflunomide	Not studied	No data	Avoid

Azathioprine	Yes	None reported	Nursing possible. Caution in thiopurine methyltransferase deficient individuals
Cyclosporine	Yes	None reported	Nursing possible
Tacrolimus	Yes	None reported	Nursing possible
Methotrexate	No	No data	Avoid
Cyclophosphamide	Yes	Bone marrow suppression	Avoid
Mycophenolate mofetil	Not studied	No data	Avoid

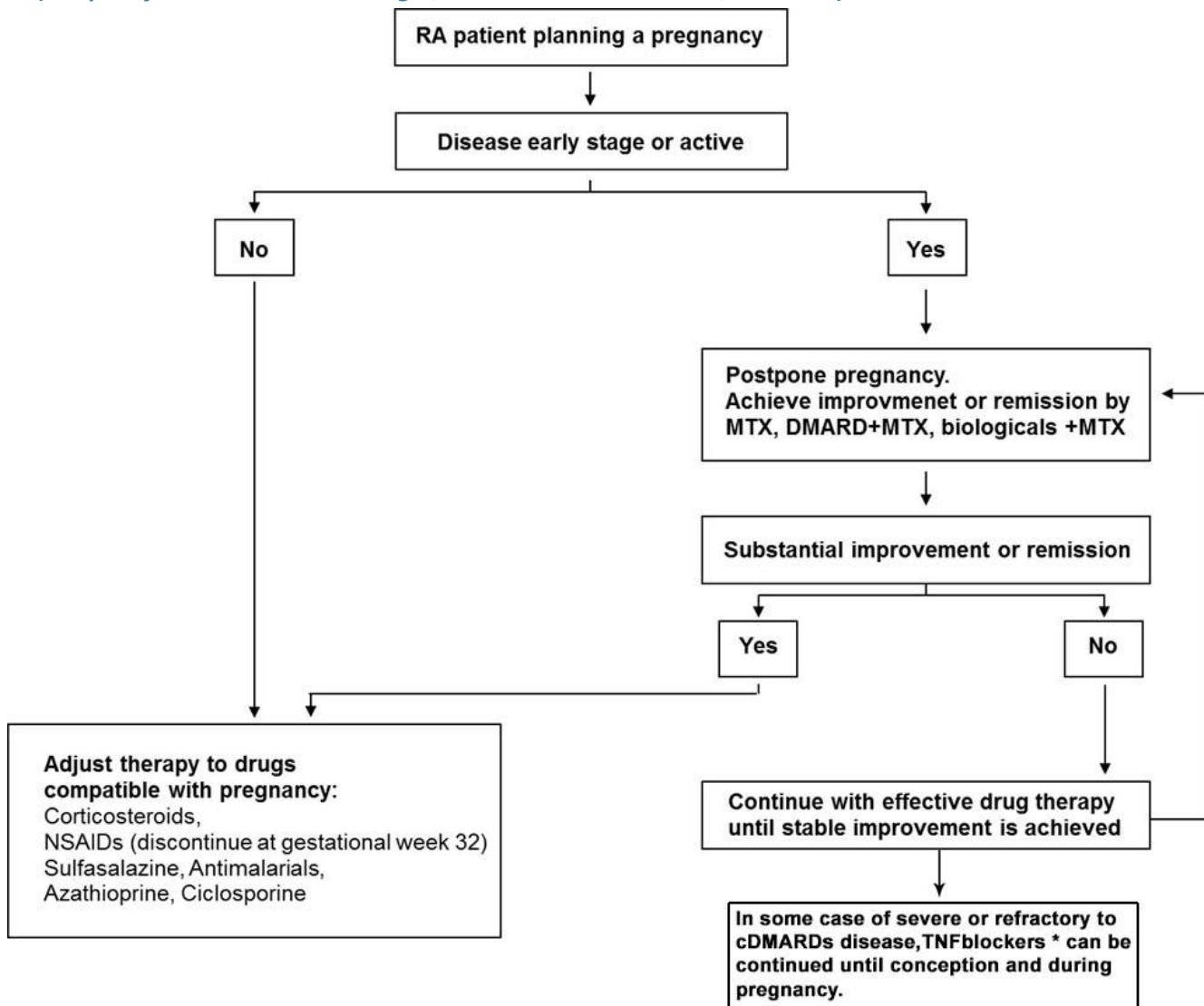
NSAID, non-steroidal anti-inflammatory drug. IVIg: intravenous immunoglobulins.

Table 7 Biological agents during lactation

Drug	Detected in milk	Adverse effect on infant	Recommendation
Etanercept	Yes, minute amount	None reported	Compatible with lactation
Infliximab	Yes, minute amount	None reported	Compatible with lactation
Adalimumab	Yes, minute amount	None reported	Compatible with lactation
Golimumab	Not studied	No data	No data*
Certolizumab	No	None reported	Compatible with lactation
Abatacept	Not studied	No data	No data*
Tocilizumab	Not studied	No data	No data*
Rituximab	Not studied	No data	No data*
Ustekinumab	Not studied	No data	No data*
Anakinra	Not studied	No data	No data*
Belimumab	Not studied	No data	No data*

**Large protein molecule, absorption unlikely due to low bioavailability. Biological DMARDS with no data on breast feeding should be avoided during lactation if other therapy is available to control the disease. Based on pharmacological properties of biological nDMARDS, lactation should not be discouraged when using these agents, if no other options are available (Götestam Skorpen et al, 2016*).*

Figure 4. Algorithm of a treatment strategy for patients with RA planning a pregnancy. In patients with stable disease, or with mild-to-moderate disease activity, treatment should be adjusted from drugs incompatible with pregnancy (eg, methotrexate) to compatible drugs. In patients with early RA or with active and uncontrolled disease activity, pregnancy should preferentially be postponed until substantial improvement in disease activity or remission is achieved. Once RA is stable, and after a switch to drugs compatible with pregnancy, conception can be attempted. DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis. (Adapted from Østensen and Förger, Nat Rev Rheumatol 2009;5:382–90.)



**Most of the safety data available of TNF blockers is based on women discontinuing TNF α therapy in the first trimester. TNF blockers can cross the placenta from the end of the second trimester of gestation and little data exists on exposure throughout the pregnancy. Their use during pregnancy should be based on a collegial decision after discussion with the patient.*

- Drugs to be withdrawn before a planned pregnancy: methotrexate, cyclophosphamide, leflunomide, mycophenolate mofetil, abatacept, tocilizumab, belimumab, ustekinumab and rituximab.
- Drugs that can be continued until conception: TNF inhibitors. TNF inhibitors differ in structure and show differences in transplacental passage. Complete monoclonal antibodies infliximab, adalimumab and golimumab are actively transported through the placenta, whereas certolizumab pegol and

etanercept has minimal passage to the foetus and may be a choice when active disease in pregnancy requires a TNF inhibitor.

- Drugs that are compatible with pregnancy: colchicine, sulfasalazine, azathioprine, cyclosporine and tacrolimus.
- Drugs that can be safely administered throughout pregnancy: antimalarial agents, glucocorticoids and analgesics such as paracetamol (acetaminophen).
- Drugs that can be safely administered until gestational week 24 in some countries as in France or gestational week 32 in others: NSAIDs.

Supplementation with folic acid, calcium and vitamin D (the latter especially in women taking glucocorticoids or low molecular weight heparin) should be recommended.

When immunosuppressive or biologic agents have been used during pregnancy, children must be considered as immunocompromised until 6 months of life (live attenuated vaccines are contraindicated during this period). Paediatricians must be informed of the use of such treatment during pregnancy.

16. Vaccinations

Vaccinations need to be updated before pregnancy.

Reminder: live attenuated vaccines are contraindicated during pregnancy and/or when patients receive immunosuppressive agents, biotherapy or corticosteroid up to 10 mg per day for more than 2 weeks.

Pertussis is a highly infectious disease that can cause serious complications. Newborn babies are especially vulnerable until they have had at least 2 doses of the vaccine (i.e. until they are 3-4 months old). Babies under 3 months old are at greatest risk of complications and death from pertussis. So it is important for women to get the whooping cough vaccine before or during pregnancy (according to each country recommendations).

Pregnant women have to be vaccinated against influenza viruses because flu is more likely to cause severe illness in pregnant women than in healthy women who are not pregnant and because vaccination seems to increase the likelihood of having a live birth. Many scientific studies support the safety of flu vaccine in pregnant women and their babies.

17. Risk assessment and monitoring of pregnancies

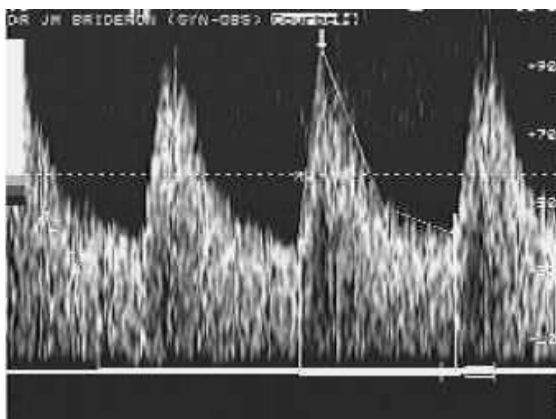
Risk assessment of possible maternal or foetal risks during a future pregnancy is essential. Major risks are active disease at conception, a flare during pregnancy, conception in a stage of active organ involvement or at severe organ damage, presence of antiphospholipid and antibodies against SSA (Ro) and SSB (La). A clinical investigation and laboratory tests will show the presence of risk factors for a future pregnancy, and will allow

stratification into a high-, moderate- or low-risk profile. Treatment adjustment and type and frequency of monitoring will depend on the risk profile of the individual patient.

At the start of pregnancy a complete clinical and laboratory assessment is necessary in order to monitor disease activity. High-risk pregnancies are best monitored by an interdisciplinary specialist team, including the internist or rheumatologist, obstetrician and paediatrician. The frequency of visits depends on disease severity, type of treatment and the stage of pregnancy. In uncomplicated cases, visits once a month can be scheduled until gestational week 20, then more often in late pregnancy. The diagnosis of a disease flare must be based on clinical and laboratory assessment. Regular assessment of foetal growth can predict whether the foetus is at risk. Doppler flow techniques allow evaluation of the uteroplacental and umbilical circulation. Electronic foetal heart rate monitoring has proved effective for detecting foetal distress. Foetal echocardiography is important for detecting myocarditis in a foetus with congenital heart block. The best guarantee for an optimal pregnancy outcome is close monitoring of mother and foetus and appropriate treatment of complications during pregnancy.

Figure 5

Normal uterine artery Doppler waveforms



Abnormal uterine artery Doppler



18. Counselling women

Better treatment and better prognosis of many of the rheumatic diseases have resulted in more patients considering pregnancy. A previous study found that 95% of women with rheumatic diseases wanted children, even those with disabling disease. Pregnancy in patients with connective tissue disease requires preconceptional counselling (see online in-depth discussion). The task of the physician is to discuss the possible problems, identify risks and organise adequate monitoring during pregnancy and post-partum.

In Western affluent countries the birth rate has decreased to between one and three children. At the same time women have postponed the time for having a first child to the fourth decade of life. This means that

many patients will plan their first pregnancy at about the age of 35 years. The internist or rheumatologist counselling a patient with rheumatic disease should consider the stage of the disease, disease activity and presence of factors that increase the risk for an adverse pregnancy outcome, especially antiphospholipid antibodies, anti-SSA antibodies or organ damage. An early stage of disease implies that the pattern of disease severity is not yet apparent and complications might still develop in the near future. SSc is an example. A patient with active rheumatic disease should postpone pregnancy until remission or stable disease is achieved and has persisted for at least 6 months. Before pregnancy, access to familial and social support should be evaluated. Therefore, it is advantageous to include the patient's partner or a family member in preconceptual counselling. In order to prepare for the task of child caring after delivery, consulting an occupational therapist is advisable for the patient with impaired function. A meeting with an interdisciplinary team including a physiotherapist, an occupational therapist and a social worker can help to prepare the rheumatic mother for parenting. Finally, the possible difficulties of parenting should be discussed.

Drug treatment before and during pregnancy needs to be discussed. It is important that the treating physician warns against discontinuation of all treatment when an attempt at conception is made. Withdrawal of drug treatment may result in a disease flare. The better approach is to adjust treatment and continue with drugs that are compatible with first trimester exposure. Other physicians, especially the gynaecologist, involved in patient treatment should be informed about necessary antirheumatic therapy in order to avoid contradictory advice.

SUMMARY POINTS

- The interaction of rheumatic diseases and pregnancy is variable and related to the pathogenesis of the maternal rheumatic disease.
- Rheumatoid arthritis improves in 40–75% of patients during pregnancy; the chance of improvement is highest in patients negative for rheumatoid factor and citrullinated antibodies.
- Ankylosing spondylitis remains active during pregnancy in about 80% of patients, with frequent aggravation of symptoms during the second trimester.
- Polyarticular or oligoarticular juvenile idiopathic arthritis is not reactivated by pregnancy but tends to improve during gestation.
- Symptoms of primary Sjögren's syndrome are not influenced by pregnancy.
- Systemic lupus erythematosus (SLE) may be associated with a bad obstetrical outcome, in particular in active disease.
- Pregnancy can induce a flare of SLE.
- The presence of SSA/SSB antibodies is associated with a risk of neonatal lupus syndrome.
- Successful pregnancy is possible in women with systemic sclerosis provided that they have no severe organ manifestations.
- Most women with polymyositis or dermatomyositis with inactive disease at conception have normal pregnancies with a good outcome.
- The course of familial Mediterranean fever during pregnancy is variable, with the best chances for a good outcome achieved by continuing colchicine during pregnancy.
- Women with any type of vasculitis should attempt pregnancy only at a stage of quiescent and well-controlled disease.
- Pregnancies in women with active rheumatic disease or vasculitis, in women with severe organ manifestations or with repeated high-titre phospholipid antibodies or SSA/SSB antibodies are high risk.
- Blood pressure increase has a strong association with unfavourable pregnancy outcomes. New onset of hypertension in pregnancy may be a first sign of emerging pre-eclampsia or other organ involvement

Drug treatment requires adjustment to the stage of pregnancy and must be tailored according to maternal disease severity and safety for the foetus. High-risk pregnancies require a multidisciplinary approach with frequent monitoring of mother and child during pregnancy and post partum.

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Part II: antiphospholipid syndrome

LEARNING OBJECTIVES

- ➔ Recognise the classical manifestations of antiphospholipid syndrome (APS) (thrombotic events and pregnancy morbidity) and the laboratory assays for detection of antiphospholipid antibodies
- ➔ Recognise that APS may present as a primary form as well in association with other systemic autoimmune diseases, mainly systemic lupus erythematosus
- ➔ APS is a 'systemic' disease: neurological, cardiac, renal, and cutaneous manifestations may be present
- ➔ Design a diagnostic screening algorithm for the individual patient
- ➔ Critically evaluate the limited scientific evidence for the diagnosis and treatment of patients with antiphospholipid antibodies with and without APS
- ➔ Develop treatment strategies for patients with APS, tailored to the clinical picture

1. Introduction

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by arterial and/or venous thrombosis and/or pregnancy morbidity, associated with the presence of a specific group of autoantibodies called antiphospholipid antibodies (aPL) (Miyakis et al, 2006*). APS was initially described in patients with systemic lupus erythematosus (SLE), but it was soon recognised as a primary form in those people who did not have features (clinical and serological) of other systemic autoimmune diseases. A European study of 1000 patients showed that APS was associated with SLE in 36% of the cases.

Although APS is largely recognised as a disease of young women, owing to the association with SLE and pregnancy loss, men can also be affected. It is estimated that aPL can be found in 9.5% of the patients with unexplained venous thrombosis and in 13.5% of those with stroke (Andreoli et al, 2013).

However, the presence of aPL is not limited to those people who have the typical picture of APS. These autoantibodies are detectable in several different conditions, mainly in patients with systemic autoimmune diseases, but also in infectious conditions, cancer, use of particular drugs and even in healthy individuals (table 1).

Table 1 Conditions in which antiphospholipid antibodies have been reported

Systemic autoimmune disorders	Infection
– Systemic lupus erythematosus	– Leprosy
– Rheumatoid arthritis	– Syphilis
– Sjögren's syndrome	– HIV
– Scleroderma	– Hepatitis C
– Myositis	– Cytomegalovirus
– Systemic vasculitis	– Parvovirus
– Crohn's disease	– Mycoplasma
Drugs	Others
– Hydralazine	– Diabetes
– Procainamide	– Malignancy
– Phenytoin	– Sarcoidosis
– Quinine/quinidine	– Accelerated atheroma
– Interferon	– Healthy adults and children

The relevance of testing for aPL concerns their pathogenic role. In vitro and in vivo studies in animal models showed that aPL are mediators of both thrombosis and pregnancy morbidity by the engagement of multiple pathogenic mechanisms involving inflammation and disruption of the coagulation pathways. Moreover, aPL are considered as a risk factor for the development of APS, so they should be assessed in patients with systemic autoimmune diseases in order to establish an adequate prophylaxis.

Treatment of APS means prophylaxis. It is primary in those individuals who are aPL carriers and should be prevented from the development of their first event; and secondary in those patients who need to be protected from recurrence of either thrombosis or pregnancy morbidity.

2. Antiphospholipid antibodies

aPL are a family of the immunoglobulins IgG, IgM, IgA or a combination of these isotypes, which were initially thought to recognise anionic phospholipids, particularly cardiolipin (Giannakopoulos and Krilis, 2013*). Over the years, this concept has changed and different specificities have been described for aPL (table 2). The main finding was that aPL mostly recognise phospholipid-binding proteins rather than the phospholipids.

Table 2 Different specificities of antiphospholipid antibodies

Antibodies to phospholipids
Cardiolipin
Phosphatidylserine
Phosphatidic acid
Phosphatidylinositol
Phosphatidylcholine
Phosphatidylethanolamine
Antibodies to phospholipid-binding proteins
β 2-Glycoprotein I (β 2GPI) Factor XIIIG
Prothrombin C4b binding protein
Annexin V Complement C4 and C5
Protein C Heparin sulphate
Protein S Thrombin
Low and high molecular weight kininogens Other

2.1 Lupus anticoagulant

Lupus anticoagulant (LA) is a functional measurement of the ability of heterogeneous aPL that interfere with phospholipid-dependent stages of blood coagulation in vitro and inhibit both the intrinsic and common pathways of coagulation. Paradoxically, LA-positive results are associated with a thrombotic tendency rather than bleeding, which is generally associated with coagulation inhibitors. LA has been reported in a wide variety of patient populations, ranging from those with autoimmune diseases (eg, SLE, rheumatoid arthritis (RA)), drug exposure (eg, chlorpromazine, procainamide and hydralazine), infections and lymphoproliferative disorders to individuals with no apparent underlying disease. The estimated prevalence in patients with SLE ranges from 6% to 65%. Not all patients with LA have anticardiolipin (aCL) and vice versa. In most cases LA are specific for either phospholipid-bound β 2-glycoprotein I (β 2GPI) or prothrombin. LA are strongly associated with the risk of thrombosis and adverse obstetrical outcome (Lockshin *et al*, 2012*).

2.2 Anticardiolipin

The aCL test was originally described in 1983 as a radioimmunoassay. The first aCL enzyme-linked immunosorbent assay (ELISA) was carried out in 1985, using cardiolipin as antigen and foetal calf serum or adult bovine serum in the buffers. The addition of serum was essential for performance of the assay, owing to the presence of β 2GPI, a glycoprotein that binds negatively charged phospholipids, such as cardiolipin itself. Therefore, an aCL assay can detect several subpopulations of autoantibodies—that is, those directed against phospholipid-binding proteins such as β 2GPI (β 2GPI-dependent aCL), the phospholipid itself or against the phospholipid-binding protein/phospholipid complex. As a consequence, a positive test for aCL may be less specific for APS, since it is commonly found in non-autoimmune conditions, especially infections. These aCL are

usually IgM and low titre and are not associated with aPL-related clinical features. Instead, the risk of thrombosis, recurrent pregnancy loss and thrombocytopenia has been associated with high levels of aCL. IgG isotypes are more related to clinical complications than are IgM isotypes. The role of IgA aCL is still controversial.

2.3 Antibodies to β 2-glycoprotein I

In 1990, two independent groups identified β 2GPI as the plasma cofactor required for aCL binding to cardiolipin. β 2GPI is a normal plasma glycoprotein, a single-chain 50 kD polypeptide consisting of 326 amino acids arranged into five short consensus repeats or domains. Its function is not completely understood, although it may act as a natural anticoagulant. ELISA tests using β 2GPI coated in the absence of phospholipids were developed for the detection of antibodies against human β 2GPI. It was found that anti- β 2GPI were more specific than aCL in predicting thrombosis and differentiating pathogenic (autoimmune) from non-pathogenic (infection or drug induced) antibodies, since β 2GPI is an absolute requirement for binding of autoimmune aCL to cardiolipin in ELISA. Moreover, it is estimated that 3–10% of patients with APS have anti- β 2GPI as the only positive test.

2.4 'Non-criteria' aPL

As described in table 2, aPL may have different specificities other than cardiolipin and β 2GPI—for example, antiprothrombin, antiphosphatidylethanolamine, anti-Annexin V, antiprotein C and S, and others. These antibodies were not recognised as laboratory criteria in the last international consensus, mostly owing to weak and discordant evidence for the association with APS manifestations. To this group belong also IgA aCL and anti- β 2GPI. However, there is much interest in this field and an international task force is currently examining the subject (Bertolaccini et al, 2011).

2.5 Standardisation concerns

Although they have different methodological approaches (LA is a functional test that explores the coagulation in vitro; aCL and anti- β 2GPI are detected by quantitative ELISAs that can test different isotypes), all three tests still suffer from poor standardisation (Pengo et al, 2009). Despite many international efforts for more than 20 years, reports of inconsistencies, interassay and interlaboratory variation, and problems with the interpretation and clinical value of the tests still exist. As an example, there are still no international units for the measurement of anti- β 2GPI, so results are reported arbitrarily. Therefore, the consistency of the diagnosis of APS is greatly

affected by laboratory procedures, making it difficult to compare patients from place to place. International committees and task forces are working to deal with these problems (Pierangeli et al, 2011*).

3. Origin of aPL

The origin of aPL and mechanisms involved in their production are not understood. The origin of aPL was extensively investigated and several research groups have induced high levels of aPL in experimental animals by immunisation with β 2GPI. However, although immunisation with foreign β 2GPI can induce pathogenic aPL, it is unlikely that aPL production is induced with foreign β 2GPI in patients with APS. The observation that aPL of the autoimmune type may be associated with thrombosis in patients with Epstein–Barr virus, cytomegalovirus, hepatitis C virus, adenovirus or parvovirus suggests that certain infections may induce autoimmune aPL that are not transient.

Recent data show that aPL may be induced in experimental animals by immunisation with products from bacteria or viruses, supporting the hypothesis that these antibodies may be generated after incidental exposure or infection, a mechanism involving ‘molecular mimicry’. Immunisation of mice with viral and bacterial peptides with function and sequence similar to the phospholipid-binding site of β 2GPI (table 3) induced high levels of aPL and anti- β 2GPI. These peptide-induced aPL can also enhance thrombosis and activate endothelial cells in vivo and in vitro (Giannakopoulos and Krilis, 2013*).

Table 3 International classification criteria for definite antiphospholipid syndrome. (Modified from Miyakis et al, J Thromb Haemost 2006;4:295–306*)

Clinical criteria	
<i>Vascular thrombosis</i>	<i>Pregnancy morbidity</i>
<ul style="list-style-type: none"> One or more clinical episodes of arterial, venous, or small-vessel thrombosis, with the exception of superficial venous thrombosis, in any tissue or organ. Thrombosis must be confirmed using imaging or Doppler studies or histopathology. For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall 	<ul style="list-style-type: none"> One or more unexplained death of a morphologically normal foetus at or beyond the 10th week of gestation One or more premature birth (<34 weeks of gestation) of a morphologically normal neonate, because of eclampsia, severe pre-eclampsia and placental insufficiency Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation (excluded maternal anatomical or hormonal abnormalities and chromosomal cause)
Laboratory criteria	
<ul style="list-style-type: none"> Lupus anticoagulant (LA), detected according to the guidelines of the International Society on Thrombosis and Haemostasis (scientific subcommittee on LAs/phospholipid-dependent antibodies), is considered positive if present in plasma, on two or more occasions at least 12 weeks apart Anticardiolipin antibodies of IgG and/or IgM isotype measured by a standardised ELISA are considered positive if present in serum or plasma, in medium or high titre (ie, >40 GPL or MPL, or >99th centile), on two or more occasions, at least 12 weeks apart 	

- Anti- β_2 -glycoprotein I antibodies of IgG and/or IgM isotype measured by a standardised ELISA, according to recommended procedures, are considered positive if present in serum or plasma, in titre >99th centile, on two or more occasions, at least 12 weeks apart

ELISA, enzyme-linked immunosorbent assay; GPL, IgG phospholipid units; MPL, IgM phospholipid units.

4. Pathogenic mechanisms of aPL

Several animal studies of both thrombosis and pregnancy loss have shown that aPL are pathogenic. aPL exert their pathogenic action through interaction with many different cell types (Giannakopoulos and Krilis, 2013*).

Recent research indicates the central role of endothelial cells, monocytes, platelets and complement in inducing thrombosis and foetal death in APS. Endothelial cells and monocytes can be activated by aPL with anti- β_2 GPI activity. In turn, endothelial cells express adhesion molecules such as intercellular adhesion molecule 1, vascular cell adhesion molecule 1 and E-selectin, and both endothelial cells and monocytes upregulate the production of tissue factor. Activated platelets increase the expression of glycoprotein IIb–IIIa and the synthesis of thromboxane A₂. Nuclear factor- κ B (NF- κ B) and p38 mitogen activated protein kinase are important mediators of these processes. Additionally, interaction of aPL with proteins implicated in clotting regulation, such as prothrombin, factor XII, protein C and plasmin, may hinder inactivation of procoagulant factors and impede fibrinolysis.

Pierangeli et al proposed that after activation of endothelial cells, monocytes and platelets by aPL, a procoagulant state is induced, mainly mediated by the increased synthesis of tissue factor and thromboxane A₂ (Pierangeli et al, 2011*). Activation of the complement cascade may ‘close the loop’ and provoke thrombosis, often in the presence of a ‘second hit’.

What is a ‘second hit’? The so called ‘two hits hypothesis’ claims that aPL alone are not sufficient to generate thrombosis, but they require ‘activation’ by a second triggering factor. Traditional cardiovascular risks factors may play an important role at this point. Such risk factors are present in more than 50% of patients with APS, with a recent epidemiological study showing that the risk of myocardial infarction or stroke in young women with LA multiplies in those who smoke or take oral oestrogenic therapy.

A different mechanism is claimed for obstetric disease. Thrombotic events do not appear to play a major role in obstetric APS, whereas direct reactivity of β_2 GPI-dependent aPL on decidual and trophoblast cells was reported. There is probably a local tropism of the autoantibodies to the placenta, since a local expression of β_2 GPI was shown in both physiological conditions and in women with APS. β_2 GPI is present on placental membranes: binding of autoantibodies directed against this protein may modulate several cell biological functions producing a state of acute inflammation and complement activation, inhibition of trophoblast growth and differentiation and, finally, defective placentation, inducing an inflammatory phenotype on decidual cells. The presence of β_2 GPI has been demonstrated in vivo on endothelial cells of uterine vessels and trophoblast in pregnant mice. This shows that proinflammatory factors are probably not needed for uterine and placental localisation of β_2 GPI

that is probably dependent on hormonal changes. The role of anti- β 2GPI as major players in the pathogenesis of placental damage is also supported by the detection of anti- β 2GPI in the eluates from human APS placentas.

In vitro studies showed that aPL antibodies, especially anti- β 2GPI, can disrupt the anticoagulant annexin 5 shield on trophoblast and endothelial cell monolayers. β 2GPI binds human trophoblast through the phospholipid-binding site in the fifth domain of the molecule. It has been shown that a synthetic peptide (TIFI) obtained from human cytomegalovirus, is similar to the β 2GPI phospholipid-binding site and therefore may compete with β 2GPI, thus displacing the molecule from the cells' surface and inhibiting the binding of aPL to the target tissue. Repeated infusions of TIFI protected naïve pregnant mice from foetal loss induced by human aPL IgG. This is indirect evidence that anti- β 2GPI play a major role in defective placentation. This supports the in vitro results that showed the ability of aPL to modulate trophoblast cellular functions at different levels (Meroni et al, 2012).

A number of animal models for aPL-induced pregnancy loss exist, therefore many different pathogenic mechanisms are likely to be involved. For instance, the role of acute inflammation and complement activation has been greatly debated. aPL were shown to activate the complement system with subsequent placental damage mediated by neutrophils. On the other hand, pregnant mice deficient in complement C3 or C5 or treated with an inhibitor of C3 convertase did not experience foetal loss upon immunisation with aPL. This observation might be an additional explanation for the protective role of heparin because of its anti-complement activity. Human placentas have also been studied to clarify the role of complement, in both deposition and activation. Although case reports failed to show any complement deposition in abortive material from patients with APS, prospective studies did find complement deposition and activation. However, this finding was not exclusive to abortive specimens, but was also found in APS placentas at term. Moreover, complement activation was not widespread and the presence of inflammatory cells was scarce; no relationship was found between complement patterns on placentas and either treatment during pregnancy or pregnancy outcome itself. As a whole, these data suggest that local activation and deposition of complement may occur at the placental level in APS human pregnancy, but do not have a major effect on the outcome.

5. Clinical manifestations

5.1 Thrombosis

The APS is a non-inflammatory autoimmune disease in which the most critical pathological process is thrombosis, which results in most of the clinical features of these patients.

Arterial or venous thrombosis, with or without a history of adverse pregnancy, can be present. Deep vein thrombosis has been the most commonly reported venous manifestation, often recurrent and accompanied by pulmonary embolism. Occlusion of the intracranial arteries is the most common arterial manifestation, with most patients presenting with stroke.

As any organ and any size of vessel may be affected, the range of clinical features is extremely wide.

5.1.1 Central nervous system

There is a very broad spectrum of central nervous system involvement in APS. Cerebral ischaemia associated with aPL is the most common arterial thrombotic manifestation. Many studies have found that aPL are associated with an increased risk for cerebral ischaemia, but some have not. The age of onset of cerebral ischaemia in APS is several decades earlier than in the typical stroke population and the ischaemic events may occur in any territory. A less common form of cerebral thrombotic disease associated with aPL is sagittal venous sinus thrombosis.

Migraine is one of the most prominent complaints in patients with APS, but its association with aPL is still controversial. Several studies have failed to show an association between the presence of aPL and migraine. Although the prevalence of headache in SLE is similar to that reported for the general population, aPL are significantly more prevalent in the group of patients with headache than in patients without.

Cognitive deficits associated with APS may vary from mild neurocognitive disorders to severe vascular dementia. Patients affected by mild cognitive dysfunction often complain of poor concentration or forgetfulness. Verbal memory deficits, decreased psychomotor speed and decreased overall productivity have been correlated with aPL. Whether these cognitive deficits result from recurrent cerebral ischaemia or whether there are other underlying mechanisms remains unknown. Psychiatric problems, such as mood disorders and psychosis, have also been associated with aPL.

Some patients with APS may exhibit features often seen in multiple sclerosis. Myelitis, balance and sensory problems not surprisingly often lead to an erroneous diagnosis of multiple sclerosis. Differential diagnosis is difficult, and compounded by a number of features—notably, single MRIs may fail to differentiate, and borderline positive aPL levels may be dismissed as being of no significance. The clinical findings of livedo point towards APS. Also, a previous history of thrombosis or pregnancy loss, an abnormal localisation of the lesions on MRI, and the response to anticoagulant therapy might be helpful in the differential diagnosis.

Seizures have been consistently associated with the presence of aPL. The cause is still unknown, but some authors have suggested direct interaction between aPL and neuronal tissue.

Less frequently described manifestations of APS include chorea, transverse myelopathy, Guillain–Barré syndrome, sensorineural hearing loss and ocular syndromes with retinal and choroidal ischaemia.

5.1.2 Heart

Several cardiac conditions apart from coronary artery disease have been reported in association with aPL. Heart valve lesions are the most common cardiac manifestations described in patients with aPL. The

prevalence of valvulopathy has been reported in 35–75% of patients with APS, according to different series. Most of the patients are asymptomatic, with around 5% of patients progressing to cardiac failure requiring valve replacement. Valve masses (vegetations) and diffuse valvular thickening are the two morphological echocardiographic patterns most frequently seen in APS. The predominant functional abnormality is regurgitation, whereas stenosis is rarely seen. Although the mitral valve is the most commonly affected site, followed by the aortic valve, isolated tricuspid valve involvement has also been described.

Acute coronary syndromes are well documented in patients with aPL. However, the association between aPL and myocardial infarction or sudden cardiac death is still debated in case–control and prospective studies. In young women myocardial infarction may present without any sign of coronary atherosclerosis.

Uncommon cardiac manifestations of APS include intracardiac thrombus, which can be misdiagnosed as a cardiac tumour, myocardial dysfunction and syndrome X, characterised by angina-like chest pain, a positive exercise test and angiographically normal coronary arteries.

5.1.3 Lungs

Patients with APS may develop a broad spectrum of pulmonary involvement. The most common pulmonary manifestation of APS is pulmonary embolism and infarction, usually seen as the first manifestation of the disease. Pulmonary hypertension is found in around 1.8–3.5% of patients with APS (a prevalence of 2.2% was found in a cohort of 1000 European patients).

Adult respiratory distress syndrome is a very rare but devastating clinical syndrome with a mortality of 52%, usually seen in patients with catastrophic APS.

5.1.4 Kidney

The kidney is a major target organ in APS where both arterial and venous vessels, as well as the intraparenchymatous arteries and microvasculature, may all be affected. As renal damage in SLE is primarily due to immune complex-mediated glomerulonephritis, patients with SLE and APS can develop kidney involvement owing to a combination of both processes. Moreover, the impairment of renal function in patients with SLE and aPL can also occur in the absence of APS-related manifestations. In this case, distinguishing between SLE nephritis (immune complex disease) and APS nephritis (thrombotic disease) can only be accomplished by kidney biopsy.

Renal artery occlusion and renal artery stenosis have been described in patients with APS and hypertension. The localised and stenotic (thrombotic) arterial lesions have a totally different appearance from those of renal artery disease seen in atheroma in older patients. Renal infarction may result from partial or total, transient or

permanent occlusion of the renal arteries. Thrombosis of the renal veins and thrombotic microangiopathy has also been described in APS.

5.1.5 Skin

The most frequent skin manifestations are livedo reticularis (figure 2) and skin ulcers (figure 3).

Figure 2. Irregular networks of livedo with fixed broken circular segments of the calf.



Figure 3. Skin ulcer due to antiphospholipid syndrome.



Livedo reticularis is characterised by a mottled purple reticular pattern with different localisation, extension, infiltration and regularity of the fishnet pattern. In APS, livedo reticularis is usually disseminated (present on the limbs, but also on the trunk and/or the buttocks), not infiltrated and has an irregular branching or broken pattern.

It is a powerful physical sign when suspecting APS. Moreover, it is a marker of poor prognosis and more severe disease in APS. Skin ulcers are often present in the extremities. However, extensive cutaneous necrosis associated with aPL has been reported.

Subungual splinter haemorrhages are seen in around 5% of patients with APS and their presence in a patient with aPL may alert the physician to the occurrence of other thrombotic events.

Digital gangrene has been described in patients with aPL. A variety of other cutaneous lesions, including purpura, tender nodules, papules and palmar–plantar erythema and anetoderma (figure 4), have been described in APS. Anetoderma is a rare elastolytic disorder. Recently, there has been a growing body of evidence linking primary anetoderma with a wide range of immunological abnormalities, the most common of which is the presence of aPL, with or without APS.

Figure 4. Numerous lesions of anetoderma of the arm: circumscribed areas of slack skin associated with a loss of substance on palpation.



5.1.6 Liver and gastrointestinal tract

Liver thrombosis, including Budd–Chiari syndrome, was a feature of the original clinical description of the syndrome. Liver function abnormalities are common in patients with APS, possibly as a result of either vascular ‘sludging’ or small-vessel thrombosis. Intestinal ischaemia and perforation due to thrombosis and coeliac artery stenosis have been described.

5.1.7 Haemocytopenias

Thrombocytopenia is a common haematological manifestation of APS, seen in around 25% of patients. It is rarely severe; platelet counts are usually $50\text{--}100 \times 10^9$, and bleeding is not a common problem. Haemolytic anaemia may be present in patients with APS and is sometimes associated with thrombocytopenia, the so-called Evans syndrome. Although a positive Coombs test is not rare in APS, haemolytic anaemia is not often seen (less often than thrombocytopenia). A small number of cases of marrow infarction have been described.

5.1.8 Musculoskeletal

Avascular necrosis of bone is most commonly of the femoral head, but also of other bones such as the navicular bone, and is a complication of APS, presumably as a result of ischaemia in vulnerable sites. Metatarsal fracture and other spontaneous fractures have been reported in the spine, ribs and elsewhere.

5.1.9 Endocrine system

Adrenal insufficiency is the most common endocrine manifestation and can be the presenting symptom of APS. A few cases of hypopituitarism and ovarian and testicular involvement have been reported.

Figure 10 : Left adrenal haemorrhage due to adrenal infarction in the antiphospholipid syndrome



5.2. Pregnancy

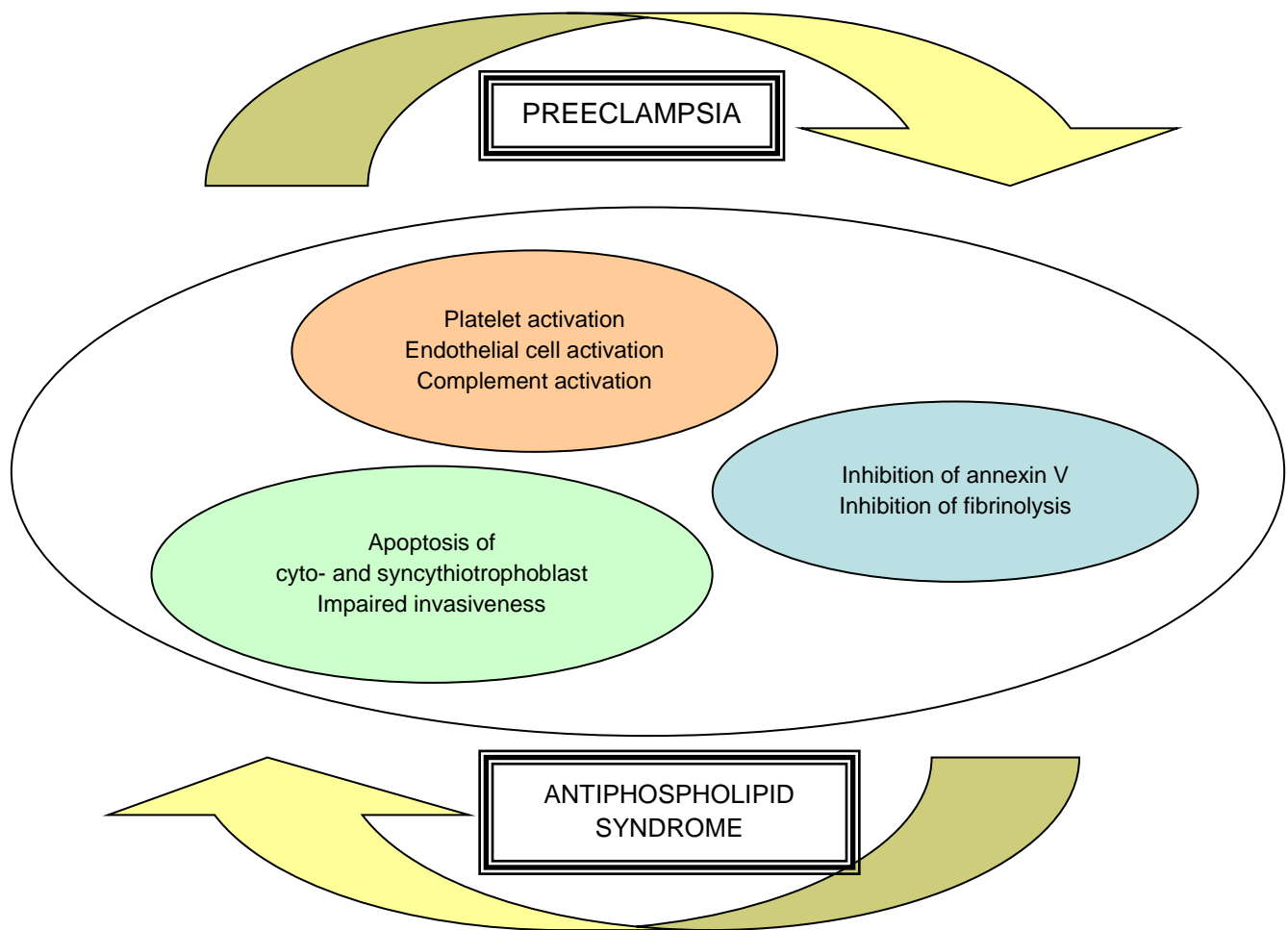
APS is frequently diagnosed following investigation for recurrent miscarriage, pregnancy morbidity being one of the major manifestations of the syndrome. In pregnancies that do not end in miscarriage or foetal loss, there is a high incidence of early onset pre-eclampsia, intrauterine growth restriction (IUGR), placental abruption and premature delivery (Branch *et al*, 2001; Lockshin *et al*, 2012*).

Pre-eclampsia has been reported in around one-third of patients with APS, being usually of early onset (before 34 weeks of gestation) and severe, and contributing to preterm delivery in these patients. Pre-eclampsia near term in the general population seems not to be associated with the presence of aPL. The risk of HELLP, a syndrome characterised by haemolysis, elevated liver enzymes, low platelets and proteinuria, is increased in APS with a wide range reported (0.66–10.6%). HELLP syndrome, pre-eclampsia and APS may share certain pathogenic mechanisms (figure 5). A peculiar feature is that the time of onset of HELLP in APS pregnancy is earlier than in the general obstetric population, occurring more frequently in the second trimester.

Placental insufficiency may also be manifested by foetal growth restriction, which is found in about 30% of patients with APS. Foetal distress has been reported in up to 50% of the offspring, although its association with aPL has not been confirmed. Pre-eclampsia and foetal growth restriction are responsible for the preterm delivery occurring in around 30% of pregnant women with APS.

Placental pathology may show extensive infarction, necrosis and thrombosis. However, these histological abnormalities are non-specific and are not always present in the placenta of women with APS. Thrombotic placental pathology is not specific for APS and pregnancy outcome is often unrelated to it.

Figure 5. Pathogenic mechanisms of pre-eclampsia and antiphospholipid syndrome. (Modified from Tincani et al, Nat Rev Rheumatol 2009;5:382–90.)



5.3 Pregnancy loss

Women with aPL have an unusually high proportion of pregnancy losses within the foetal period (≥ 10 weeks of gestation), in contrast with unselected women with sporadic or recurrent miscarriage, in whom the pregnancy losses occur more commonly in the pre-embryonic period (< 6 weeks of gestation) or the embryonic period (6–9 weeks of gestation). The prevalence of aPL in the general obstetric population is low ($< 2\%$), so universal screening is not warranted. However, any woman with a history of three or more first trimester miscarriages should be tested for these antibodies, once other causes have been excluded (chromosomal abnormalities, uterine anomalies, luteal phase insufficiency, cervical infections and thyroid hormone dysfunctions).

6. Catastrophic APS

Catastrophic APS (CAPS) is a life-threatening situation that develops in $< 1\%$ of patients with APS. CAPS discloses the APS in about 50% of cases. It is characterised by thrombosis at multiple organ sites, occurring concurrently or over a short period of time in association with positive aPL tests. Ischaemia of the kidneys, lungs, heart and/or

brain is most frequent. Adrenal, testicular, intestinal, splenic, pancreatic or skin involvement has also been described. Typically, occlusion of small vessels occurs (thrombotic microangiopathy), resulting in symptoms related to dysfunction of the affected organs.

It is recognised that precipitating factors, such as infections, postpartum period and surgery, may contribute to the development of CAPS. Additional precipitating clinical features include malignancy, medication, anticoagulation withdrawal and SLE exacerbation. Cerebral involvement (mainly, stroke), cardiac involvement and infections are the main causes of death in patients with CAPS. Recurrence of CAPS in the same patient is unusual.

CAPS overall mortality rate has decreased in the past decade and is now around 30%. The prevention of CAPS is based upon the adequate management of the perioperative period when surgery cannot be avoided, the prompt treatment of infections and the education of patients with APS.

Preliminary classification criteria for CAPS have been validated after analysing data from an international registry of patients with this condition (CAPS registry), and an international task force has been updating evidence on the management of this dramatic and life-threatening condition (Cervera et al, 2011*).

7. Classification criteria for definite APS

The definition of APS has been discussed in several international meetings involving experts from different specialties (rheumatology, obstetrics, neurology, haematology, nephrology, etc).

In 1998, the preliminary classification criteria for APS were proposed at Sapporo, Japan. Classification for APS required at least one clinical manifestation together with positive tests for circulating aPL, including LA and/or aCL at medium-high levels, detected at least twice in a 6-week period.

In 2006 the classification criteria were updated (Miyakis et al, 2006*). Essentially, the clinical criteria remained unchanged; however, two important modifications were agreed: the time between two positive determinations was extended to 12 weeks, in order to ensure the detection of persistent antibodies only; and anti- β 2GPI, both IgG and IgM, were added to the laboratory criteria. IgA isotypes as well as antiprothrombin and antiphosphatidylserine/prothrombin antibodies continued to be excluded from the criteria, since the committee felt that evidence for their inclusion was insufficient (table 3).

Other important points raised by the committee were the following:

- In patients with autoimmune disorders (SLE and RA) it is possible to find aPL associated with typical APS clinical manifestations. The episodes of thrombosis are similar in 'primary APS' (without other connective tissue disease) and 'secondary APS' (with connective tissue disease). The revised international consensus statement eliminated the 'primary' versus 'secondary' distinction, because there are no differences in the clinical consequences of aPL among patients in these two categories.

The new proposal is that patients with 'primary APS' should be described simply as having APS, and the term 'secondary APS' be replaced with APS together with specific mention of the autoimmune disorder with which it is known to be associated (i.e., APS and SLE).

- In patients with thrombotic events, it is strongly recommended to assess the presence of additional risk factors, either inherited or acquired, in order to better establish the role of aPL in the genesis of the thrombosis.
- Multiple aPL positivity is associated with a more severe course of the disease, increasing the rate of thrombosis and pregnancy morbidity; therefore, it is recommended that patients are tested for all three criteria tests, in order to distinguish triple positive patients from those with a single positive test.

8. Management of APS

Management of APS means prophylaxis. aPL are risk factors for thrombosis and pregnancy morbidity, therefore in carriers, occurrence of a first episode (primary prophylaxis) or recurrence (secondary prophylaxis) should be prevented. In the absence of solid guidelines derived from clinical trials (which are few in the field of APS), management of APS is still controversial and experts from different fields are trying to develop evidence-based recommendations. Management of patients with APS/aPL carriers should take many different aspects into consideration and provide a treatment tailored to the individual (Ruiz-Irastorza et al, 2011).

8.1 Management of thrombosis-free aPL-positive subjects (primary thromboprophylaxis)

aPL carriers, who can be either asymptomatic individuals or patients with SLE or other systemic autoimmune diseases, and women with obstetric APS need only to be protected against their first thrombotic event. The annual incident thrombosis risk is estimated to be no higher than 3.8%, on the basis of a few studies that also included patients with SLE.

The following recommendations should be considered:

- Any subject with aPL should strictly monitor and control modifiable vascular risk factors (hypertension, diabetes mellitus, obesity, cigarette smoking, high cholesterol, etc).
- In high-risk situations (surgery, post partum, long-lasting immobilisation) subjects should receive adequate thromboprophylaxis (eg, low molecular weight heparin (LMWH)).
- aPL asymptomatic carriers (on two or more occasions at least 12 weeks apart) and patients with obstetric APS may receive low-dose aspirin (eg, 100 mg/day) or no treatment (if no other risk factor is present).

- Patients with SLE or other autoimmune disorders (who have increased cardiovascular risk owing to the disease) should receive low-dose aspirin and/or hydroxychloroquine (a drug that has antiaggregant properties and was shown to be protective against the development of thrombosis).

8.2 Management after thrombotic episode (secondary thromboprophylaxis)

Based on current knowledge, which largely comes from retrospective studies and very few prospective, randomised trials, patients with definite APS should be treated with long-term anticoagulation.

For venous events the suggested target for the international normalised ratio (INR) is 2.0–3.0, while it is suggested that arterial events should be managed with high-intensity oral anticoagulation (INR = 3.0–4.0). However, new recommendations take into account both the clinical and the immunological profile of patients and suggest that a subgroup of patients could be treated less aggressively or for shorter periods (according to management in the general population). These are the patients with single positivity for aCL or anti- β 2GPI, preferentially at low titre, who had experienced thrombosis in the setting of reversible triggers.

Recurrence is not infrequent in patients with APS. Physicians may treat the recurrence by either increasing the intensity of anticoagulation or, if already at high intensity, adding low-dose aspirin. They must be aware, however, that the risk of bleeding is increased. An alternative strategy might be the use of immunomodulatory agents such as hydroxychloroquine and statins.

The role of steroids and immunosuppressive drugs in the treatment of patients with aPL and thrombosis is uncertain. Such drugs have severe side effects when given for prolonged periods, and aPL are not always suppressed by these agents. Furthermore, some series of patients with APS have shown that glucocorticoids and immunosuppressive drugs, prescribed to control lupus activity, did not prevent further thrombotic events. The use of these drugs is probably justified only in patients with CAPS. In this rare but life-threatening condition, the combination of anticoagulation, steroids and plasmapheresis or intravenous immunoglobulins is recommended. For CAPS and other severe manifestations, such as refractory thrombocytopenia, the use of B cell target therapies may be considered based on anecdotal reports of success (Berman et al, 2013; Erkan et al, 2014*).

Finally, management of pregnancy in these women is important (see next section and the online in-depth discussion).

8.3 Management in adverse pregnancy history (see also the online in depth discussion)

Pregnancy complicated by APS requires expert care and a team approach by APS-devoted physicians (obstetricians, rheumatologists, haematologists, etc). Patients with APS should undergo preconceptional assessment and counselling (see the online in-depth discussion). A detailed medical and obstetric history

should be obtained, and the presence of significant levels of aPL should be confirmed. The patient should be informed of the potential maternal and obstetric problems, including foetal loss, pre-eclampsia, HELLP syndrome, foetal growth impairment, preterm delivery and thrombosis or stroke.

The pharmacological management of pregnancy in women with APS is the subject of much debate (de Jesus et al, 2014*). It has included prednisone and aspirin, aspirin alone, low-dose aspirin (LDA) and heparin, intravenous immunoglobulins and even supportive care alone. Randomised controlled trials are few, small and have contradictory results. They showed that the effect of high-dose glucocorticoids on pregnancy outcome was no better than that of aspirin/heparin, while more side effects were seen (gestational diabetes, hypertension and infection as well as prematurity and foetal growth restriction). Treatment with LMWH plus LDA achieved 80% of live births, with few maternal complications in the European Registry on Obstetric Antiphospholipid Syndrome (Alijotas-Reig et al, 2015).

The management of pregnancy in APS may comprise the following situations:

- Women with 'definite' APS (according to the criteria): randomised controlled trials and systematic review of the literature support the combined treatment with LDA and LMWH as the most effective in preventing foetal loss. This will also protect the mother from thrombosis risk. However, 20% of pregnancies still have a negative outcome despite conventional treatment. An international multicentre case–control study of pregnancies prospectively followed up identified the following as negative prognostic factors: the association of APS with autoimmune diseases (particularly SLE), a history of both thrombosis and pregnancy morbidity, and triple aPL positivity (LA, aCL, anti- β 2GPI). This was confirmed in a recent prospective study, LA being associated with the worst obstetrical prognosis (Lockshin et al, 2012*). The management of these 'difficult cases' has not yet been standardised. There are multiple options—for example, increasing the anticoagulation dose or immunomodulation (glucocorticoids, hydroxychloroquine, intravenous immunoglobulins, plasmapheresis).
- Women with 'incomplete' APS (obstetric history not fulfilling criteria) or asymptomatic aPL carriers (without any clinical manifestation of APS): there is no codified treatment in these cases. However, treatment with LDA and/or LMWH could be given, based on a personalised approach (and with the additional goal of protecting the mother from thrombosis risk).
- Women with APS and previous thrombosis: the mother should be protected against the risk of recurrence; therefore a full anticoagulation during pregnancy is warranted. Most women will be taking warfarin and should be informed about the embryotoxicity of this drug. The strategy might be to stop warfarin as soon as the pregnancy test is positive, switching to LMWH and LDA. After delivery, warfarin can be resumed, as it is not contraindicated during breast feeding.

- Primary prevention of a first thrombotic event: women with pure obstetric APS, and asymptomatic carriers, should be protected against their first thrombosis. Puerperium is a high-risk period, so LMWH in a prophylactic dose is recommended for 6 weeks post partum. In addition, women should be screened for traditional cardiovascular risk factors (hypertension, dyslipidaemia, diabetes mellitus, etc) and informed they should avoid smoking, a sedentary lifestyle and the use of oestrogen-containing contraceptives.
-



SUMMARY POINTS

- Antiphospholipid syndrome (APS) is a complex systemic autoimmune disease.
- The clinical hallmarks are thrombosis and pregnancy morbidity, but multiple organs may also be affected.
- The diagnosis of APS is defined by the presence of antiphospholipid antibodies (aPL). However, aPL testing is affected by lack of standardisation despite international efforts, so the laboratory definition of APS is unresolved.
- The pathogenesis of APS is multifactorial and involves inflammatory pathways. aPL are risk factors for APS: a 'second hit' (triggering factor) is usually necessary for the development of aPL-mediated damage.
- Management of APS means prophylaxis. aPL carriers should be prevented from their first thrombotic event or pregnancy loss; patients who have already had an APS-related event must be protected against recurrence.
- International committees are working on several different topics to promote research on APS and produce evidence-based indications for the diagnosis, management and treatment of APS.

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Pregnancy related problems in rheumatic diseases, including the antiphospholipid syndrome

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IN-DEPTH DISCUSSION I

Management of pregnancy in the antiphospholipid syndrome

1. Pregnancy counselling

Complications during pregnancy are common in antiphospholipid syndrome (APS) and include maternal thrombosis, recurrent spontaneous abortions before 10 weeks of gestation, and late adverse pregnancy outcomes such as foetal death, preeclampsia, foetal growth restriction, and pre-term birth. Even with optimal management the live birth rate for women with APS remains around 80% and adverse outcomes occur in a “refractory” 20-30% of cases. Pre-pregnancy and antenatal care in APS is crucial for minimising morbidity.

Preconception counselling is based on risk assessment in the individual patient. Important risk factors are concomitant autoimmune disease, history of both pregnancy morbidity and thrombosis, presence of lupus anticoagulant (LA) and triple positive aPL. Pregnancy should be discouraged in women with significant pulmonary hypertension due to the high risk of maternal death and postponed in the setting of uncontrolled hypertension or whenever a recent thrombotic event, particularly stroke, has taken place or in patients suffering from unexplained thrombosis recurrences.

2. General care of pregnancy in women with APS

A complete aPL profile, including repeated positive aCL and LA, must be available before planning pregnancy. Repetition of aPL tests can be helpful for assessment of maternal and foetal risks during pregnancy. A recent study (PROMISSE Study: Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus) showed that LA is the main predictor for adverse pregnancy outcome, more than aCL and anti- β 2 GPI alone. Triple antibody positive women carry the highest risk for thrombosis and pregnancy complications. Women with thrombotic APS have worse obstetric outcomes than those with obstetric APS. Others risk factors for pregnancy failure are the association with SLE or other autoimmune diseases and a previous obstetrical complication. APS patients diagnosed on the basis of a single positive test and/or of history of early foetal loss alone were generally found to have successful pregnancies.

During pregnancy, women should be under the dual care of obstetricians and physicians specialising in APS. Monitoring should be undertaken more frequently as pregnancy advances, with prenatal visits every two weeks or more frequently if needed. At these visits blood pressure and urine protein should be measured, along with frequent ultrasounds to check foetal growth and well-being. Uterine artery Doppler flow studies at the 20th and 24th weeks of gestation are useful for predicting preeclampsia and placental insufficiency in APS.

3. Pharmacological management of APS in pregnancy

The goals of treatment in pregnant women with APS are to improve maternal and foetal-neonatal outcomes by minimising the risks of the recognised complications of APS, including maternal thrombosis, foetal loss, preeclampsia, HELLP syndrome, placental insufficiency and foetal growth restriction, and the need for

iatrogenic preterm birth. Heparin and low dose aspirin (LDA) are widely considered the current treatments of choice for APS in pregnancy. Heparin is initiated after a positive pregnancy test. Randomised trials have demonstrated that either the addition of intravenous immunoglobulins (IVIG) to heparin or IVIG alone offers no better outcomes. A subsequent Cochrane analysis concluded that IVIG was associated with an increased risk of pregnancy loss or premature birth compared to heparin and LDA.

Venous contention should be associated with the pharmacologic treatment.

New anticoagulants are easier to use and require less monitoring than traditional anticoagulants. However, experience from human pregnancy is limited to case reports and there are no publications on randomized controlled trials in APS. New Oral Anticoagulants should probably not be used so far. Several case reports showed healthy outcomes at exposure to the indirect factor-Xa inhibitor fondaparinux in pregnant women. Little is known about the safety of rivaroxaban, argatroban and dabigatran during pregnancy, and, therefore, their use is not recommended

a. Recurrent early (pre-embryonic or embryonic) miscarriage

Three randomised trials and one trial with consecutive treatment assignment have addressed pregnancy in APS patients with predominantly recurrent early miscarriage. In two trials, the proportion of successful pregnancies significantly improved adding unfractionated heparin to LDA. Two other randomised trials, both using low molecular weight heparin (LMWH) proved negative. It is noteworthy that the heterogeneity in the results was attributed to women receiving aspirin only. In addition, two studies found no differences in pregnancy outcomes when comparing unfractionated heparin with LMWH, both combined with aspirin. Among pregnancies progressing beyond 20 weeks gestation, maternal and foetal-neonatal outcomes were relatively benign, with the frequencies of foetal death, preeclampsia, severe placental insufficiency, and iatrogenic preterm delivery similar to those of the general obstetric population. On the other hand, several observational studies have reported 79% to 100% pregnancy success rates with LDA alone. Moreover, a recent meta-analysis has demonstrated a significant reduction of pregnancy complications among women at high risk for preeclampsia who were treated with anti-platelet agents (mostly aspirin).

Despite the obvious controversy raised by these trials, a 2005 Cochrane systematic review concluded that women with recurrent miscarriage and APS should be treated with a combination of unfractionated heparin 5000U subcutaneously twice daily and LDA, and recent expert guidelines recommend the combination of aspirin with either low-dose unfractionated heparin or LMWH. Preliminary results from the PROMISSE study indicate that the option of monotherapy with LDA cannot be discarded in this subgroup of women except for those who have a high-risk antibody profile.

b. Foetal death (>10 weeks of gestation) or prior early delivery (<34 weeks gestation) due to severe preeclampsia or placental insufficiency

The optimal treatment for women in this category is not defined by randomised trials. Most experts recommend LDA and either prophylactic, intermediate or curative dose heparin. The preponderance of data indicate that good pregnancy outcomes are achieved with heparin initiated in the early first trimester when a live embryo is discernible by ultrasound.

c. APS with thrombosis

For pregnant women with APS who have had a prior thrombotic event, LDA and therapeutic dose unfractionated heparin or LMWH anticoagulation are recommended. Vitamin K antagonists are teratogenic and should be avoided between the 6 and 12 weeks of gestation. Due to the risk of foetal bleeding thereafter, the use of warfarin after 12 weeks of gestation should only be undertaken in exceptional circumstances.

d. Refractory APS in pregnancy

There have been no properly designed studies to evaluate treatment modalities for the 20-30% of patients who fail to respond to LDA and heparin. Whether increase in the dose of anticoagulation or therapy with hydroxychloroquine, prednisone, azathioprine, IVIG or plasmapheresis is efficacious in the obstetric APS refractory to anticoagulant standard treatment is unanswered.

4. Labour and postpartum period

Thromboprophylaxis may represent a risk during labour, particularly, with the use of epidural anaesthesia. Stopping heparin 12 hours previous to and 12 hours after any interventional procedure is generally considered safe. Many anaesthesiologists would also require a minimum of 3-7 days without aspirin to perform a spinal tap. Several prospective studies of patients on LDA have not found an increased risk for epidural hematoma after epidural anaesthesia. According to recommendations, epidural anaesthesia should be realized in women taking LDA providing some conditions:

- Absence of any anticoagulant therapy before the spinal tap
- Absence of associated haemostasis disorders
- Avoid using medication which could interfere with haemostasis
- Close and regular neurologic monitoring after the spinal tap

Antithrombotic coverage of the postpartum period is recommended in all women with APS and also positive aPL, with or without prior thrombosis. Those with previous thrombosis would need long-term anticoagulation,

and we prefer switching the patient to warfarin, as soon as she is clinically stable after delivery. In cases of no previous thrombosis, the recommendation is for prophylactic dose unfractionated heparin or LMWH therapy for 6 weeks after delivery. Both heparin and warfarin are safe for nursing mothers. As pregnancy, heparin, and breastfeeding can all reduce bone mineral density, taking additional calcium 1000mg and vitamin D 800 IU daily can lower the occurrence of osteoporosis.

Although there have been suggestions that aPL may cause failure of in-vitro fertilisation (IVF), a literature review of 16 studies has found no association. Nevertheless, the high exposure to oestrogens during IVF causes a high risk of maternal thrombosis and it would be advisable to use prophylactic heparin and aspirin during this time if the woman has aPL.

Table 1 Recommendation for management during pregnancy

Antiphospholipid antibodies * without thrombosis without adverse pregnancy outcome in history:	
* triple positive, significantly and persistently elevated	Low dose aspirin (LDA): 100 mg/d
Antiphospholipid syndrome without thrombosis (exclusively obstetric complications) in history:	
Recurrent early miscarriage (< 10 WoG)	LDA 100 mg/d (pre-conception) <i>alone or in combination</i> with LMWH in <i>prophylactic</i> doses when preg. test positive
Foetal death (>10. WoG) or previous early delivery (<34 WoG) due to severe pre-eclampsia or placental insufficiency	LDA 100 mg/d (pre-conception) in combination with LMWH in <i>prophylactic</i> doses when preg. test positive
Antiphospholipid syndrome with thrombosis in history*:	
Without previous anticoagulation (coumadine)	LDA 100 mg/d (pre-conception) in combination with LMWH in <i>prophylactic</i> doses when preg. test positive LMWH may be increased in 2 nd and 3 rd trimester
With previous anticoagulation (coumadine)	Change to LMWH in <i>therapeutic</i> doses, + LDA (100 mg/d) at the latest with positive preg. test
During pregnancy in addition: control of blood pressure, proteinuria, weight from 16. - 20. WG monthly control of foetal growth and placental blood flow	
Post-partum:	
For 6 weeks heparin (LMWH), then therapy according to indication (APS) (i. e. LDA or anticoagulation). Also: prophylaxis for osteoporosis with heparin / LMWH; Compression stockings, gymnastics	

**Usually these patients would be anticoagulated!*

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IN-DEPTH DISCUSSION II

Preconception counselling

Pregnancy in women with a systemic disease must be planned to reduce the risk of maternal and foetal complications. A consultation for preconception counselling is therefore an essential prerequisite to such a pregnancy. Several key points will be discussed during this visit:

1. Screening of contraindications to pregnancy:

Contraindications to pregnancy are now rare. They are principally active underlying disease or a recent flare at the time of the visit, especially in systemic lupus erythematosus (SLE). This contraindication is therefore generally transient. Moreover, damage such as organ failure, history of severe preeclampsia, or HELLP syndrome despite appropriate treatment can be contraindications to pregnancy and must lead the couple to envision other ways of becoming parents. Table 1 summarizes the principal contraindications.

Table 1: Principal contraindications to pregnancy: to discuss on a case-by-case basis with the couple and the different specialists.

Current or recent flare of the systemic disease
Corticosteroid dependency greater than 0.5 mg/kg/d
Pulmonary arterial hypertension
Uncontrolled hypertension
Heart failure with an ejection fraction less than 30%
Severe valve disease and in particular shrinkage of the mitral or aortic valves
Aortic dilatation greater than 50 mm
History of postpartum cardiomyopathy resulting in chronic heart failure *
Forced expiratory volume less than 50%
Treatment incompatible with pregnancy
± Creatinine clearance less than 40 ml/min**
Severe malabsorption

* Regardless of the severity of the heart failure.

** Creatinine clearance less than 40 ml/min is a relative contraindication to be discussed with nephrologists on a case-by-case basis.

2. Assessment of the risks:

- Potential repercussions of the systemic disease on the pregnancy

Situations at risk of complication include: a history of complications during any previous pregnancy, a recent flare (less than 6 months for SLE), a corticosteroid dosage greater than 10 mg daily, resultant chronic organ failure (cardiac, renal, and pulmonary in particular), hypertension, antiphospholipid antibodies or antiphospholipid syndrome (APS), in particular with a history of thrombosis (especially arterial), and/or anti-SSA or anti-SSB antibodies. Age greater than 40 years, multiparity, and diabetes are also risk factors for complications during pregnancy, even without any autoimmune disease.

- Potential repercussions of the pregnancy on the systemic disease

The principal potential repercussion is the risk of a flare of the underlying disease but also decompensation of disease-related organ failure.

For each disease, see the corresponding section in the course.

- Planning management

The treatment procedures and follow-up are determined at the visit of counselling, in order to plan an optimal multidisciplinary management (obstetricians, internists or rheumatologists, anaesthetists) and thus increase the likelihood of success. These procedures will be determined by the woman's clinical history and her laboratory and immunological profile.

Table 2 summarizes the laboratory tests to be performed for the preconception consultation.

Table 2: Laboratory tests for the preconception consultation

Complete blood count
ACT (activated clotting time)
Transaminases
Creatinine
Serology for HIV, hepatitis B, toxoplasmosis, and rubella
Urinary sediment: leukocyturia, haematuria
Urinary PCR (protein/creatinine ratio) or 24-h urinary protein
LDH (lactate dehydrogenase), haptoglobin, GGT (gamma glutamyl transpeptidase), serum uric acid
TSH (thyroid-stimulating hormone), thyroid peroxidase antibodies
Lupus anticoagulant, anticardiolipin and anti-β2GP1 antibodies (± TPHA-VDRL) *
Anti-SSA and anti-SSB antibodies
According to the underlying disease: anti-dsDNA antibodies, complement C3, ANCA (anti-neutrophil cytoplasmic antibody, Scl70 antibodies, anti-RNA polymerase III

**The higher risk-profiles are the triple positivity (3 antibodies positive) followed by lupus anticoagulant.*

3. Interview with the couple

The preconception counselling visit allows the doctor to explain to the couple the potential risks for the baby and for the mother. If the doctor is recommending to avoid or postpone pregnancy, this visit allows him or her to explain both the reasons for this to the couple and the objectives to be reached before pregnancy can be medically authorized (for example, better disease control in the case of a recent renal flare).

4. Adaptation of treatments to pregnancy

Finally, if pregnancy is envisioned, the drugs advised against or forbidden during pregnancy must be stopped and, if necessary, replaced. Safety of treatment during pregnancy should be addressed and explained in order

to reassure the mother. Folic acid supplementation is routine, essential in women previously treated by methotrexate or with haemolytic anaemia, even well compensated, to limit the risk of neural tube defects. Adequate calcium and vitamin D intake is desirable, in particular in women receiving corticosteroid therapy and heparin together. Bisphosphonates prescribed before pregnancy should be stopped. Calcium supplementation should target 1500 mg/d, including food intake and pharmacological supplementation (Fardelonne's formula for calcium intake available on line: <http://www.grio.org/calcul-apport-calcique-quotidien.php>).

This consultation is also an ideal time to approach the difficulties of adherence to treatment.

5. Updating vaccinations

Vaccinations should be updated if necessary: rubella if serology is negative, unless strong immunosuppression is present (biologics or immunosuppressive agents, corticosteroids up to 10 mg per day for more than 15 days), whooping cough if the last booster date was more than 10 years earlier (verify the future father's vaccination at the same time), and influenza depending on the time of year.

6. Specific cases

- SLE:

During pregnancy of women with SLE, the previous treatment is usually continued: hydroxychloroquine, even corticosteroids, ideally not exceeding 10 mg/d. When an immunosuppressant is necessary, azathioprine is preferred.

- Aspirin

Aspirin at a dose that inhibits platelet aggregation is indicated when there is pre-existing kidney damage, hypertension, a history of preeclampsia, antiphospholipid antibodies, or when the disease is known to increase the risk of foetal damage (foetal growth restriction, small for gestational age, preterm delivery). Aspirin has to be started before conception (or at the latest in the first trimester).

- Antiphospholipid antibodies

In addition, heparin, at a preventive or curative dosage, should be discussed if the laboratory results reveal antiphospholipid antibodies and the woman has a history of thrombosis and/or obstetric complications and/or high-risk antibody profile (3 tests positive at high titer, lupus anticoagulant). Table 3 describes appropriate management according to the different clinical situations. Wearing support stockings is usually recommended. Ideally, the prescription should be given to the patient at the preconception consultation, especially if she is treated with oral anticoagulants: this will allow her to switch to heparin as soon as she knows she is pregnant.

Table 3: Suggested management for antiphospholipid antibody syndrome or antiphospholipid antibodies.

	Treatment during pregnancy
Positive antiphospholipid antibodies with no history of thrombosis or obstetric complications	Aspirin alone (100 mg/d). If a lupus anticoagulant is present and/or in case of multiple positivity, preventive LMWH could/should be considered. Preventive LMWH in the postpartum period (for 6 weeks), and then aspirin to be considered for the long-term.
APS with a history of thrombosis	Low-dose aspirin (100 mg/d) combined with a curative dosage of LMWH (e.g., enoxaparin 100 IU anti-Xa/kg every 12 hours, subcutaneously)**. Regular adaptation to anti-Xa activity can be discussed. Resumption of a vitamin K antagonist in the postpartum period*.
APS without a history of thrombosis but with recurrent spontaneous miscarriages	Low-dose aspirin (100 mg/d) associated with LMWH (enoxaparin 0.4 ml daily, subcutaneously***). Preventive LMWH in the postpartum period (for 6 weeks), and then aspirin for the long-term.
APS with no history of thrombosis but with a history of intrauterine death, preeclampsia, HELLP syndrome, or other manifestations of placental insufficiency	In the absence of previous treatment: Low-dose aspirin (100 mg/d) combined with LMWH (enoxaparin 0.4 ml daily, subcutaneously). Despite previous treatment (or sometimes from the start): low-dose aspirin (100 mg/d) combined with a curative dosage of LMWH (e.g., enoxaparin 100 IU anti-Xa/kg every 12 hours subcutaneously). Regular adaptation to anti-Xa activity can be discussed. Preventive LMWH in the postpartum period (for 6 weeks), and then aspirin for the long-term.

APS: antiphospholipid syndrome, HELLP: Haemolysis, Elevated Liver enzymes, Low platelets, LMWH: low-molecular-weight heparin.

* Only warfarin is authorized among the vitamin K antagonists for women who are breastfeeding.

** In the particular case of women with APS with a history of thrombosis but who are no longer taking a vitamin K antagonist (previous thrombosis, either distal or with a precipitating factor that is no longer present), it is possible to give enoxaparin at a lower dosage. Moreover, some replace enoxaparin-Lovenox® at a curative dose with tinzaparin-Innohep®, for example.

*** In the presence of a high-risk antibody profile or in case of obesity, higher dose of LMWH might be used.

7. Planning monitoring

Monitoring will be adapted to the underlying maternal disease and to the antibodies present (see course).

For SLE, which remains the disease most sensitive to the risk of flares and complications during pregnancy, monitoring should be regular and adapted to the maternal and obstetric history. It is generally monthly, or

even more frequent if necessary, at closer intervals during the last trimester, and continues during the postpartum period. Table 4 summarizes these monitoring rules.

Table 4: Monitoring the pregnancy of a woman with SLE

Clinical	Weight, blood pressure, Urinary dipstick +++
	Hypertension defined by SBP \geq 140 mmHg or DBP \geq 90 mmHg
	Joints
	Cutaneous lesions
	Oral ulcers
	Alopecia
	Oedema of the lower limbs
	Chest pain, severe epigastric pain
	Headaches, tinnitus, phosphines
Laboratory results	Complete blood count, platelets
	Serum creatinine level and estimated GFR by MDRD formula
	Serum uric acid
	Transaminases
	Haptoglobin
	Proteinuria: 24-hr collection or UPr/Cr fresh urine sample
	CH50, C4, C3
	Anti-DNA antibodies
	Blood glucose, K ⁺ especially for women with corticosteroid therapy
Ultrasound	Serology for toxoplasmosis, if negative initially
	Foetal ultrasound each trimester*
	If anti-SSA and/or anti-SSB antibodies: every two weeks between 16 and 24 WG or every week if sibling with neonatal lupus.
	If antiphospholipid antibodies or APS: Doppler around 20-22 WG (to be repeat if abnormal)
	If there is a risk of foetal growth restriction or preeclampsia: Doppler of the uterine and umbilical arteries at 20 weeks, to be repeated according to the need in case of abnormalities

SBP: systolic blood pressure; DBP: diastolic blood pressure; U Pr/Cr: urine protein-to-creatinine

For women with antiphospholipid antibodies, especially if there is an APS: monitoring must also be monthly, at closer intervals at the end of pregnancy for clinical and laboratory monitoring of the onset of preeclampsia or HELLP syndrome. Monitoring also includes ultrasonography, with a Doppler of the uterine and umbilical arteries at 20 weeks, to be repeated according to the need in the case of abnormalities (foetal growth restriction, a notch, increase in the resistance index, diminution of placental perfusion).

For women with anti-SSA and/or anti-SSB antibodies: because these antibodies expose the foetus to the risk of neonatal lupus, foetal cardiac ultrasound monitoring is currently recommended every two weeks between 16 and 24 weeks (every week if a previous foetus/child had congenital heart block). These recommendations may be alleviated in the future, if the absence of efficacy of fluorinated steroids is confirmed.

Systemic sclerosis

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LEARNING OBJECTIVES

- Describe and explain the principal mechanisms of the pathogenesis of the disease
- Acquire the competence of making a diagnosis of the disease
- Knowing the main predictive factors for severity
- Describe and explain the main complications of the disease
- Investigate internal organ involvement through lab and instrumental examinations
- Evaluate the disease activity of the patients
- Prescribe an overall treatment of the disease
- Prescribe a treatment specific for target organs

I Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by fibrosis of the skin and internal organs, pronounced alterations in the microvasculature and frequent cellular and humoral immunity abnormalities. SSc is part of a more extensive group of diseases called scleroderma spectrum (table 1) (Subcommittee for scleroderma criteria, 1980).

Table 1: The scleroderma spectrum of disorders

Localized scleroderma	Morphea
	Linear scleroderma
	En coup de sabre
Systemic sclerosis	Limited cutaneous systemic sclerosis
	Diffuse cutaneous systemic sclerosis
	Systemic sclerosis <i>sine scleroderma</i>

The distinction between localized scleroderma and systemic sclerosis is based on clinical presentation and on visceral involvement. Localized scleroderma is restricted to fibrotic involvement of the skin and subcutaneous tissues, while SSc (“systemic scleroderma”) affects also internal organs. There are some histopathological, pathogenetic and serological features common to localized and systemic forms of scleroderma, suggesting some similar pathogenic mechanisms. Therefore, a skin biopsy is not indicated to make a diagnosis or try to differentiate localized versus systemic disease. However, conversely to what is seen in lupus, the progression of localized scleroderma toward systemic sclerosis is exceptional and patients with morphea should be reassured concerning the risk of systemic involvement. This suggests some additional risk factors and/or biological actors driving the disease toward the systemic feature.

In the absence of one diagnostic test proving the absence or presence of SSc, some sets of classification criteria have been developed. Classification criteria are not similar to diagnostic criteria but they mirror the list of criteria that are used for making the diagnosis. Therefore, the purpose of a classification aims at including for research patients who have the disease as determined through a uniform definition. Until 2013, the standard classification criteria for SSc were the 1980 preliminary criteria for the classification of SSc, developed by the American College of Rheumatology. However, they had been developed using patients with longstanding SSc and mainly to classify patients with diffuse skin involvement. Indeed, by example, auto-antibodies and capillaroscopy were not taken into account despite the accumulating amount of work reported on these parameters. LeRoy et al proposed in 1988 a new set of criteria that included all clinical features, autoantibodies, and capillaroscopy. This resulted in a pragmatic sub-classification in limited cutaneous and

diffuse cutaneous (measured at the peak of skin extent) which remains very helpful as associated with various outcomes and organ involvement in these 2 subsets.

Limited cutaneous systemic sclerosis (lcSSc) is defined by skin involvement only distal to the elbows and knees, while diffuse cutaneous systemic sclerosis (dcSSc) is characterized by presence of skin thickening proximal to the knees and elbows. SSc sine scleroderma refers to patients who demonstrate vascular and serological features of SSc without any skin involvement (Diab et al, 2014). This sub-setting is important to know and use in clinical practice. It has an important impact with regards to the profile of the SSc patients, the risk of organ involvement and disease progression. Limited cutaneous disease is usually considered as a milder form with slow progression of skin involvement and rather late visceral complication (after 10-15 years) mainly exposing to pulmonary arterial hypertension and gastro-intestinal disease with malabsorption. Therefore, a long and sustained follow-up is mandatory although the disease may be seen as not severe at the beginning. SSc sine scleroderma has a very close profile to the one observed in lcSSc. The diffuse cutaneous form could be regarded as the opposite with fast progression of skin sclerosis within weeks / months and concomitant organ injuries, mainly lung, heart, kidney, before a plateau reached in about 5 years and thereafter a slow spontaneous regression of skin fibrosis. These patients need a very scrupulous follow-up in the first years with regular appointments and can be partly reassured once the first 5 years are over.

However, because of the insufficient sensitivity of 1980's criterial, the ACR and the EULAR promoted a joint proposal for new classification criteria for SSc. The aims were to develop criteria that 1) encompass a broader spectrum of SSc including patients whose disease is in the early stage as well as those in the late stage; 2) include vascular, immunologic, and fibrotic manifestations; 3) are feasible to use in daily clinical practice; and 4) are in accordance with criteria used for diagnosis of SSc in clinical practice. The updated classification is detailed in Table 2 (Van den Hoogen, 2013).

CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia) syndrome is an outdated term for lcSSc and should not to be used as a synonym for limited SSc because many patients with lcSSc do not develop all the features of CREST. This acronym does not recognise important complications of this subset including pulmonary arterial hypertension, mid-gut disease and lung fibrosis. SSc can also overlap other autoimmune diseases such as systemic lupus erythematosus, dermatomyositis and rheumatoid arthritis (overlap syndromes). More and more evidence also show that multiple autoimmune disease can coexist in a single patient; this has been measured at about 25% with thyroiditis or Sjögren's syndrome being the most commonly associated autoimmune disease with SSc. Out of 3240 registered patients in the German network, 10% were diagnosed as SSc-overlap syndrome (two connective tissue diseases at the same time). The main characteristics of this subset were earlier and more common musculoskeletal involvement than patients diagnosed as lcSSc or dcSSc. The onset of lung fibrosis and heart involvement in SSc-overlap patients was significantly earlier than in patients with lcSSc but occurred later than in patients with

dcSSc. Oesophagus, kidney and PH progression was similar to lcSSc patients, whereas dcSSc patients had a significantly earlier onset. These data suggest that the concept of SSc-overlap syndrome might be regarded as a separate SSc subset, distinct from lcSSc and dcSSc (Moinzadeh et al, 2015).

Table 2: Systemic sclerosis 2013 ACR/EULAR classification

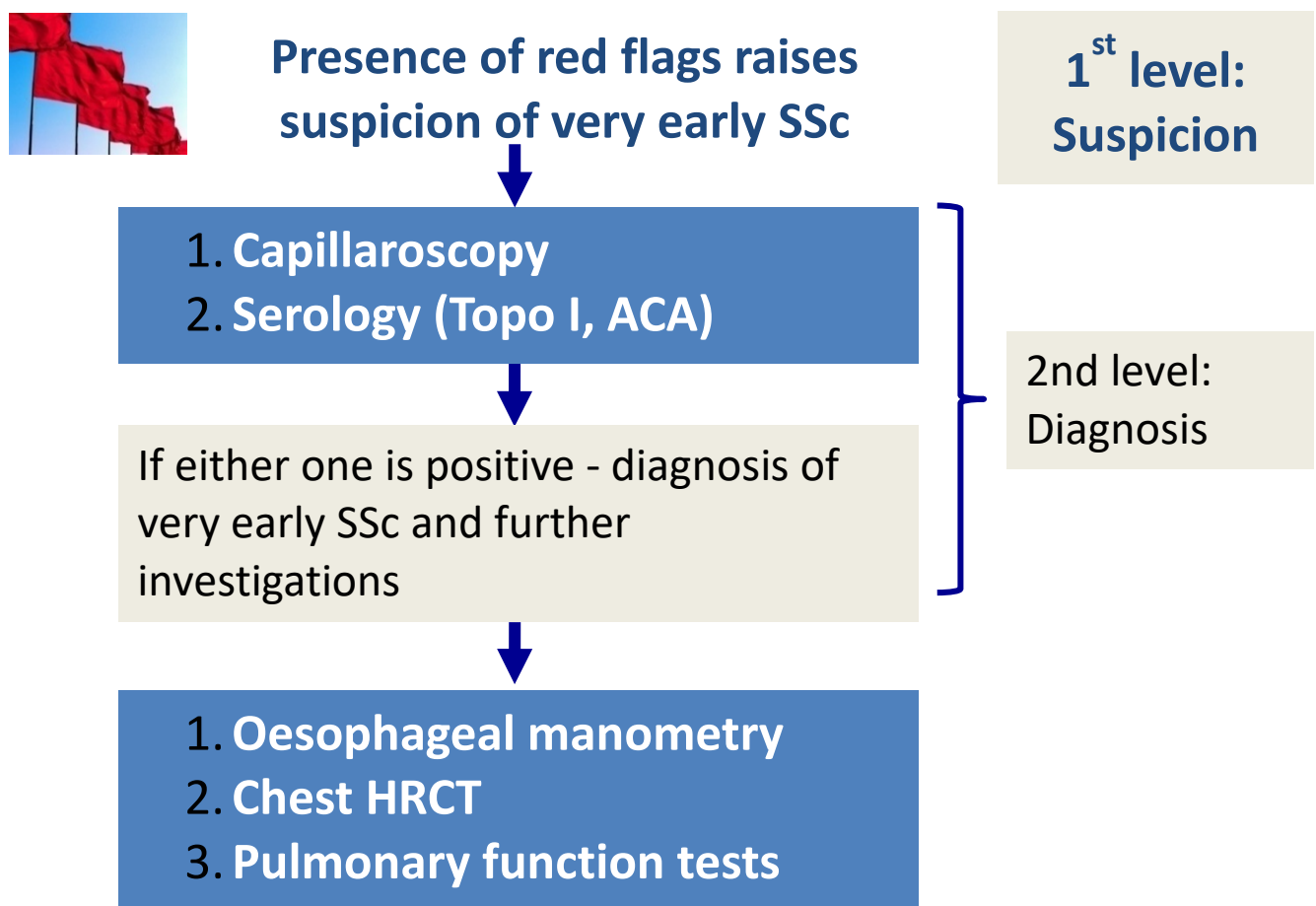
Item	Sub-item(s)	Weight/ Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (<i>sufficient criterion</i>)	–	9
Skin thickening of the fingers (<i>only count the higher score</i>)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (<i>only count the higher score</i>)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillary	–	2
Pulmonary arterial hypertension and/or interstitial lung disease (<i>maximum score is 2</i>)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) (<i>maximum score is 3</i>)	Anticentromere	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleroderma diabeticorum, scleromyxoedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy). (a) The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥ 9 are classified as having definite SSc.

Leroy and Medsger proposed some years ago potential criteria for the classification of early SSc, defined by patients with features of SSc who do not fulfil the ACR or LeRoy classification criteria for SSc, consisting of Raynaud's phenomenon, scleroderma-type nailfold capillary pattern and scleroderma selective antibodies (LeRoy et al, 2001). Recently EUSTAR (European League Against Rheumatism Scleroderma Trial and Research Group) has proposed new criteria, refining the previous ones, for a very early diagnosis of SSc (VEDOSS) that are represented by the presence of the three red flags (Raynaud's phenomenon, puffy fingers and antinuclear antibodies (ANAs) positivity) plus disease-specific autoantibodies (anticentromere Ab (ACA) or anti-topo I Ab (Scl70)) or microvascular alterations detected by nailfold videocapillaroscopy. These criteria have been selected through a large Delphi technique among experts and is the basis of a large and ambitious project

aiming at the validation of VEDOSS criteria through the follow-up of a cohort of about 1000 individuals (Avouac et al, 2011) (figure 1). The aim of the VEDOSS criteria is to facilitate SSc diagnosis at the earliest possible stage so that early screening for pre-clinical internal organ involvement can be implemented. Very preliminary data have recently showed that puffy finger could be a critical criterion of very early disease (Minier et al, 2013). In line with the “window of opportunity” highlighted in rheumatoid arthritis, early diagnosis in SSc is essential for starting appropriate treatment aimed at blocking disease evolution or progression and huge efforts are made on the early steps of the disease to try to identify very early patients and predictors of poor outcomes.

figure 1: Flow chart for patients in whom the very early diagnosis of SSc should be considered is proposed. Red flags should trigger the differential diagnosis of SSc and guide the general practitioner to send the patient to the referral centre where capillaroscopy and specific autoantibodies are ordered and the diagnosis of very early SSc is made. HRCT, high resolution CT; PFT, pulmonary function tests. (Ann Rheum Dis. 2011;70(3):476-81.)



II Epidemiology

Available studies have reported divergent prevalence and incidence estimates of SSc in different areas of the planet. Lower estimates of prevalence (<150 per million) and of incidence (<10 per million per year) have been observed throughout northern Europe to Japan whereas higher estimates have been found in southern Europe, northern America and Australia (Barnes J et al, 2012).

SSc is an orphan disease and it seems to be more prevalent in the United States (276 cases per million adults) (Minier et al, 2013), than in Europe 80-150 cases per million adults (Czirjak et al, 2005).

The real prevalence of SSc has been probably underestimated because the mild disease remains often undiagnosed. The annual incidence of new cases has been reported from 1 to 20 cases per million (Allcock et al, 2004). SSc is three times more common in women than in men (Kettaneh et al, 2007). Several recent series estimate in different populations a prevalence of approximately 1 in 10000, with incidence rates about 1 in 100000 (figure 2)

Figure 2: Age-specific incidence of SSc by gender and race (Mayes et al, A&R 2003;48:2246)

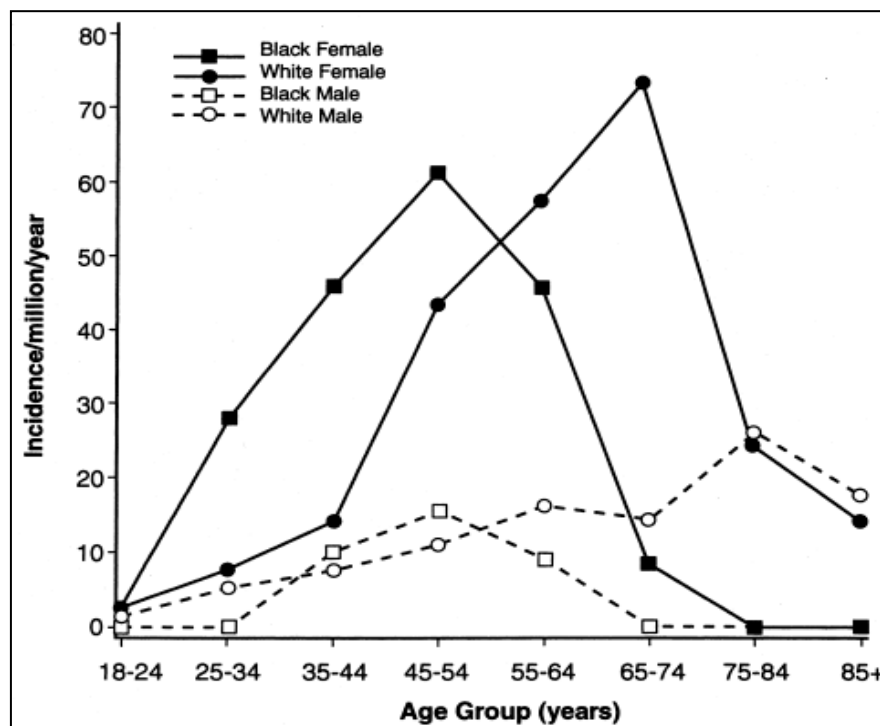
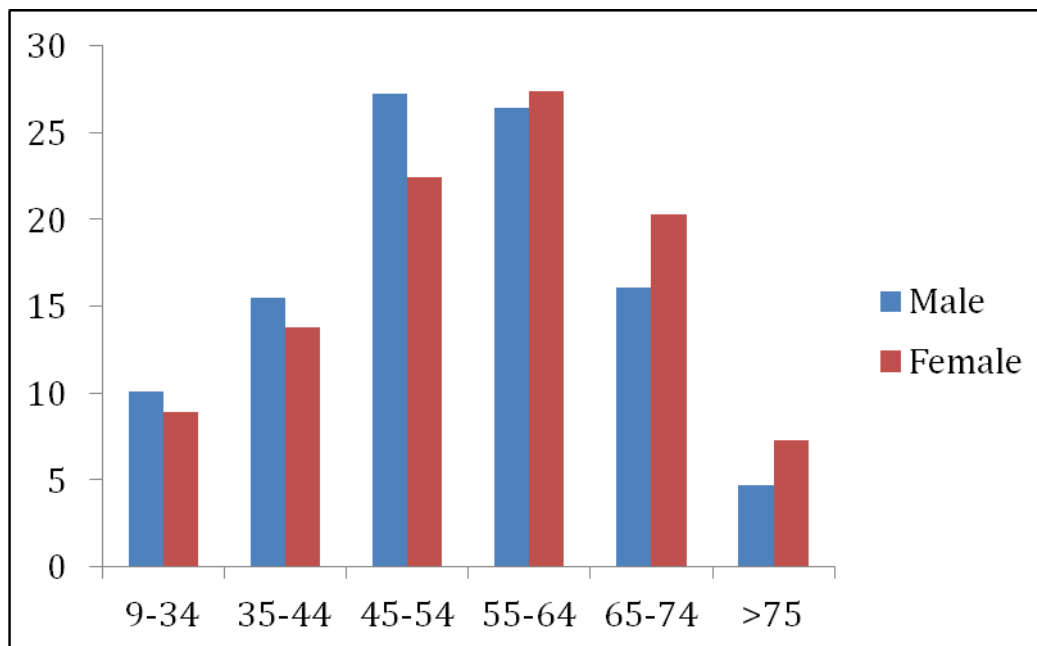


Figure 3: Age of onset of the first non-Raynaud's symptom (% of patients) in male and female SSc patients throughout 11318 registered patients



The EUSTAR cohort has provided insight in gender effect by looking at 9182 SSc-patients, including 1321 males (Elhai et al, 2014). The figure 3 shows gender distribution according to age. In a cross-sectional approach, male gender was independently associated with a higher risk of diffuse cutaneous subtype (OR: 1.68, [1.45-1.94]; $p < 0.001$), a higher frequency of digital ulcers (OR: 1.28 [1.11-1.47]; $p < 0.001$) and pulmonary arterial hypertension (OR: 3.01 [1.47- 6.20]; $p < 0.003$). In a longitudinal part based on 4499 patients with follow-up (mean 4.9 ± 2.7 years), male gender was predictive of new onset of pulmonary arterial hypertension (HR: 2.70 [1.38-5.29]; $p = 0.004$) and heart failure (HR: 2.15 [1.03-4.48]; $p = 0.04$). It predicted deaths of all origins (HR: 1.48 [1.19-1.84]; $p < 0.001$), but did not significantly account for SSc-related deaths.

An epidemiological study performed in a southern region of Sweden (total population 1.2 million), reported that using the 1980 ARA criteria, the adult prevalence and annual incidence of SSc were 235 and 14 per 1 million inhabitants respectively. Applying the 2013 ACR-EULAR criteria, the corresponding figures were 305 and 19 per 1 million inhabitants. The use of the recent criteria resulted in 30-40% higher estimates of SSc prevalence and incidence and with a majority of lcSSc cases recognised selectively by the new criteria (Andréasson et al, 2014).

The prognosis of SSc remains poor but it is apparent that subsets of patients have very bad outcomes sometimes after a short time of disease duration and with impact on life expectancy whether some others will remain stable with a milder disease. A consideration regarding the prediction of outcomes is therefore a critical challenge and deciphering the factors that impact the prognosis of this highly polymorphic disorder is a challenge. Clearer views are emerging taking advantage of large large cohorts and with the standardization of follow-up of the patients and more precise definitions of organ damages. Predicting the disease is critical to

contribute to the evaluation of potential benefits and risks of the various old and new drugs that are under evaluation in SSc.

To focus on the final outcome that is mortality some efforts have been done to try to identify SSc patients with the highest risk. Indeed, EUSTAR promoted the evaluation of a simple prognostic model to predict 5-year survival in SSc throughout Europe (Fransen et al, 2011). The predefined prognostic model uses the following baseline variables: age, gender, presence of urine protein, erythrocyte sedimentation rate (ESR) and carbon monoxide diffusing capacity (DLCO). Data were available for 1049 patients of whom 119 (11%) died within 5 years after diagnosis. The prognostic model with age (OR 1.03), male gender (OR 1.93), urine protein (OR 2.29), elevated ESR (1.89) and low DLCO (OR 1.94) had an area under the receiver operating characteristic curve of 0.78. Death occurred in 12 (2.2%) of 509 patients with no risk factors, 45 (13%) of 349 patients with one risk factor, 55 (33%) of 168 patients with two risk factors and 7 (30%) of 23 patients with three risk factors (Table 3).

Table 3: A simple prognostic model using three disease factors to predict 5-year survival at diagnosis in SSc

No of risk factors	Total no of patients	No of patients deceased	Mortality%
0	509	12	2.2
1	349	45	12.9
2	168	55	32.7
3	23	7	30.4

Using an inception cohort of US Caucasian patients with early dcSSc (<2 years from the appearance of the first symptom) and a UK external replication cohort, 6 independent predictors of death at 5 years were identified. They include age at first visit, male gender, tendon friction rubs, gastrointestinal involvement, RNA polymerase III antibodies and anaemia (Domsic et al, 2016). This is a simple scoring system requiring only history, physical examination, and basic laboratory assessments.

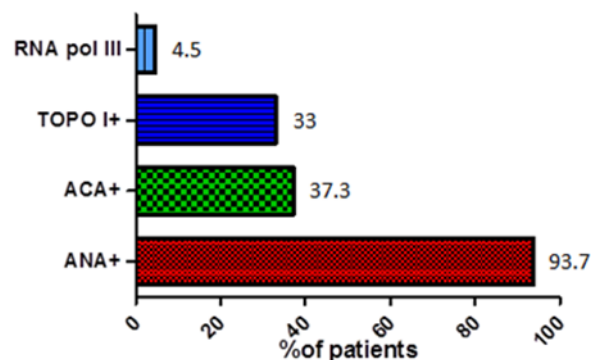
These examples highlight the input of prospective cohorts and the ongoing works aiming at the risk stratification, which is highly, needed to better manage SSc patients. Autoantibodies targeting characteristic nuclear antigens are one of the hallmarks of SSc. The occurrence of different antinuclear antibodies (ANAs) is associated with distinct disease subtypes and with differences in disease severity, including extent of skin involvement, internal organ manifestation and also prognosis. For example and of most importance for clinical practice, the presence of anticentromere antibodies (ACAs) has been noted in association with PAH, anti-topoisomerase I (anti-topo I) antibodies in association with interstitial lung disease, and anti-RNA polymerase III (anti-RNAP III) antibodies in association with renal crisis. The main auto-antibodies, their frequencies and

associated features are summarised in Table 4 and the prevalence observed within EUSTAR cohort are shown in Figure 4.

Table 4: Main associated SSc auto-antibodies

Auto-antibody	Frequency (%)	Main clinical associations
Anti-centromere	30-40	LcSSc, PAH, older age at onset, other autoimmune disease
Anti-topoisomerase I	20-30	DcSSc, ILD, renal crisis, joint involvement
Anti-RNA pol III	1-10	DcSSc, renal crisis, GAVE, cancer
Anti-fibrillarin (U3RNP)	<5	DcSSc, PAH, musculo-skeletal
Anti-Th/To	<5	LcSSc, PAH
Anti-Pm-Scl	<5	Myositis
Anti U1RNP	<5	SSc overlap syndrome
Anti-Ku	< 5	SSc overlap syndrome and with muscular involvement

Figure 4: prevalence (% positive patients) of antinuclear antibodies in the EUSTAR cohort throughout 13996 registered SSc patients (Database extraction April 2017) (ANA: anti-nuclear; ACA: anti-centromere; TOPO: topo-isomerase; RNA poly III: RNA polymerase III)



The influence of ethnicity is a matter of concern in other connective tissue disorder like systemic lupus. A large monocentric study has been performed in the US (Gelber et al, 2013), showing that African American patients with SSc presented at a younger mean age than white patients (47 vs. 53 years; $p < 0.001$). Furthermore, two-thirds of white patients exhibited the limited cutaneous subset of disease, whereas the majority of African American patients exhibited the diffuse cutaneous subset ($p < 0.001$). In addition, African American patients experienced an increase in risk of mortality (relative risk 1.8; 95% CI, 1.4-2.2), after adjustment for age at disease onset and disease duration. Another recent large study from the US documented that the frequency of severe pulmonary fibrosis and related outcomes were higher in African Americans than in Caucasians even within some autoantibody subsets, particularly the subsets of patients who were positive for anti-topo I and anti-U1 RNP,

both of which are intrinsically associated with pulmonary fibrosis (Steen et al, 2012). Therefore, race is related to a distinct phenotypic profile having a trend toward more unfavourable outcomes in African Americans.

III Aetiology

Environmental factors have been proposed as possible causative factors (Bovenzi et al, 2004 ; Dospinescu et al, 2013). The most intensively described is silica dust, and many reports have initially detailed the illness in gold miners and coal miners exposed to crystalline silica. It is a disease determinant mainly in male systemic sclerosis, with disease features including a long latency and clinical characteristics indistinguishable from idiopathic disease. Cross-sectional 'current' occupational data underestimate cumulative occupational silica exposure which is not easy to measure / quantify.

In more recent years, SSc and scleroderma-like illness have been associated with exposures to other substances in industrial settings (Dospinescu et al, 2013 ; Diot et al, 2002 ; Garabrant et al, 2003). Examples include vinyl chloride used in the manufacturing of plastics, epoxy resins, and many solvents. Some of the solvents that have been implicated are trichloroethylene, benzene, xylene, and toluene. Among subjects with occupational exposure to solvents, men are at higher risk than women for the disease. The presence of microchimerism (Jimenez et al, 2005), infectious agents such as cytomegalovirus (Hamamdzc et al, 2002 ; Lunardi et al, 2006) and the inherent propensity for oxidative stress with associated generation of free radicals (Herrick et al, 2001) are also candidate factors that might contribute to disease progression.

III.1 Pathogenesis and Genetic predisposition

Pathogenesis of SSc is very complex and at present there is no unifying theory that may explain all its aspects. However, there are three main mechanisms responsible for the clinical and pathologic manifestations of SSc: 1) Vascular damage, principally of microcirculation; 2) Immune system activation/Auto-immunity/Inflammation, 3) Fibrosis.

The role of genetic factors is supported by the observation of familiar clustering of the disease; the high frequency of occurrence of other autoimmune disorders and autoantibody positivity in SSc family members; differences in SSc prevalence and clinical manifestations among different ethnic groups and the increased prevalence of certain human leukocyte antigen (HLA) and major histocompatibility complex (MHC) in various ethnic populations with SSc (Johnson et al, 2002 ; Allanore et al, 2010).

Multi-centre and trans-national efforts have allowed the building of large cohorts, which are mandatory to investigate the genetic component in complex disorders. The most convincing results to date have been obtained for the autoimmune component, with replication in large studies identifying HLA, IRF5, TNFAIP3 and STAT4 as the principal genes involved. As in many multi-factorial diseases, the presence of several polymorphisms in a given individual probably contributes to the risk of the disease, with each polymorphism

having only a minimal effect on its own. Several of these genes are already well-established risk factors for other autoimmune diseases, raising the possibility of shared autoimmunity (Allanore et al, 2010). However, this highly complex puzzle is not yet complete and the so-called missing heritability is still challenging. These results raising the critical role of autoimmunity is nonetheless a major paradigm shift in a disease which was until recently considered only as a fibrotic condition driven predominantly by fibroblast dysfunction. In contrast to genetic alterations, an epigenetic change is defined as a heritable change in gene expression that does not involve a change in the DNA sequence. Epigenetic mechanisms play an essential role in eukaryotic gene regulation by modifying chromatin structure, which in turn modulates gene expression. Convincing evidence indicates that epigenetic mechanisms, and in particular impaired T cell DNA methylation, provide additional factors contributing to the pathogenesis of SSc (Jungel et al, 2010).

In addition to providing a permissive environment for the development of SSc, genetic factors may also be involved in the phenotypic expression of the disease (Derk et al, 2003).

-Causative agents: Environmental and infectious agents

According to the theory of “molecular mimicry” autoantibodies (antibodies against self-antigens) are produced because the self-antigens contain epitopes that share structural similarities with viral or bacterial proteins. In SSc, it has been hypothesized infectious agents (herpes viruses, retroviruses and human cytomegalovirus) as possible causative/co-causative agents. This hypothesis is supported by: 1) the observation of a higher prevalence of IgA antihuman cytomegalovirus antibodies in patients with SSc (Lunardi et al, 2006 ; Neidhart et al, 1999); 2) the demonstration of sequence homologies between retroviral proteins and topoisomerase I antigen which is the target of Scl-70 (Jimenez et al, 1995); 3) the observation that the induced expression of retroviral proteins in normal human dermal fibroblasts results in the acquisition of a SSc-like phenotype in the production of extracellular matrix proteins (Jimenez et al, 1995). Despite these findings more consistent evidence for the involvement of the infectious agents in the aetiology or pathogenesis of SSc is still needed.

III.2 Microchimerism

Microchimerism has been defined by the presence of a low number of circulating cells transferred from one individual to another, during pregnancy, blood transfusion, blood-marrow and solid-organs transplants. An increased presence of microchimeric cells has been observed in peripheral blood and tissues of patients with SSc (Artlett et al, 1998 ; Artlett et al, 2003 ; Nelson et al, 2001).

III. 3 Vascular damage

Vascular dysfunction is one of the earliest alterations considered to be one of the initiating steps in SSc pathogenesis (Matucci-Cerinic et al, 2013). Endothelial injury, preceded by endothelial activation, involves mainly microcirculation and is mediated by cytokines produced by activated lymphocytes (Jungel et al, 2010)

and by antibodies against endothelial cells (AECA) (Renaudineau et al, 1999). Activated lymphocytes secrete cytokines and chemokines, that will lead to endothelial cell injury and expression of MHC and intercellular adhesion molecule-1 (ICAM-1) favouring inflammatory recruitment. Thereafter, growth factors such as TGF beta and connective tissue growth factor CTGF are produced increasing the production of the extracellular matrix, and upregulate platelet derived growth factor (PDGF). Increased PDGF expression promotes endothelial cell proliferation and downregulates vascular endothelial growth factor (VEGF), which usually promotes neovascularisation (Kahaleh, 1994).

Events that follow endothelial activation and endothelial damage are:

- The loss of normal vasomotor tone regulation with a decrease of vasodilators as nitric oxide, and increase of vasoconstrictors as endothelin I (Gruschwitz et al, 1995).
- The chemo-attraction and adhesion of inflammatory cells (Kuryliszyn-Moskal et al, 2005 ; Cutolo et al, 2000).
- The exposure of sub-endothelium to the blood stream: this may induce circulating platelets, to adhere to it and initiate fibrin deposition and intravascular thrombus formation.
- Activation of vascular muscle cells and their migration into the intimal layer of the blood vessel where they differentiate into myofibroblasts.

These alterations lead to the enhancement of vascular damage, with proliferation of vascular intima, narrowing of the vessel lumen with reduction of blood flow, and subsequent clinical manifestations such as digital ischemia and ulcers.

A later stage of the disease is characterised by vessel loss (Cutolo et al, 2000). In SSc, this seems to be due to an abortive neoangiogenesis. The levels of circulating endothelial progenitor cells (EPCs) that differentiate into endothelial cells were found significantly higher in SSc patients than healthy controls (Avouac et al, 2008). However, low EPC levels were associated with higher disease severity and the presence of digital ulcers, suggesting their recruitment in ischaemic tissues and sites of injury during active vascular lesion or severe disease (Avouac et al, 2008). In addition, EPCs from early SSc gave rise to some degree of in vitro endothelial differentiation and their circulating levels were significantly higher than in patients with a late disease suggesting that an altered differentiation may be a later step of the disease pathogenesis (Del Papa et al, 2006). Furthermore, EPCs functions seem to be impaired in SSc (Kuwana et al, 2014) and this might relate to the role of pentraxin 3 (Shirai et al, 2015).

Besides this, a failure of endothelial repair following SSc-related damage seems also to be linked to an alteration in endothelial differentiation of mesenchymal stem cells. These are multipotent cells present in

adult bone marrow and display some features of mature endothelial cells, such as the expression of vWf, VEGFR1, VEGFR2, VE-cadherin and VCAM1. In mesenchymal stem cells of SSc patients a decreased percentage of VEGFR2+, CXCR4+, VEGFR2+/CXCR4+ cells has been found; indeed, the angiogenic potential of endothelial like mesenchymal stem cells was reduced after being stimulated with VEGF and SDF-1, suggesting that endothelial repair may be affected in SSc starting from the bone marrow (Cipriani et al, 2007).

Oxidative stress has been also suggested to play a role in SSc pathogenesis. Ischemia/reperfusion injury following Raynaud's phenomenon can generate reactive oxygen species (ROS) that may result in vascular endothelial damages (Butler et al, 1995 ; Herrick et al, 1994). Furthermore, 8-isoprostane, which is a reliable oxidative stress marker, increases in urine, bronchoalveolar lavage, and serum samples in patients with SSc. Elevated urine levels of 8-hydroxy-2'-deoxyguanosine (8-oxodG) has been found in SSc patients, especially in those with a fibrotic phenotype, supporting high DNA oxidative damage in SSc (Avouac et al, 2010).

Increased levels of serum heat shock protein (Hsp) 70, which is a biomarker of cellular stress, are observed in SSc patients and correlate with disease severity, especially fibrosis and vascular damage (Ogawa et al, 2008). A recent paper has highlighted a potential role of antibodies to methionine sulfoxide reductase A (MSRA), one of the antioxidant repair enzymes, in SSc pathogenesis. In fact serum anti-MSRA levels were significantly elevated in SSc patients with pulmonary fibrosis, cardiac involvement and renal vascular damage and correlate positively with serum levels heat shock protein 70 that are markers of oxidative and cellular stresses. Besides this, MSRA activity was inhibited by IgG isolated from SSc sera containing IgG anti-MSRA antibody, indicating that these antibodies may enhance the oxidative stress by inhibiting MSRA enzymatic activity (Ogawa et al, 2010).

Interestingly, a growing body of evidence suggests that endothelial cell plasticity may play a critical role in various developmental and pathological processes, and, recently, it has been proposed a possible pathogenic role of endothelial mesenchymal transition (EndMT) in SSc (Cipriani et al, 2016). During EndMT, resident endothelial cells may delaminate from the polarized cell layer, invade the underlying tissue and acquire myofibroblast features, thus, contributing to fibrosis production. Specifically, EndoMT is a phenotypical conversion in which endothelial cells downregulate the expression of their specific markers and acquire mesenchymal cell products such as α -SMA, S100A4/fibroblast-specific protein-1 and type I collagen, together with the nuclear translocation of the transcriptional regulator Snail1, a trigger of mesenchymal transition (Manetti et al, 2017). EndoMT may contribute to the pathogenesis of tissue fibrosis and fibroproliferative vasculopathy such as cardiac fibrosis and primary pulmonary arterial hypertension (PAH) and multiple pathways implicated in SSc pathogenesis, such as transforming growth factor- β (TGF β), endothelin-1 (ET-1), oxidative stress and hypoxia, may activate and participate in the molecular mechanisms of the EndoMT process (Mendza et al, 2016; Good et al, 2015). In fact, it has been shown that EndoMT may be induced by TGF β and ET-1 in cultured endothelial cells from SSc patients and healthy controls (Cipriani et al, 2015a).

Therefore, taking together these data it has been proposed that during SSc, profibrotic myofibroblasts may also derive from activation of resident endothelial cells and perivascular pericytes. Interestingly, macitentan, a novel specific endothelin receptor antagonist may interfere with EndMT process in vitro, thus suggesting a new potential therapeutic target in SSc patients (Cipriani et al, 2015b).

III. 4 Immune activation\Inflammation

Innate, humoral and cellular immune system alterations and persistent tissue inflammation play an important pathogenetic role in SSc.

Recent data have highlighted a potential contribution of innate immunity in the pathogenesis of SSc. The strong association of IRF5 variants with SSc as in many other CTDs is an important clue and in addition recent data have showed that Toll-like receptor (TLR) agonists may be important stimuli of dermal fibrosis, which is potentially mediated by TLR3 or other innate immune receptors (Farina et al, 2010).

The activation of humoral immunity is demonstrated by the numerous autoantibodies that have been described in SSc. The presence of antinuclear antibodies can be found in more than 90% of patients with SSc. Anti-Scl-70 antibodies react with nuclear enzyme DNA topoisomerase I and are almost exclusively found in patient with dcSSc, but only 30-40% of these patients present anti-Scl 70. Anticentromere antibodies are present in 80-90% of patients with lcSSc and recognize several protein components of the three-laminar kinetochore. Anti-Scl 70 and anticentromere antibodies rarely coexist in the same patient. Other autoantibodies are less common in SSc, as anti-RNA polymerases II and III antibodies, found in patients with rapidly progressive disease and severe internal organ involvement. Studying cancers occurring in SSc patients, genetic alterations of the POLR3A locus were identified in patients with positive RNAPolIII antibodies (Joseph et al, 2014). Analyses of peripheral blood lymphocytes and serum showed that POLR3A mutations triggered cellular immunity and cross-reactive humoral immune responses. These results offer insight into the pathogenesis of SSc with “off-targets” effects of autoantibodies. It raises that cancer should be extensively screened in RNAPolIII positive SSc patients. Finally, it provides support for the idea that acquired immunity helps to control naturally occurring cancers. Interestingly, in the EUSTAR registry, anti-RNAPIII were associated in multivariable analysis with malignancies concomitant to SSc onset (Lazzaroni et al, 2017).

Antifibrillarin antibodies may be found in dcSSc and anti-PM-Scl antibodies found in SSc patients without inflammatory myopathy. Although autoantibodies are very common in SSc, it is not yet demonstrated that they are directly involved in the disease pathogenesis.

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Autoantibodies against angiotensin II type I receptor (AT1R) and endothelin-1 type A receptor (ETAR) may play important roles in the pathogenesis of SSc. These autoantibodies regulate physiological processes ranging from production of collagen by skin fibroblasts to angiogenesis modulation (Cabral-Marques et al, 2016). In a previous study, serum samples from 478 patients with SSc, 372 healthy subjects and 311 control-disease subjects were analysed for AT1R and ETAR. These autoantibodies were detected in most patients with SSc. These autoantibodies specifically bound to respective receptors on endothelial cells. Higher levels of both autoantibodies were associated with more severe disease manifestations and predicted SSc-related mortality, suggesting possible biomarkers. Furthermore, both autoantibodies showed biological effects inducing extracellular signal-regulated kinase 1/2 phosphorylation and increased transforming growth factor β gene expression in endothelial cells which could be blocked with specific receptor antagonists (Riemekasten et al, 2011).

The cellular immune system and the consequent chronic inflammation has an important role as mononuclear cell infiltrates are found in affected skin and visceral organs of SSc patients. The mononuclear cells within the skin infiltrates are predominantly CD4+T cells and express the activation marker class II MHC antigen DR (Kraling et al, 1995 ; Chizzolini, 2015). Subsequent oligoclonal expansion of these cells within the tissues has been observed (Sakkas et al, 2002), suggesting an antigen-driven response, although there is no information on the putative antigen or antigens that may be involved.

Recently also CD4+CD25+ regulatory T cells has been investigated in SSc pathogenesis; these cells are able to suppress proliferation of effector T cells playing a crucial role in determining the self-tolerance. In SSc sera CD4+CD25+ were markedly increased but showed an aberrant expression of phenotypic markers that is associated with a reduced suppressive function (Radstake et al, 2009 ; Klein et al, 2011).

The role of T cells in the development of dermal fibrosis has been recently suggested by the invalidation of STAT4 in the mouse model of bleomycin induced dermal fibrosis, mimicking early inflammatory stages of SSc. STAT4 is a transcription factor that promotes inflammation during protective immune responses and immune-mediated diseases. STAT4 deficient mice were protected from the development of dermal fibrosis, in this mouse model. In addition, STAT4 also regulated fibroblast activation and collagen release indirectly, by orchestrating T cell infiltration and regulating proinflammatory cytokine production (Avouac et al, 2011). These findings support the contribution of STAT4 and T cells in the development of inflammation driven fibrosis, hallmark of early stages of SSc, characterized by the infiltration of inflammatory cells in lesional tissue.

IL-17 is a proinflammatory cytokine with non-redundant functions in the clearance of extracellular pathogens. An increase in frequency of Th17+ cells has been reported in several autoimmune diseases. Some recent reports suggest an increased frequency of Th17 cells in peripheral blood of patients with SSc together with a decrease in frequency or suppressive activity of Tregs in these patients although some discrepancies have

been found regarding peripheral blood versus dermal tissue (Brembilla et al, 2012). Larger studies and functional data are now required to confirm the potential role of Th17 and Tregs in SSc. A large candidate gene study further highlighted the potential implication of Th17 pathway in SSc, by establishing CCR6 (a surface marker for Th17 cells) as a new susceptibility factor for anti-topoisomerase-positive SSc and showing a robust association of a regulatory variant (Koumakis et al, 2013).

In SSc the B cell hyperactivity and hyper-g-globulinaemia suggests the presence of an abnormal B cell activation (Fujimoto et al, 2005); then the presence of B cell infiltration has been detected in the skin and the lung of SSc patients (Lafyatis et al, 2007). In particular, CD22, a B cell-specific inhibitory receptor, has a disrupted cell signalling in SSc, leading to abnormal B cell activation and autoantibody production (Fujimoto et al, 2007). A recent study has demonstrated the presence of circulating autoantibodies to CD22 in SSc patients and these antibodies were capable of reducing phosphorylation of all CD22 tyrosine motifs, interfering with the suppression on B cell activation (Odaka et al, 2010).

Chemokines could be of major importance in SSc. Previous reports have highlighted the potential implication of MCP-1 by example but a recent study raised the potential important role of CXCL4. Using an unbiased proteomic approach and plasmacytoid cells, the authors identified CXCL4 as overexpressed by cells issued from SSc patients (Van Bon et al, 2014). They then were able to correlate CXCL4 levels with skin and lung fibrosis and with pulmonary arterial hypertension. CXCL4 is a protein that was first identified as a product of megakaryocytes and is well accepted as one of the most potent antiangiogenic chemokines. In addition, CXCL4 inhibits the expression of the antifibrotic cytokine interferon- γ and up-regulates profibrotic cytokines interleukin-4 and interleukin-13, and also stimulates the proliferation of T regulatory cells with impaired suppressive function. The exact source of CXCL4 remains to be determined such as platelets were found to be critical to mediate experimental liver fibrosis but CXCL4 appears as an attractive candidate to link vascular, immune and fibrotic features related to SSc and potentially others fibrotic diseases.

III. 5 Fibrosis

Fibrosis is the final step of SSc pathogenesis and is responsible of the most prominent clinical manifestations of disease. It is due to an increased fibroblast production of collagen, especially types 1 and 3, with type 1 being the most abundant. It is not known if the excessive production of connective tissue represent an altered response to an unknown injury or if is due to the primary alteration in the regulation of expression of matrix protein genes. The persistent activation of collagen genes differentiates the uncontrolled fibrosis of SSc from normal response to injury. The persistent activation of collagen genes differentiates the uncontrolled fibrosis of SSc from normal response to injury. In this context, it has been suggested that, after vascular and immunological damage, the development of fibrosis, in different organ, may be related to several pathogenic mechanisms, including expansion and activation of resident tissue fibroblasts, endothelial cells and perivascular pericytes,

recruitment of bone marrow-derived circulating precursors, transformation of white adipocytes and transdifferentiation of epithelial cells as well as endothelial cells into mesenchymal cells, resulting in hyperactivation of fibroblasts and myofibroblasts (Zeisberg et al, 2010; von Gise et al, 2012). A number of cytokines and growth factors released from the tissue inflammatory cells can stimulate collagen gene expression (White, 1996 ; Postlethwaite 1995).

Transforming growth factor beta (TGF β), produced by activated lymphocytes and monocytes, plays a crucial role in SSc related fibrosis as it stimulates the extracellular matrix synthesis (Varga et al, 1987), but also decreases the production of collagen degrading metalloproteinases and stimulates the production of protease inhibitors (as tissue inhibitor of metalloproteinases-1), which prevent break-down of the extracellular matrix (Gerber et al, 2013). The production of TGF β is consistently upregulated in SSc, maintaining fibroblasts from SSc patients in an activated state. SSc fibroblasts on the other hand express increased number of TGF β receptors, enhancing collagen production. The main alterations of TGF β signalling that play an essential role in the persistent activation of SSc fibroblasts are represented by an up-regulation of α v β 5 and α v β 3 integrins, which contribute to activation of latent TGF β and establishment of the autocrine TGF β loop. Additional changes include alterations of the TGF β receptor ratio and the presence of persistently phosphorylated Smad3. Nuclear receptors are good candidate to play a primary role in fibrosis. NR4A1 recruits a repressor complex and acts as an endogenous inhibitor of TGF- β . Even though temporary upregulation of TGF- β in physiologic wound healing induces NR4A1 expression and thereby creates a negative feedback loop. The persistent activation of TGF- β signalling in fibrotic diseases uses AKT- and HDAC-dependent mechanisms to inhibit NR4A1 expression and activation. NR4A1 small-molecule agonists showed their ability to overcome this lack of active NR4A1 and inhibit experimentally-induced skin, lung, liver, and kidney fibrosis in mice, providing a proof of concept for targeting NR4A1 in fibrotic diseases (Palumbo-Zerr et al, 2015). Several lines of evidence suggest that peroxisome proliferator-activated receptors (PPARs) could play an important role in SSc-related fibrosis. Low levels of both PPAR α and PPAR γ were detected in the skin of patients with SSc compared with controls. The use of IVA337, a pan-PPAR agonist, in mice was associated with decreased extracellular matrix deposition and reduced expression of phosphorylated SMAD2/3-intracellular effector of TGF- β 1. Furthermore, a dampening effect on both inflammation and fibrosis was observed in mice challenged by bleomycin. Simultaneous activation of all three PPAR isoforms exerts an anti-fibrotic action, making IVA337 a potentially therapeutic candidate in fibrotic diseases including SSc (Ruzehaji et al, 2016).

Fibrillin-1 is a modular glycoprotein encoded by the large (230-kb) FBN1 gene located in 15q21.1 region. This region has been mapped in Choctaw Indians as potentially harbouring SSc associated genes and the animal model TSK-1, which recapitulates some of SSc changes, relates to a Fibrillin-1 gene duplication. Fibrillin is a major constituent of microfibrils in the extracellular matrix and is highly homologous to latent TGF-beta binding proteins. These proteins bind to the small latent TGF-beta complex and sequester it to the extracellular matrix.

Mutations of the FBN1 gene cause Marfan syndrome and also stiff skin syndrome that is characterized by hard, thick skin, usually over the entire body, which limits joint mobility and causes flexion contractures. Failed matrix sequestration of the latent complex in fibrillin-1-deficient patients and mice promotes increased signalling by TGF- β . The stiff skin syndrome mutations are specifically localized to the fourth TGF- β -binding protein-like domain, which encodes the RGD motif, through which fibrillin-1 binds several integrins. Two Fbn1-targeted knock-in mouse models were recently generated to demonstrate that impaired interaction between integrins and fibrillin-1 initiates skin fibrosis (Leask et al, 2002). Moreover, mutant mice exhibit skin infiltration of pro-inflammatory immune cells and also autoantibody production and of the most interest, these findings could be normalized by integrin-modulating therapies or TGF- β blockers (Gerber et al, 2013). Altogether, these data highlight that cell–matrix interactions are critical in the relationships between inflammation/immunity and fibrosis and might represent promising new therapeutic avenues.

Connective tissue growth factor (CTGF) is another potentially important mediator of tissue fibrosis (Ihn, 2002). It stimulates the synthesis of extracellular matrix components in dermal and lung fibroblasts: it is produced by fibroblasts, vascular smooth muscle cells and endothelial cells in response to TGF β stimulation and in autocrine fashion CTGF can stimulate its own production (Svegliati et al, 2005). It has been hypothesized that CTGF might act as a downstream mediator of TGF β effects, that once activated, could chronically perpetuate collagen overproduction in SSc.

Besides this, oxidative stress in SSc affects fibroblasts, which show the accumulation of large amounts of reactive oxygen species (ROS); these are key cell transducers of fibroblast proliferation and collagen-gene expression. A pathway linking the signalling proteins Ha-Ras, growth-factor–activated extracellular-signal–regulated kinases 1 and 2 (ERK1/2), and ROS is amplified in fibroblasts from patients with scleroderma (Baroni et al, 2006).

IV Clinical manifestations

The disease is commonly called "scleroderma" because the most visible aspect is "hard skin", however, scleroderma is a systemic disease and besides the significant aesthetic changes of the face (figure 5) and extremities, organ involvement leads to a functional reduction, sometimes progressing to organ or multiorgan end-stage failure. The disease has various clinical characteristics because it involves the skin as well as the internal organs. At onset, some patients present with few changes, making the diagnosis sometimes difficult to establish even for scleroderma experts. Below is an in-depth description of the various types of internal organ involvement observed in SSc.

Table 5: Prevalence of clinical features in EUSTAR cohort by disease subtype

n/total (%) or mean \pm SD EUSTAR ^a # n=13996	Limited (n=7273)	Diffuse (n=4034)
Female	6525 (89.8%)	3152 (78.2%)
Age at recruitment, mean \pm SD (range), years	57.00 \pm 13.67	51.58 \pm 13.81
Disease duration at recruitment*, years	9.10 \pm 8.62	6.79 \pm 7.22
Anti-centromere pattern ANA	3487 (50.8%)	282 (7.7%)
Anti-Scl 70 +ve	1534 (22.6%)	2226 (58.9%)
Anti-RNAP +ve	64 (2.6%)	109 (9.0%)
Raynaud's phenomenon	6929 (96.4%)	3855 (96.1%)
Rodnan skin score (highest ever)	6.78 \pm 5.42	17.64 \pm 10.24
Digital ulcers ever	1936 (27.1%)	1530 (38.4%)
Digital gangrene/ amputation	42 (3.5%)	29 (4.2%)
Joint contractures	1454 (20.3%)	1849 (46.5%)
Tendon friction rubs	338 (4.8%)	683 (17.3%)
Synovitis	896 (12.5%)	785 (19.7%)
ILD (HRCT scan)	1663 (27.0%)	1675 (48.6%)
Pericardial effusion	174 (2.4%)	141 (3.5%)
Renal crisis ever	82 (1.1%)	161 (4.0%)
Malabsorption	33 (3.2%)	31 (5.0%)
Home oxygen ever	75 (2.1%)	51 (2.5%)

*Disease duration from first non-Raynaud disease manifestation. Disease manifestations defined as present if ever present from SSc diagnosis. Data are presented as number and percentage of those with data available.

^a15-40% missing data; [#]41-75% missing data; ^bmore than 75% missing data. EUSTAR database, unpublished data.

Figure 5 - Face in acute diffuse SSc

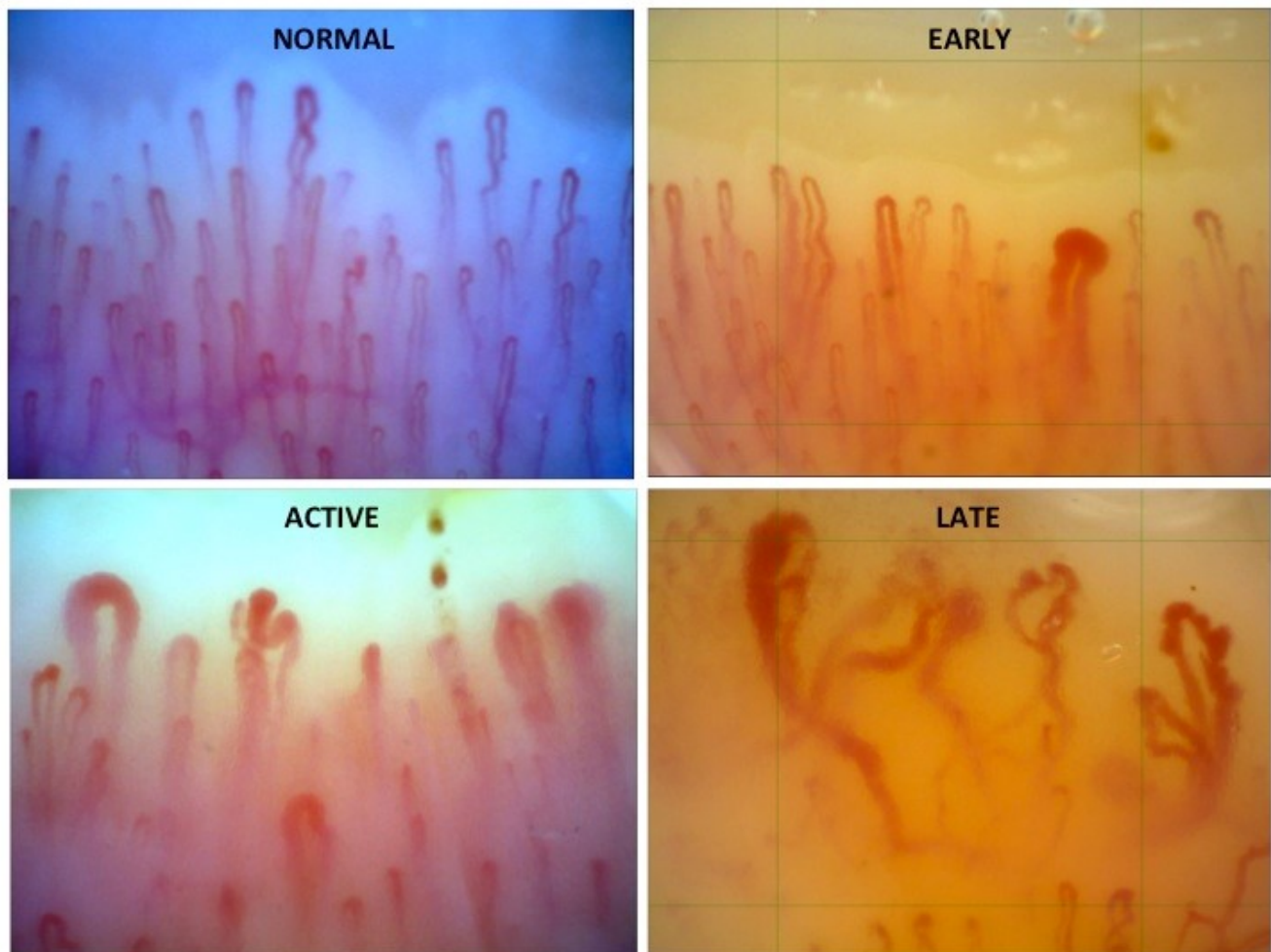
IV.1 Vascular manifestations

The earliest symptom of SSc is Raynaud's phenomenon (RP) of the fingers, toes, ears, and nose: it is characterized by episodic vasospastic attacks that cause the blood vessels in the fingers and toes to constrict. RP presents with three changes in skin colour (Neidhart et al, 1999). Pallor (in response to spasm of the arterioles and the resulting collapse of digital arteries) followed by cyanosis (due to ischemia) and finally, as the reperfusion dilation, rubor occurs. The duration of an attack varies from less than one minute to several hours. As the attack ends, throbbing and tingling may occur in the fingers and toes. Connective tissue diseases, such as SSc, are the most common cause of secondary RP (LeRoy et al, 1988).

Nailfold video-capillaroscopy (NVC) shows a variety of morphological changes including enlarged capillaries, bushy capillary formations, micro haemorrhages, and a variable loss of capillaries with or without avascular areas. Capillaroscopic patterns in SSc may vary according to the disease stage and Early (new enlarged/giant capillaries, few capillary haemorrhages, relatively well-preserved capillary distribution, no evident loss of capillaries), Active (frequent giant capillaries, frequent capillary haemorrhages, moderate loss of capillaries, mild disorganization of the capillary architecture, absent or mild ramified capillaries) and late (irregular enlargement of the capillaries, few or absent giant capillaries and haemorrhages, severe loss of capillaries with extensive avascular areas, disorganization of the normal capillary array, ramified/bushy capillaries) stages have been identified (figure 6) (Cutolo et al, 2003). Some studies have described the morphological aspects of vascular damage in patients with SSc by NVC, correlating these capillary abnormalities to selected

characteristics of the disease. Further scoring systems are also under investigations in an attempt to evaluate capillaroscopy not only as a diagnostic tool but potentially as an activity or severity marker.

Figure 6: Normal and systemic sclerosis nailfold capillaroscopy patterns

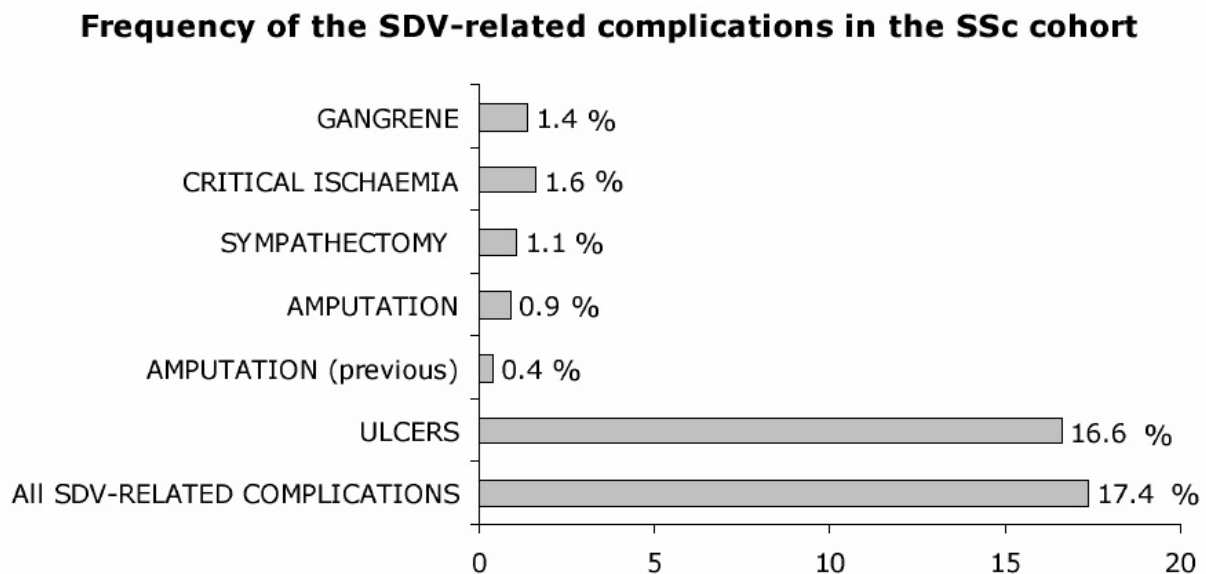


The prospective follow-up of 586 consecutive patients referred for evaluation of RP who had no definite connective tissue disease at baseline revealed that 74 (12.6%) developed definite SSc. Scleroderma capillaroscopic pattern and SSc specific auto-antibodies were both predictors of SSc and had additive effects (the higher risk, close to 60 fold, was observed for patients with both abnormal capillaroscopy and positive SSc autoantibodies at baseline) (Koenig et al, 2008).

Fingertips ulcers may arise as a complication of RP and chronic ischemia and occur in patients both with limited or diffuse systemic sclerosis (SSc). Usually ulcers heal slowly and become portals for infections that may evolve to gangrene and, as they deepen into the tissues, bone involvement can occur, which may result in osteomyelitis. In the worst refractory cases, digital amputation may be needed (Bogoch et al, 2005). In SSc, digital tip ulceration occurs in about 31.8–71.4% (median 45.2%). Digital ulcerations are usually slow healing and 14–29% progress to gangrene and auto amputation (Nihtyanova et al, 2008). The frequency of severe

digital vasculopathy related complications emerged in a recent study (Amanzi et al, 2010) is reported in figure 7.

Figure 7: Complications of ulcers in a SSc cohort of patients (from Nihtyanova ARD 2008)



In the early phase of SSc, ulcers are localised on fingertips (figure 8A), malleoli, heel, and great toe. With disease progression, ulcers may be found over bony prominences (figure 8B), and may be provoked mainly by mechanical retraction of the skin, especially to the dorsal aspect of the interphalangeal joints and elbows. Usually, these parts are exposed to repetitive trauma at sites of chronic contractures. The avascular, atrophic nature of the tissue overlying these sites results in vulnerability to injury and impaired healing.

Figure 8A and 8B: Localisation of digital ulcers in early diffuse SSc (A) and gangrene with amputation in late diffuse SSc (B)



In SSc, a clinical evidence-based classification of DU is still lacking and today the increase in studies on DU highlights the need for a clear-cut classification of DU. This has become a major necessity to make both studies and outcomes uniform, as in previous randomized controlled trials and open studies, different definitions have been proposed.

A recent study has classified fingertip ulcers as follows (Amanzi et al, 2010):

1. Derived from Digital pitting scar: these ulcers are hyperkeratotic and thick small (2-3 mm) scars are localised on the fingers. They are a white or yellow, undermined and continuously painful (figure 8).
2. Characterized by Loss of tissue: ulcers are characterised by loss of tissue, at different levels and at different sites that may deepen down to the bone (figures 9). They are frequently undermined and painful. When they occur over bony prominences they are due to tissue retraction, as showed in figure 7.
3. Derived by Calcinosis: it is defined as deposits of calcium phosphate in soft tissues, visible to the naked eye and/or confirmed by X-ray They may occur anywhere, with variable dimension and are hard, adherent to the bottom of the ulcer or tissues, painful and are frequently complicated by infection, with or without fistulisation (figure 10)

Ulcers may evolve in gangrene that is defined as the death of tissues caused by a total lack of blood supply. Macroscopically, the affected part is dry, shrunken and dark black. On the dorsal aspect of the fingers in particular on PIJ skin retraction may provoke cutaneous breaks forming ulcers.

Figure 9: Yellow (9A) and white (9B) pitting scar

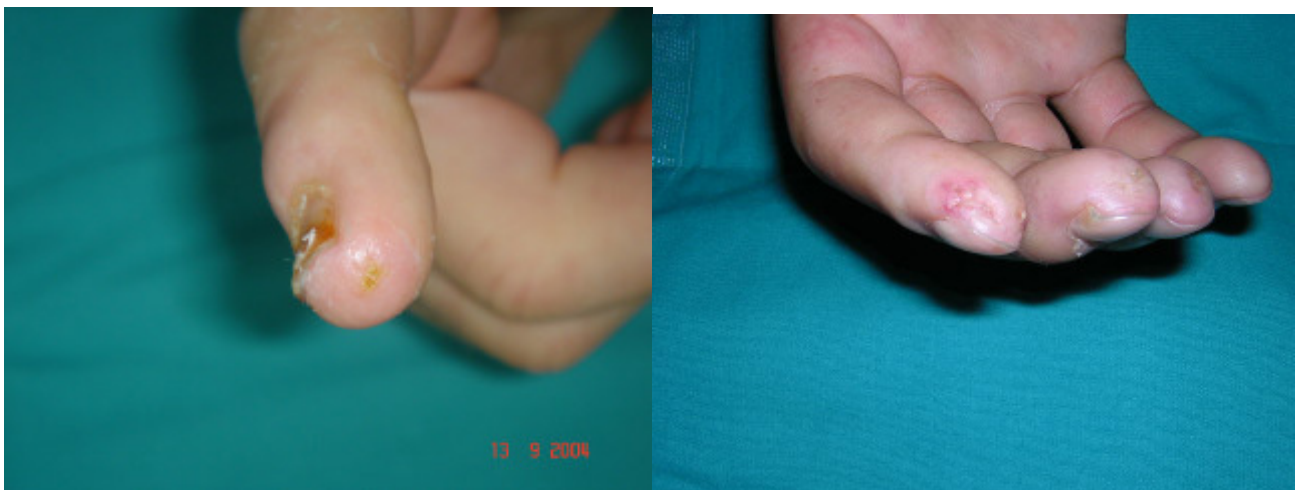


Figure 10: Ulcers developed on calcinosis of the knee in a patient with SSc. In the box calcium depositions that have been removed are shown.



-according to the depth:

1. Superficial: partial thickness skin loss involving epidermis. The ulcer is superficial and presents clinically as an abrasion, blister or tiny crater.
2. Intermediate: full thickness skin loss involving damage to, or necrosis of, subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue.
3. Deep: full thickness skin loss with extensive destruction, or damage to muscle down over the fascia, supporting structures (e.g. tendon, joint capsule) and bone)

The main features that should be evaluated when dealing with SSc ulcers are:

- localization (fingertips, nail area, dorsal and palmar aspect of the finger);
- dimensions (area in square millimetres);
- bed of the lesion (re-epithelialization, granulation tissue, fibrin, wet or dry necrosis, eschar and gangrene);
- exudate (low, high, pus);
- borders of the lesions (regular or irregular);
- perilesional skin (normal or inflamed) and oedema;
- bone and tendon exposure and auto amputation;
- pain

Using the Eustar registry, the prevalence and outcomes of SSc-DU patients have been described. Out of 3196 patients with longitudinal data (malegender 13%, 33% diffuse subset), 1092/3196 patients had a history of DU at baseline. In multivariable analysis adjusting for age, gender and all parameters considered potentially

significant, a history of DU was predictive for the presence of active DUs at prospective visits (HR (95% CI)): 2.41 (1.91 to 3.03), $p < 0.001$, for an elevated systolic pulmonary arterial pressure on heart ultrasound :1.36 (1.03 to 1.80), $p = 0.032$, for any cardiovascular event (new DUs, elevated US-PAPs or heart failure): 3.56 (2.26 to 5.62), $p < 0.001$, and for death (1.53 (1.16 to 2.02), $p = 0.003$). As expected a history of DU is the strongest predictor of new DU but also seems to predict overall worse cardiovascular outcomes (Mihai et al, 2015).

IV .2 Gastrointestinal Tract Involvement

Fibrosis can involve the entire gastrointestinal (GI) tract, making the muscle wall of these organs atrophic. Damage to the gut's nervous system may cause dysmotility, it is thought to be an early event and might be promoted by the vasculopathy. Oesophageal dysmotility is very common and its problems occur in 75-90% of SSc patients, stomach involvement in at least 50%, small bowel involvement in 40-70%, colon involvement in 20-50%, and anorectal involvement in 50-70% (Sjögren, 1994).

IV.2.1 Upper Tract: Oesophageal disease is characterized by poor functioning of the muscle of the lower part of the oesophagus (Cohen et al, 1972). This causes a reduction of the peristalsis and of the continence of the lower oesophageal sphincter (LES) that manifests as dysphagia and reflux episodes that are responsible of oesophagitis of lower part of oesophagus, causing heartburn, pyrosis, and regurgitation. Other less common symptoms are sore throat, laryngitis, inflammation of the gums, erosion of tooth enamel, chronic irritation in the throat, and hoarseness in the morning. Sometimes there are no symptoms, and the presence of gastro oesophageal reflux is revealed through other complications (Zamost et al, 1987). Oesophageal motility is usually tested by manometry. This test evaluates the amplitude, the duration, the velocity and the presence or absence of peristaltic contractions and determines whether the measurements are within normal range (Klein HA et al, 1992). In a recent series of about 60 patients fulfilling the VEDOSS criteria, it has been shown that the lower oesophageal sphincter pressure and peristalsis were significantly abnormal (peristalsis was absent in 25.5% of the patients), and oesophageal symptoms were detected in 49%. This confirms that upper GI is an early event in the disease course (Lepri et al, 2014).

In a small subset of patients, Barrett's oesophagus can develop as a complication of oesophagitis. This is a potentially precancerous condition in which the mucosa of the oesophagus is transformed into a "specialized intestinal metaplasia" (figure 11A). To evaluate tissue damage, upper endoscopy is recommended. If Barrett's oesophagus is detected, routine endoscopic screening is advised usually every 3 years in the case of lack of dysplasia, every year if low grade dysplasia is found and every 3 months in the case of high grade dysplasia with discussion of local therapy if in situ cancer occurs (Wipff et al, 2005 ; Wipff et al, 2011).

For people with symptoms of gastro oesophageal reflux, a pH-monitoring test can be performed (Leite et al, 1997). The abnormality of the gut's nervous system present in SSc also can involve the stomach's electrical

rhythm, with the motility becoming weakened, spastic, or failing completely. In the most severe forms, nausea, vomiting, abdominal pain, and severe constipation are unrelenting.

Gastroparesis, or small bowel dysmotility, is at the extreme end of the symptom spectrum. The range of symptoms includes nausea, vomiting, belching, reflux, sensation, early satiety, abdominal pain, abdominal bloating, change in bowel habits, and weight loss (Wegener et al, 1994). Gastric emptying time (GET) is the diagnostic test used for gastroparesis.

Watermelon stomach (WS) or Gastric Antral Vascular Ectasia (GAVE) is a very rare gastric complication of SSc. It has a unique endoscopic appearance that is characterized by multiple longitudinal stripes of red vessels, which are limited to the gastric antrum and which radiate in a spoke-like fashion from the pylorus to the antrum (figure 11B). WS seems to be a component of the general microangiopathy that characterizes the disease. However, despite the large use of gastroscopy, prevalence of SSc-WS remains unclear with only one monocentric, retrospective study, which reported 5.7% of WS among 264 SSc patients with anaemia (Ingraham et al, 2010). However, in a recent large Eustar survey, the prevalence of GAVE was estimated at about 1% of patients with SSc (49 cases identified) (Ghrénassia et al, 2014). In this controlled study, GAVE was associated with the presence of anti-RNA-polymerase III antibodies (OR 4.6; 95% CI 1.2-21.1). In a clinical perspective, SSc-GAVE was mainly associated with anaemia (82%) requiring blood transfusion (45%). Therapeutic endoscopic procedures were performed in 45% of patients with GAVE. After a median follow-up of 30 months (range 1-113 months), survival was similar in patients with SSc-GAVE compared to controls, but a higher number of scleroderma renal crisis cases occurred (12% vs 2%; $p = 0.01$).

These results support previous findings with early occurrence predominating in diffuse cutaneous SSc versus late onset (over 15 years) in limited cutaneous, such as a probable link with anti RNA polymerase III antibodies. The more common clinical manifestation is anaemia, which could be present in 95 to 100% of cases with 90% of chronic occult bleeding and 10% of acute haemorrhage. Various therapies have been reported for the treatment of WS, including blood transfusion, oestrogen-progesterone treatment, iron supplementation, steroids, and surgery. Laser YAG can be a useful treatment with 85% of success at the short-term, like argon plasma electrocoagulation (Shibukawa et al, 2007).

Figure 11: Histological and macroscopic picture of some upper GI complications

11A: BE was defined by the finding of intestinal architecture in the lower oesophagus displaying a villiform columnar-lined mucosa with goblet cells; these features of BE were identified by classic coloration on haematoxylin and eosin staining. 11B: Endoscopic aspect of watermelon stomach

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IV.2.2 Lower Tract

The small bowel can become dilated and often atonic, losing its propulsive function. Under these conditions bacteria that normally live in the small bowel grow enormously, damaging the mucosa that absorbs food. This leads to malabsorption, with significant loss of absorption of essential nutrients. Bacterial overgrowth syndrome or Small Intestinal Bacterial Overgrowth (SIBO) occurs when the normally low colonization of bacteria in the upper GI tract increases significantly (Greydanus et al, 1989). Fat, protein, carbohydrate and vitamin malabsorption result from poor enterocyte function and from bacterial transformation of nutrients into nonabsorbable and toxic metabolites, all of which contribute to damage of the intestinal mucosa.

Breath tests using by-products of bacterial metabolism to identify malabsorbed substances are useful in determining the diagnosis. The most sensitive and specific is the xylose breath test, which is based on the fact that overgrowth of Gram-negative bacteria in the small bowel, which occurs during dysmotility disorders, leads to metabolism of xylose and results in the release of radioactive carbon dioxide. In the most severe cases, bowel dilatation may result in a condition known as intestinal pseudo-obstruction (figure 12). Clinical expression is characterised by nausea, diarrhoea, abdominal distension, weight loss and commonly intermittent abdominal crisis with frank distension and postprandial bloating. Such cases, patients should avoid oral feeding and will require the use of continuous nasogastric suction. When malnutrition is evident, total parenteral nutrition is indicated.

Because gastrointestinal tract (GIT) involvement occurs in approximately 90% of patients with SSc and also because it has a negative impact on health-related quality of life, it is important to carefully assess this part of

the disease, and include it in future trials. Following the Food and Drug Administration draft guidance on the development of a patient-reported outcome measure, the UCLA Scleroderma Clinical Trial Consortium GIT 2.0 has been built and its reliability and validity recently demonstrated (Khanna et al, 2009). Sensitivity to change is now under examination but this tool should improve the management of SSc patients (it is available through EUSTAR website).

A summary of the various GI involvements, mechanisms and tools of assessment is presented in Table 5.

Figure 12: lower GI involvement: abdominal CT scan showing that the small intestine is filled and distended with air and fluid, with air-fluid levels, evocative of pseudo-obstruction

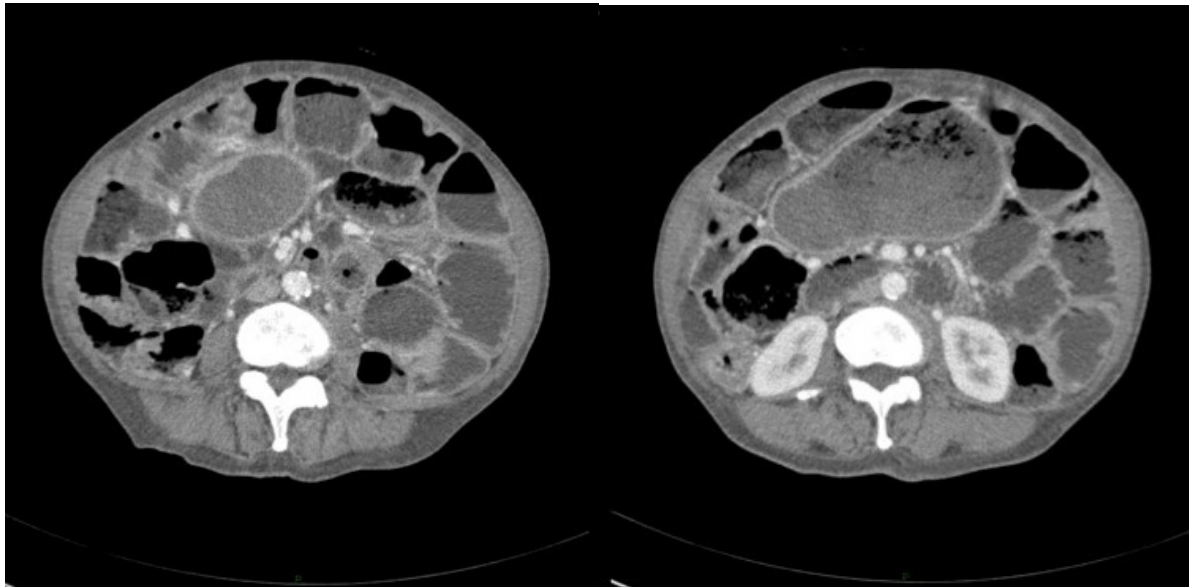


Table 6: summary of the GI symptoms, mechanisms and tools for assessment

GI	Symptoms	Mechanisms	Assessment
Esophagus	Reflux Heartburn Dysphagia Bleeding	Dysmotility Esophagitis Ulcers	Manometry Endoscopy 24h Ph-metry
Stomach	Satiety, bloating Nausea Vomiting Bleeding	Gastroparesis Telegiectasia	Manometry Scintigraphy Baryum Endoscopy
Intestine	Constipation Diarrhea Abdominal bloating and pain Weight loss	Dysmotility Bacterial overgrowth Pneumatosis Malabsorption	Breath test CT scan Ileocolonoscopy Video capsule endoscopy
Ano-rectal	Incomplete stools outlet Fecal incontinence		Manometry

IV.3 Lung involvement

Pulmonary involvement is the leading cause of morbidity and mortality in SSc patients (Steen et al, 1994) as it frequently complicates SSc provoking loss of quality of life and a poor expectation of survival. Alveolitis, membrane thickening and/or the modification of microvascular structure are the main hallmarks of lung involvement that may lead, with the progression of the disease, to ILD and to pulmonary artery hypertension. Non-specific interstitial pneumonia (NSIP) is the most histopathological pattern found in SSc lung, although usual interstitial pneumonia (UIP) can be present (Kim et al, 2002 ; Bouros et al, 2002). NSIP is characterized by varying degrees of inflammation and fibrosis but does not present the heterogeneity of UIP (it lacks fibroblast foci and honeycombing) (Travis et al, 2008). In idiopathic lung fibrosis patients with NSIP have better prognosis than those with UIP. This difference has not been observed in SSc, although overall all forms of lung fibrosis have a better outcome in SSc.

Dyspnoea on exertion, non-productive cough and hypoxemia are the most common manifestations of pulmonary fibrosis. Haemoptysis, airway and lung inflammation can also be observed in advanced fibrosis. Fine bibasilar crackles at chest auscultation are characteristic.

In the early stages there are often no clinical signs to suggest the development of pulmonary arterial hypertension. Increased and palpable pulmonary components of the second heart sound, right ventricular gallops, murmurs of pulmonary and tricuspid insufficiency, jugular distension, hepatojugular distension and feet oedema can reflect signs of pulmonary hypertension.

Chest X-rays can detect lung volumes, the distribution of infiltrates, pleural disease and lymphadenopathy. Chest radiography is not sufficiently sensitive to exclude lung fibrosis in SSc: 10% of symptomatic patients may have a normal chest radiograph as CXR have a low sensitivity for early lung involvement. The pulmonary function test (PFT) in SSc may show a restrictive pattern with decrease of forced vital capacity (FVC) or total lung volume (TLC) –(which is less effort dependent and so can be more reliable than FVC) and diffusion capacity for carbon monoxide (DLCO) (Guttadauria et al, 1977).

Restrictive ventilatory defects are the most common finding (Peters-Golden et al, 1984). However, by the time these defects are diagnosed on spirometry the pulmonary disease is fairly advanced. A reduction in pulmonary carbon monoxide diffusion capacity (DLCO) is reportedly to be an early sign of pulmonary disease in SSc, as well as an important predictor of mortality (Wells et al, 1997). Even so, diffusion across the alveolar capillary units may be altered by parameters other than interstitial fibrosis. The reduction of DLCO alone may also suggest the presence of pulmonary hypertension (Steen, 2003 ; Steen et al, 2000). Assessment of PFT is recommended in SSc since chest radiography or respiratory symptoms cannot predict early lung involvement. However, and despite its value for the functional assessment of the patients, pulmonary PFTs perform poorly to diagnose ILD in SSc patients and cannot be used solely to that end (Suliman et al, 2015).

Chest HRCT is the non-invasive gold standard technique for the diagnosis of SSc ILD (Remy-Jardin et al, 1993). HRCT is recognised as a sensitive tool for predicting the histological characteristics of lung parenchymal abnormalities, in patients with idiopathic pulmonary fibrosis. It allows imaging of the lung parenchyma in remarkable detail that is very useful in the diagnosis of fibrosing alveolitis, providing a non-invasive alternative to open lung biopsy. Ground glass opacification may reflect alveolitis but when there is associated traction bronchiectasis it is more likely due to finer fibrosis. Likewise, inflammatory change cannot be excluded by honeycomb reticular shadowing as there may be sites of inflammation within established disease (Ooi, et al, 2003). A simple staging system with minimal and severe disease on HRCT defined as clearly < 20% or clearly > 20% has demonstrated a high feasibility and a good predictivity value. Indeed, an extensive disease (>20%) on HRCT at baseline is associated with a three-fold increased risk of deterioration or death in SSc-ILD, compared with limited disease (Moore et al, 2013).

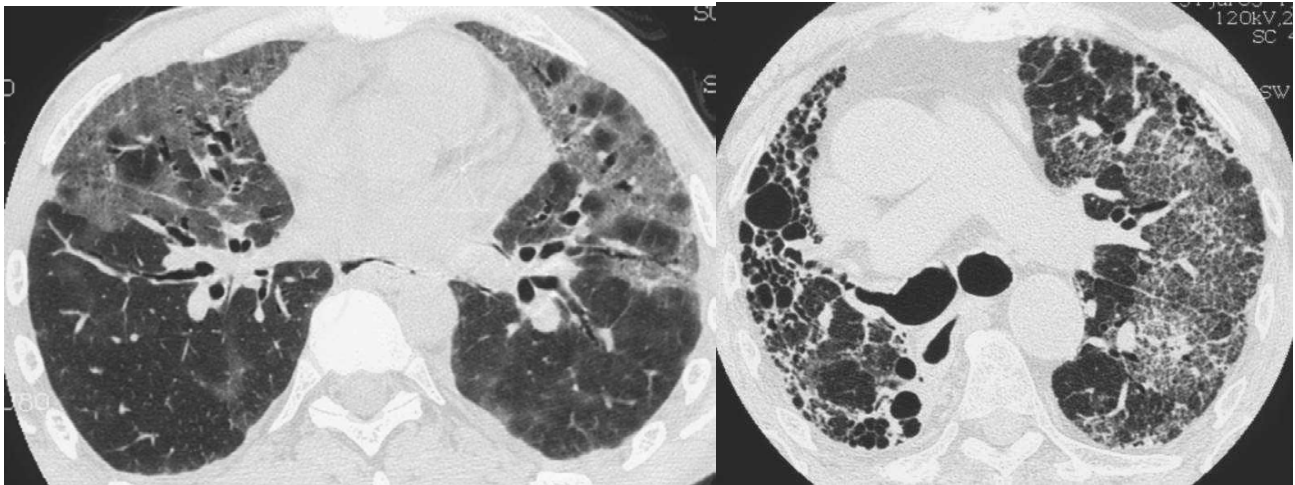
Treatment decisions should be based upon clinical evidence of declining lung function in the context of significant HRCT and PFTs changes.

Typical interstitial abnormalities identified on HRCT include thickened interlobular septa, sub pleural cysts, and honeycombing lung formation. Additional findings may include sub pleural micro nodules, small airway ectasia (bronchiectasis and bronchioloectasis) and ground glass opacification (Guttadauria et al, 1977) (figure 13). Ground glass opacification on HRCT correlates to the presence of air space inflammation in the lung (alveolitis) and decreased DLCO. HRCT allows a qualitative assessment (Normal/ground-glass/fibrosis) or semi-quantitative assessment (Wells' or Warrick's scoring systems).

Table 7: summary of the lung involvement, mechanisms and tools for assessment

	Symptoms	Mechanisms	Assessment
Interstitial lung fibrosis	Shortness of breath Exercise limitation	Inflammation Fibrosis	Chest auscultation: crackles PFTs: decline in DL_{CO}, FVC Hypoxemia 6 min walk test HRCT Biomarkers Bronchoalveolar lavage
Pleural disease	Chest pain Shortness of breath	Inflammation	X-Ray HRCT
Lung vessels Pulmonary hypertension	Shortness of breath Exercise limitation Syncope Oedema	Vascular resistance (PAH) <i>versus</i> passive elevation of pulmonary pressure (PH)	Loud pulmonary component (P2) Signs of right sided heart failure Echocardiography HRCT Right heart catheterisation 6 min walk test

Figure 13: HRCT findings in SSc-ILD. A: ground glass opacities evocative of acute alveolitis. B: reticulation and honeycombing evocative of established lung fibrosis



In patients with pulmonary fibrosis, the cell population in the BAL fluid, from different lung sections, is not uniform, and HRCT scanning appears to be a useful method to identify pulmonary areas with different inflammatory activity (Strange et al, 2008). BAL is no more use to measure disease activity and no more included for treatment decision but is still used to rule out infection when required and is a research tool to investigate lung inflammation and lung fibrosis pathogenesis (Schmidt et al, 2009 ; Pignone et al, 1992). Interestingly, a meta-analysis of 27 studies was conducted to identify variables predicting the mortality and ILD progression in SSc patients and, the extent of disease, on HRCT scan, was the only variable that predicts independently, both mortality and ILD progression. Furthermore, DLCO was the most consistent predictor of mortality and may help to identify patients with a poor prognosis; however, more rigorous studies are needed to fully elucidated these data (Winstone et al, 2014).

Clearance of inhaled ^{99m}T-DTPA is an index of lung epithelial permeability (O' Brodovich et al, 1987). Increased ^{99m}T-DTPA clearance may be a sensitive marker of inflammation (Pantin et al, 1988) and normal clearance certifies absence of inflammation (Susskind, 1994). Rapid clearance of ^{99m}T-DTPA can be useful in patients with an isolated reduction in DLCO to differentiate between those with early fibrosing alveolitis and to those with pulmonary vascular disease (Wells et al, 1993).

IV .4 Pulmonary arterial hypertension (PAH)

PAH is a serious and potentially life-threatening condition that can develop in patients with SSc. It occurs when the blood vessels supplying the lungs constrict and then become stiffer and thicker because of irreversible fibrosis. The increased resistance in pulmonary circulation makes it difficult for blood to flow through to the lung vessels, and thus the heart must pump harder leading to heart failure (figure 14) (Denton et al, 2003).

Some patients may have both interstitial lung disease and PAH; the first usually develops early in the disease, whereas PAH tends to occur later, often in the second decade of disease. The prevalence of pre-capillary PAH

has been found to be 9% in a recent meta-analysis that included more than 3800 SSc patients screened for this complication (Yamane, 1994). PAH has been commonly known as a late complication of the disease; however 2 different patient profiles has been suggested by some studies with PAH being a late complication of LcSSc subset but it may occur earlier in the DcSSc subset in particularly as a complication of severe ILD (Avouac et al, 2010).

The precise cause of PAH is unknown, but it is associated with dysregulation of blood flow that results in vasoconstriction, as is observed in Raynaud's phenomenon. Many factors may play a role in this process with imbalance between the synthesis of vasoconstrictor versus vasodilator molecules by injured endothelial cells.

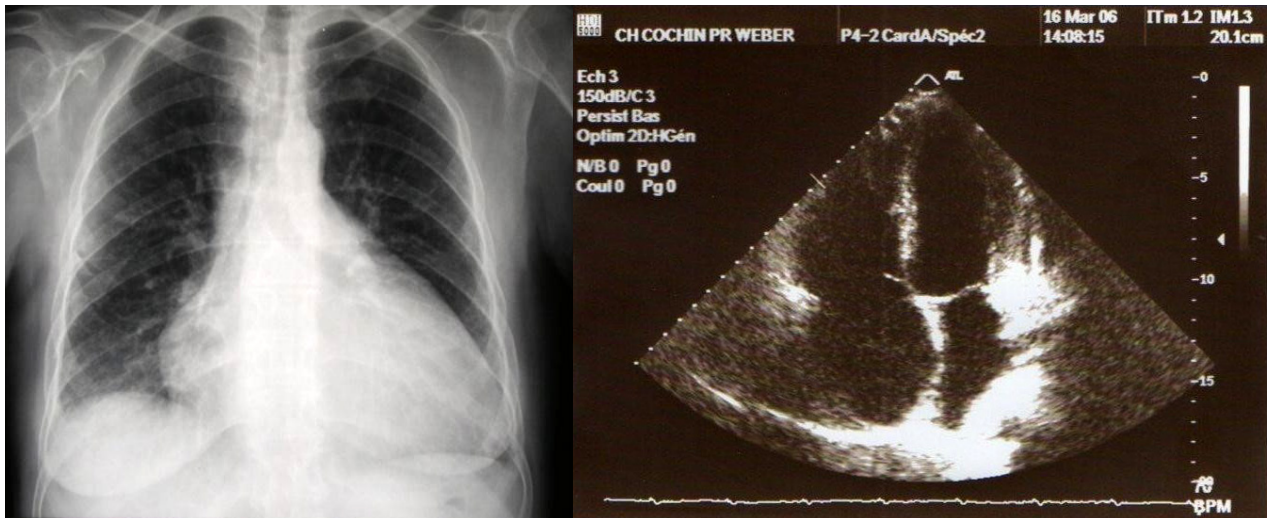
Because of the poor outcome, it is critical to diagnose PAH in an early phase, so that prompt therapy can be initiated while the condition is still reversible. For this reason an early diagnosis is mandatory in order to start an appropriate treatment as soon as possible.

In the earliest stages of PAH, the patient is asymptomatic. Then dyspnoea begins on exertion and later during ordinary activity. Non-specific symptoms such as chest pain, dizziness and fainting may also occur (Ramirez et al, 2004). At physical examination left parasternal lift, an accentuated pulmonary component of second heart sound, a pan systolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary insufficiency, and an RV third sound may be detected. Lung sounds are usually normal.

The ECG may provide suggestive evidence of PAH by demonstrating right ventricular hypertrophy and strain, and right atrial dilatation; however the absence of these findings does not exclude the presence of PAH (Rich et al, 1987).

Doppler echocardiography should be performed periodically, at least annually, also in asymptomatic SSc patients and is the first line tool to assess PAH. This technique cannot only determine the size of the cardiac chambers of the heart and the state of the valves but may also estimate pulmonary arterial pressure – by using the tricuspid regurgitant jet velocity to estimate right ventricular systolic pressure (Fisher et al, 2009). An estimate of right atrial pressure must be added to estimate PAH. Although there is a strong statistical correlation between estimated systolic PAP and mean PAP this can be misleading. Especially in the important estimated range of 30 to 50 mmHg.

Figure 14: Pulmonary arterial hypertension leading to: - Cardiomegaly with dilation of pulmonary arteries and heart cavities on a plain chest X-Ray (Left). - Dilation of the right atrium and ventricle on echocardiography (Right)



Therefore, once PAH is suspected, whatever the reason, right-heart catheterization must be performed (Galie et al, 2009). The following variables must be recorded during RHC: PAP (systolic, diastolic, and mean), right atrial pressure, PWP, and RV pressure. In PAH, vasoreactivity testing should be performed at the time to identify patients who may benefit from long-term therapy with calcium channel blockers. However, a positive testing is very uncommon in SSc-PAH and, therefore, many teams do not perform this test in SSc patients.

The proportion of post-capillary pulmonary hypertension is increasing within SSc patients. This might come from a better recognition of this situation, but also advanced age and/or more myocardial pathology in SSc patients. It becomes a routine practice to perform both right and left heart catheterization on all patients being evaluated for PH. Furthermore, when the capillary pressure and the left ventricular end-diastolic pressure are ≤ 15 mmHg, the patients are investigated using a saline load (500 ml of serum in 10 minutes) to exclude post-capillary causes of the PH, defining in that case occult PVH (Fox et al, 2013).

According to the recent guidelines, cardiac catheterisation is recommended to confirm the diagnosis of PAH, evaluate the severity, and when PAH specific drug therapy is considered. In the follow up it should be performed for confirmation of efficacy of PAH-specific drug therapy and for confirmation of clinical deterioration and for the evaluation of the effect of treatment escalation and/or combination therapy (Sitbon et al, 2005). A longitudinal study investigating survival, risk factors and causes of death in a cohort of patients with SSc without severe pulmonary fibrosis or severe left heart disease at baseline, showed that PAH increased the mortality risk in patients with SSc, suggesting that a yearly echocardiographic screening should be performed in order to make an early diagnosis (Hachulla et al, 2009).

Subclinical PAH may be evaluated through exercise echocardiography, measuring PAP during exercise and allowing to differentiate physiologic from altered PAP responses; this may identify patients that may develop

PAH (Pignone et al, 2007). This tool is under development in order to standardize the testing and determination normal values for controls but a recent report showed that exercise echocardiography may be very helpful to identify a subset of SSc patients with an inappropriate exercise-induced increase in PASP and early signs of right ventricular dysfunction that can relate to very early PAH (D'Alto et al, 2011).

A multicentre longitudinal study on a large cohort of SSc patients has further highlighted the importance of cardiac catheterisation to confirm the diagnosis of PAH; in this study cardiac catheterisation has been performed in patients in which PAH was suspected both on cardiac echo-Doppler (VTR 2.8-3.0 3.0 meters/second) associated with unexplained dyspnoea or only cardiac echo-Doppler with VTR of >3.0 meters/second. Using this algorithm the incidence of PAH was estimated to be 0.61 cases per 100 patient-years (Hachulla et al, 2009). Cardiac catheterization allows also the identification of risk factors of mortality in SSc PAH: in fact measures of RV function (SVI), pulmonary vascular compliance (SV/PP) and pulmonary vascular resistance (PVR), have been found to be strong predictors of survival (Campo et al, 2010).

The determination of the most appropriate indications for RHC in SSc patients is still an issue. But this is of importance since accurate and regular screening for PH in high risk SSc patients is paramount to improve early PH diagnosis, which may improve prognosis and optimise therapy. A Delphi technique among experts has raised the following data with three domains containing eight tools to be taken into account for referring the patients for RHC (Avouac et al, 2014): clinical (progressive dyspnoea over the past 3 months, unexplained dyspnoea, worsening of WHO dyspnoea functional class, any finding on physical examination suggestive of elevated right heart pressures and any sign of right heart failure), echocardiography (systolic pulmonary artery pressure >45 mm Hg and right ventricle dilation) and pulmonary function tests (diffusion lung capacity for carbon monoxide <50% without pulmonary fibrosis).

Discriminatory variables for identifying PAH have also been investigated through a large cross-sectional study of 466 patients (SSc for >3 years of disease duration and predicted pulmonary diffusing capacity for carbon monoxide <60%) all evaluated by a large set of non-invasive parameters and also all by RHC. Some parameters previously identified as associated with of PAH were confirmed, such as FVC/DLCO, telangiectasias, ACA, NTproBNP, right axis deviation on ECG, serum urate was raised as a new parameter, and several echocardiography variables were identified. The authors combined the data to provide a 6 simple assessment in Step 1 of the algorithm to determine referral to echocardiography and then, after adding two echocardiographic variables, to determine referral to RHC (Coghlan et al, 2013). The DETECT algorithm for PAH detection in SSc is a sensitive and non-invasive tool which, it minimises missed diagnoses and can identify milder disease.

To assess the severity of PAH WHO functional class remains a powerful predictor of survival. The New York Heart Association functional classification has been recently modified as shown below:

Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

For objective assessment of exercise capacity, the 6-minute walking test (6MWT) is technically simple, inexpensive and well standardized. However, this criterion has not been fully validated in PAH associated with SSc (Avouac et al, 2010). This test evaluates the distance walked, dyspnoea on exertion (Borg scale) and finger O₂ saturation. Reduced walking distances with O₂ desaturation indicate impaired prognosis in PAH (Miyamoto et al, 2000 ; Paciocco et al, 2001). The disadvantages of this test is that is influenced by body weight, gender, height, age, and patient motivation and also by the systemic component of SSc; indeed myalgia, fatigue, arthritis, calcinosis and also interstitial lung and primary heart disease can influence walking test than does not reflect conversely to idiopathic PAH only lung vessel involvement and secondary heart disease (Avouac et al, 2008).

For PAH diagnosis, biochemical markers are a non-invasive tool for assessment and monitoring of right ventricular dysfunction in patients with PH. Brain natriuretic peptide (BNP) is released from myocardium in response to wall stress and induces vasodilatation and natriuresis. ProBNP is a high molecular weight precursor that is cleaved into biologically inactive N-terminal segment (NTproBNP) and the proper low molecular weight BNP. NT-proBNP has a longer half-life and a better stability both in circulating blood and after sampling are for that reason it is used as a biomarker that reflects the severity of RV dysfunction. Several papers have highlighted good diagnostic and prognostic values of this biomarker (Williams et al, 2006 ; Allanore et al, 2009 ; Steen et al, 2003 ; Allanor et al, 2008).

In addition to the mandatory early diagnosis, many groups are working on the prediction of subsequent development of SSc-PAH. The more robust data have been shown for DLCO and DLCO/VA as these parameters slightly decline several years before the occurrence of PAH and thus may help for risk stratification of SSc patients (Allanore et al, 2008). NT-proBNP may also be helpful in this context and genetic markers may add to the prediction (Manetti et al, 2011 ; Wipff et al, 2010).

IV. 5 Cardiac involvement

Cardiac involvement is common in SSc and contributes to symptoms such as shortness of breath, fatigue, and palpitations (Desai et al, 2011). The heart is often sub-clinically affected by fibrosis involving both the myocardium and the conducting system. This involves both ventricles with a “patchy” distribution and can be distinguished from that occurring in atherosclerotic coronary artery disease by a number of histological features, such as the absence of a link to any single coronary artery and of typical hemosiderin deposits and involvement of the subendocardial layers (Bulkley et al, 1976). SSc heart disease has been shown in up to 80% of SSc patients, and it may be classified as primary or secondary to other organs involvement, mainly lung involvement. SSc-heart disease is often asymptomatic for a long time and, when recognized, is associated with a poor prognosis (Ferri et al, 2002).

Cardiac involvement in SSc is likely to result from the general pathogenetic mechanism(s) thought to play a role in the disease. A “myocardial Raynaud’s phenomenon” involving unaltered small arteries has been hypothesized, but conflicting results have been reported. On the one hand, reversible perfusion defects have been detected in a significant percentage of SSc patients. On the other hand, coronary vasodilator reserve has been found to be markedly reduced in SSc. Nevertheless, reproducible data have shown that primary heart disease relates to microcirculation impairment with abnormal vasoreactivity, with or without associated structural vascular abnormalities; therefore, reversibility maybe seen at early stage but it decreases with the progression of the disease and may at advanced stage reduce coronary reserve.

Autonomic neuropathy in SSc has been reported by various authors using conventional laboratory tests (Ferri et al, 1997). Tachyarrhythmias are excessively rapid and irregular heartbeats. They usually do not cause any symptoms, but they are often fatal, and SSc patients with heart involvement are susceptible to them (Kostis et al, 1988). The worst prognosis in severe cardiac arrhythmias is significantly more frequent in those patients with both skeletal and cardiac muscle involvement (Follansbee et al, 1993).

Early recognition of cardiac involvement and diagnosis of cardiotoxicity allow early treatment, prevention of cardiomyopathy and improvement in prognosis. Thus, a thorough heart-function screening and appropriate follow-up monitoring are mandatory for all SSc patients.

Table 8. Summary of the Cardiac involvement symptoms, mechanisms and tools for assessment

	Symptoms	Mechanisms	Assessment
Pericardium	Chest pain Shortness of breath Palpitations	Inflammation	Echocardiography EKG
Myocardium Heart cavities	Shortness of breath Exercise intolerance Coughing or wheezing Oedema High heart rate	Ischemia Fibrosis Inflammation Left or right sided heart failure	Echocardiography Natriuretic peptides Radionuclide ventriculography Cardiac catheterisation MRI
Valves	NA	NA	NA
Electrical system	Syncope, dizziness irregular and unreliable heart beats Palpitations Cardiac arrest	Conduction problem Arrhythmia	EKG 24h-Holter

The screening consists of various simple, non-invasive investigations:

-physical examination

-electrocardiogram that may confirm conduction abnormalities and arrhythmias; a 24 hour monitoring should be performed since the incidence and prevalence of ECG disturbances increases when the patients are monitored with 24-h ambulatory ECG.

-chest X ray to investigate pericardial effusion and/or alteration of cardiothoracic ratio.

-Doppler 2-dimensional echocardiogram that provide information left ventricular

ejection fraction (LVEF), diastolic function, tricuspid gradient, pulmonary acceleration time, right ventricular diameter and pericardial effusion, wall motion and the possible presence of PAH.

With improved echocardiographic techniques including the use of Doppler tissular indexes, increased awareness of diastolic dysfunction and primary right ventricle involvement in SSc has been reported together with more accurate assessment of systolic functions. Therefore, including tissular Doppler is highly recommended to assess heart function (Meune et al, 2008). Diastolic dysfunction has emerged as a critical concern and may be frequent in SSc patients; it can lead to post-capillary pulmonary hypertension that requires specific therapy.

Indeed, in SSc patients differentiation between pre- and post-capillary pulmonary hypertension (PAH versus pulmonary venous hypertension-PVH) is sometimes difficult with commonly borderline patients. A study based

on 107 SSc patients of whom 53 out of 107 patients had pulmonary hypertension demonstrated the input of performing a fluid challenge (500 ml of serum in 10 minutes) and also of measuring left ventricular end-diastolic pressure (Fox et al, 2013). Indeed, after considering the resting and post-fluid-challenge measurements, 11 PAH patients were reclassified as occult PVH. It is therefore highly recommended to add to the assessments a fluid challenge and to add sometimes a left heart catheter to measure left ventricular end-diastolic pressure in addition to the wedge pressure, to accurately identify PVH.

Asymptomatic, mild pericarditis is common in SSc and does not require specific treatment in the large majority of patients. In the case of recurrent or severe effusion, anti-inflammatory drugs may be required. Renal as well as cardiac monitoring is critical in such cases since pericarditis may be associated with scleroderma renal crisis, cardiac arrhythmias, pulmonary arterial hypertension and overall progression of the disease.

NT-ProBNP may be useful for the diagnosis of cardiomyopathy because its concentration is altered in patients with myocardial structural impairment, even if asymptomatic, while troponin I is an accurate index of myocytolysis (Mady et al, 2008). It allows the detection of any abnormal strain in the heart and identifies patients who need more in depth cardio-pulmonary investigations in order to establish the cause.

When needed, additional tests may be performed, including long-term ambulatory electrocardiographic recording, assessment of cardiopulmonary performance by the six-minute walking test or cardiopulmonary stress test, cardiac catheterization (mandatory to confirm and better estimate PAH), cardiac magnetic resonance imaging, and nuclear studies of myocardial function and perfusion (Allanore et al, 2008). In particular Tc-99 SPECT using vasodilators (dipyridamole) allows to demonstrating the presence of inducible ischemia. Dipyridamole causes vasodilation through the increase of adenosine locally. This vasodilation occurs in healthy arteries, whereas stenosed arteries remain narrowed. This creates a "steal" phenomenon where the coronary blood supply will increase to the dilated healthy vessels compared to the stenosed arteries. Cardiac MRI allows the evaluation of coronary reserve and may also demonstrate the presence of inflammatory oedema or fibrosis; it is the examination of choice when myocarditis is suspected such as in overlap syndrome. Furthermore, contrast enhanced-cardiac MRI showed in asymptomatic SSc patients with long-standing disease the presence of myocardial fibrosis unrelated to coronary arteries distribution without sub-endocardial layer involvement, suggesting a subclinical heart involvement (Di Cesare et al, 2013).

The following cardiac diagnostic work-up for investigations of electrophysiological disturbances in SSc patients has been proposed (Table 9) (Vacca et al, 2013)

Table 9: cardiac diagnostic work-up for investigations of electrophysiological disturbances

Clinical manifestations	Electricophysiological assessment	Heart assessment
Fatigue Palpitations Syncope, fall Dizziness	<i>Routine:</i> <ul style="list-style-type: none"> • CV risk factor assessment • Standard 12-lead ECG • 24-h Holter monitoring <i>Second level:</i> <ul style="list-style-type: none"> • Exercise testing • Upright tilt-table testing • Invasive electrophysiological studies • Measurement of HRT and HRV 	<i>Routine:</i> <ul style="list-style-type: none"> • Doppler echocardiography • Tissue Doppler echocardiography • Natriuretic peptides <i>Second level:</i> <ul style="list-style-type: none"> • Coronary angiography • Right heart catheterization • Cardiac MRI

IV.6 Kidney involvement

Kidney involvement is often clinically silent. It may progress slowly toward renal failure and thus heavily influence prognosis. In some cases, breakdown of the renal system may be abrupt, without any sentinel symptom.

Sudden onset of high blood pressure and kidney failure is known as scleroderma renal crisis (SRC). Patients with diffuse cutaneous (DC) involvement, particularly those with early, rapidly progressive skin thickening and serum anti-RNA polymerase III antibody, are at highest risk to develop SRC (128). The typical presentation is that of a stable patient who abruptly develops severe arterial hypertension accompanied by headache, visual disturbance, seizures, congestive heart failure, pericardial effusion, microangiopathic haemolytic anaemia, thrombocytopenia and accelerated oliguric renal failure. The optic fundi show acute hypertensive changes, including haemorrhages and exudates.

Other findings include microscopic haematuria and proteinuria; occasionally RBC casts are seen in the urine (Phan et al, 1999 ; Steen, 1996 ; Lee et al, 2004). The plasma renin level is extremely high, as found in malignant essential hypertension. Renal biopsy characteristically shows changes in the small interlobular and arcuate arteries. The earliest change is intimal oedema, followed by an intense proliferation of intimal cells increased mucopolysaccharide deposition. Lymphocytes and other mononuclear cells are absent.

Fibrinoid necrosis in the vessel walls or sub intimal location is typical of severe cases in small arteries.

This usually occurs in patients with diffuse scleroderma, resulting in kidney failure within a few days. Thus, to detect sudden kidney failure promptly, daily at-home monitoring of blood pressure

is recommended for SSc patients, and particularly for those with diffuse scleroderma, even if they do not have high blood pressure or other renal symptoms.

Chronic kidney disease other than renal crisis is not well described. Kidney abnormalities such as proteinuria, hypertension, or abnormal serum creatinine does not predict future renal crisis. It has been presumed that such abnormalities reflect the vasculopathy that occurs pathologically in patients with scleroderma even in the absence of renal crisis. Colour Doppler ultrasonography can confirm the early reduction of renal arterial blood flow in patients with SSc who have no clinical sign of renal involvement. Abnormal findings on renal function tests (serum creatinine, creatinine clearance, 24-hour proteinuria) may be observed at a later stage (Kovalchik et al, 1978) of the disease. It has also been demonstrated that most patients with SSc cannot increase renal filtration under the challenge of a protein overload. This defective renal response to the amino acid load test sustains the concept of the prevalence of vasoconstrictor over vasodilating factors in the kidney of these patients (Livi et al, 2002).

IV.7 Musculoskeletal involvement

Many patients may develop musculoskeletal symptoms as an early sign of the disease or during the course of their illness. Manifestations may include varying degrees of rheumatic complaints ranging from arthralgias to frank arthritis or bony lesions. Musculoskeletal involvement has been shown to strongly contribute to disability and impaired quality of life in SSc, reducing the performance of everyday occupation (Baron et al, 1982 ; Mau et al, 2005 ; Brower et al, 2004 ; Poole et al, 2000 ; Poole et al, 1991).

IV.7.1 Joint involvement

IV.7.1.1 Prevalence

Joint involvement has been described as an initial manifestation in 12% to 65% of SSc patients with SSc and as an eventual manifestation in up to 46% to 97% of patients (Poole et al, 1991 ; Tuffanelli et al, 1961). The systematic cross-sectional examination of the EUSTAR (EULAR Scleroderma Trials and Research) registry, including more than 7,000 patients, identified synovitis in 16% (1191/7286) of SSc patients, underlining that a synovial involvement may not uncommonly occur in SSc (Avouac et al, 2010). The point prevalence of joint contracture, resulting from joint destruction turning into ankylosis and fibrotic changes in the skin, was 31% (2264/7286) in this database. The latest EUSTAR data regarding respective prevalence of musculo-skeletal symptoms are provided in figure 14. These data of prevalence have been subsequently confirmed in the recent analysis of EUSTAR database (table 5).

Recently, a preliminary study included 45 consecutive patients with SSc using ultrasonography (Cuomo et al, 2009). Joint effusion was found in 22 (49%) SSc patients and synovial proliferation in 19 (42%), which was associated with a power Doppler in 11 of them. In this study, the prevalence of synovitis as detected by

ultrasounds was found to be significantly higher than that found by clinical examination. Another series confirmed that articular involvement is underestimated by a single clinical examination (Elhai et al, 2012). It showed that synovitis and tenosynovitis were more frequently detected with US (46% and 27%, respectively) than with clinical examination (15% and 6%, respectively; $P < 0.01$ for both comparisons). Furthermore, it demonstrated that when inflammation was detected (57% of synovitis), it was mostly of weak intensity (Doppler grade 1), and that tenosynovitis could be either inflammatory or fibrotic (with layered appearance) and finally, that, calcifications could be detected in about half of the patients.

Magnetic resonance imaging (MRI) is also a very promising tool to detect synovitis. Hand inflammatory joint disease has been assessed by MRI in 17 patients with history of joint pain or swelling (Low et al, 2009). Ten patients had inflammatory MRI findings with synovitis ($n=8$), joint effusion ($n=7$) or tenosynovitis ($n=8$). In line with the progresses made in rheumatoid arthritis, these tools are under development to better evaluate and manage arthritis and tenosynovitis in SSc.

IV.7.1.2 Characteristics

Arthralgia is among the most frequent presenting symptoms of SSc. True joint inflammation may occur and be the source of initial diagnostic confusion. The onset may be acute or insidious, oligoarticular, or polyarticular in pattern. The course of the joint manifestations is either intermittent or chronic remittent. Clinical findings are often minimal at the onset, aside from features that may betray the presence of early SSc. Some patients may exhibit localized joint tenderness, or swelling, and joint effusion may be detectable although they are usually mild.

The analysis of the EUSTAR database revealed that synovitis was present in SSc patients in all disease stages. However, patients with synovitis and early disease (date of first non-Raynaud symptom < 5 years) were more likely to experience diffuse cutaneous thickening. The likelihoods of severe vascular (elevated systolic pulmonary artery pressure above 40 mmHg) and muscular (muscle weakness) involvement were higher in patients with synovitis, regardless to their cutaneous subset or their disease duration (Avouac et al, 2010). Thus, synovitis could be a risk factor of bad prognosis in SSc. Two recent prospective cohort studies including patients from the EUSTAR database have identified joint synovitis as a predictor of disease progression. The first study included 1,301 SSc patients with disease duration ≤ 3 years at inclusion and with a follow-up of at least 2 years (mean follow-up : 4.5 ± 2.2 years) (Avouac et al., 2014). Joint synovitis, detected by clinical examination, was independently predictive of the worsening of the modified Rodnan skin score ($\geq 30\%$ and ≥ 5 points) and of the further occurrence of new ischemic digital ulcers and decreased left ventricular ejection fraction. The second study was performed on 637 SSc patients with the diffuse cutaneous subset (Maurer et al., 2014). Joint synovitis was also identified in univariate and multivariate analysis as a predictor for progressive skin fibrosis. Using a second validation cohort of 188 dcSSc patients, joint synovitis were confirmed

as independent predictors of progressive skin fibrosis within 1 year. Taken together, the results of these two studies support that synovitis, an easily detected clinical marker may be useful for the risk stratification of SSc patients.

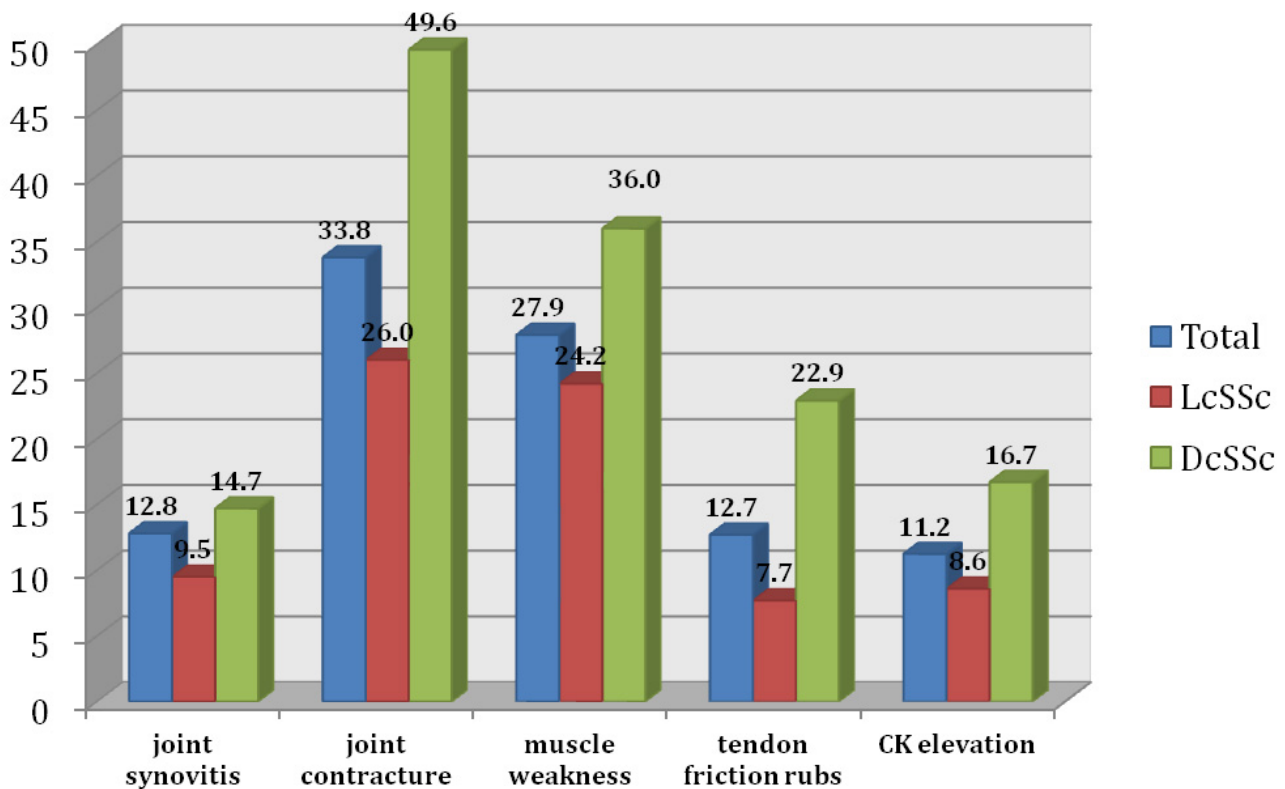
The presence of synovitis may be also related to an overlap with rheumatoid arthritis (Avouac et al, 2006 ; Cohen et al, 1982 ; Armstrong et al, 1982 ; Baron et al, 1982). Recent data support that overlaps of SSc and rheumatoid arthritis is very unusual. The prevalence of SSc-rheumatoid arthritis overlap seems close to 1-5% and its incidence is 5% (Avouac et al, 2010). Rheumatoid factor positivity may occur in about 30% of SSc patients. This test seems non-specific and do not serve to distinguish SSc patients with musculoskeletal manifestations from those not so affected. The search for anti-CCP antibodies might be of great help in the identification of the rare cases of SSc-RA overlap.

IV.7.1.3 Evaluation of structural damages

Many distinctive radiographic abnormalities have been recognized in patients with SSc. The frequency of hand radiographic erosions is estimated between 5% and 40% (Avouac et al, 2006 ; Blocka et al, 1981 ; La Montagna et al, 2005 ; Koutaissoff et al, 2011 ; Avouac et al, 2011 ; La Montagna et al, 2002). Joint space narrowing is not uncommon in SSc; its point prevalence on X-Ray has been reported to be about 30%, with a predominant involvement of DIP joints. Joint space narrowing has been found with ultrasonography in 8/45 (18%) SSc patients (Cuomo et al, 2009).

Modern techniques such as ultrasound and magnetic resonance have also been used to describe structural articular lesions. In the two studies using MRI, hand erosions were detected in 16% (6/38 patients) and 41% (7/17 patients) (Low et al, 2009; Allanore Y et al, 2007). In a recent controlled study involving 120 patients, erosive arthritis, as defined by the occurrence of both erosions and joint space narrowing, was found in 22 (18%) SSc patients (Avouac et al, 2006). The five-year longitudinal follow-up of these patients, with a systematic examination of dual time-point X-Rays, showed a total radiographic progression of erosive arthritis in 24 (23%) patients with SSc (Avouac et al, 2011). No independent predictor of the progression of erosive arthritis has been identified in SSc. This lack of predictive factor for erosive arthritis might be related to the multifactorial aspects of SSc arthropathy.

Figure 15: prevalence (% positive patients) of musculo-skeletal manifestations throughout 11318 registered SSc patients (unpublished data, Database extraction May 2014)



IV.7.2 Soft tissue, bone, and muscular involvement

In the EUSTAR database, the point prevalence of tendon friction rubs, defined as a leathery, rubbing, “squeaking” sensation detected as the tendon was moved actively or passively, was 11% (802/7286 patients) (Avouac et al, 2010). Rodnan and Medsger described this finding as “leathery crepitus” on palpation of the knees, wrists, fingers and ankles during motion in 19 of 53 patients (Rodnan et al, 1968). In the leg, tendon rubs are usually localized to the tibialis anterior, or less frequently, the peroneus muscles. In the forearm the source of this rub is usually the tendons of the flexor or extensor muscles, immediately proximal to the wrist. Median nerve compression with carpal tunnel syndrome may occur, the result, presumably of changes in the tendon sheaths beneath the transverse carpal ligament.

The prevalence of tendon involvement has been assessed by MRI in a preliminary study performed on 17 patients; eight had tenosynovitis, either of flexor (n=7) or extensor (n=3) tendons (Low et al, 2009). The frequency of tendon involvement has not yet been assessed by ultrasounds. However, this examination, as well as MRI, might be useful to discriminate fibrotic tenosynovitis secondary to fibrous deposits on the surface of the tendon sheaths and inflammatory tenosynovitis.

Tendon involvement is more prevalent in patients with the diffuse cutaneous subset and early disease. It is also associated with signs of severe vascular, muscular, renal involvement and decreased survival (Steen et al,

1997). In particular, the cross-sectional analysis of the EUSTAR database highlighted the independent association in multivariate analysis between tendon friction rubs and digital ulcerations, muscle weakness, pulmonary fibrosis on plain chest X-ray and proteinuria detected with a urinalysis dipstick. Another cohort showed that early DcSSc patients with TFRs have a about 2-fold risk of developing renal crisis and cardiac or gastrointestinal disease complications, even after adjustment for other known risk factors. Furthermore, even after age and gender adjustment, TFR cases were 1.8 times more likely to die at 5 years (95% CI 1.21–2.58, $P < 0.003$) (Doré et al, 2013). The recent prospective analysis of the EUSTAR database has also confirmed that tenosynovitis was an independent predictor of skin progression and of the further occurrence of scleroderma renal crisis (Avouac et al., 2014). Altogether, these results highlight that tendon friction rubs are an important physical finding, because they often precede widespread skin thickening and can be considered as a sign highly predictive of bad outcome.

Subcutaneous calcifications may be seen as a hallmark of SSc in comparison to other connective tissue disorders. Recent studies using consecutive X-rays or ultrasonography have allowed to clarify its point prevalence, which is about 20 to 30% (Avouac et al, 2006 ; Blocka et al, 1981 ; La Montagna et al, 2005 ; Koutaissoff et al, 2011; Avouac et al, 2011 ; La Montagna et al, 2002). The incidence of radiographic calcinosis after a median duration of 5 years is about 14% (Avouac et al, 2011). Calcinosis may also occur in other locations such as feet, knees and legs. It is noteworthy that it predominates at sites of repetitive stress or pressure, suggesting that trauma and/or ischemia may contribute to its pathogenesis as this is well known for shoulder calcifications. This has been strengthened by recent cross-sectional series showing a link between calcinosis, acro-osteolysis and digital ulcerations (Avouac et al, 2006). In addition, digital ulcers have recently been identified as independent predictors of radiographic progression of calcinosis.

Osseous resorption is a common finding and acro-osteolysis occurs in about 20% of the patients. Further other locations may be involved such as carpal bones, radius, ulna, ribs, mandible, clavicle, humerus or cervical spine (Mugino et al, 2006). Calcinosis and digital ulcers were recently identified as independent predictors of the radiographic progression of acro-osteolysis (Avouac et al, 2011). These data suggest that patients with severe digital vasculopathy are more at risk to experience radiographic progression of bone resorption and further support the role of vascular injury playing a critical role in such lesions, possibly due to repeated vasospasm, as previously suggested (Scharer et al, 1969). Other pathogenic hypotheses, such as vitamin D deficiency, have also to be taken into consideration, although they are still a matter of debate (Braun-Moscovici et al, 2008 ; Vacca et al, 2009).

Osteoporosis had not been the matter of many studies probably because SSc has many complications and also because it is not a very inflammatory disease. Nevertheless, among 1712 Taiwanese SSc patients (78% female, mean age 50 years) with a median follow-up of 5.2 years, 54 patients developed vertebral fractures, 17 hip fractures, and 7 radius fractures (IR: 6.99, 2.18 and 0.90 per 1000 person-years, respectively). Compared with

the controls, the incidence rate ratios (IRRs) (95% CIs) among SSc patients were 1.78 (1.30 to 2.39, $p<0.001$) for vertebral fractures and 1.89 (1.05 to 3.22, $p=0.026$) for hip fractures. The IRRs for overall OFs were 1.74 (1.32 to 2.27, $p<0.001$) for women and 1.06 (0.33 to 2.66, $p=0.856$) for men. Multivariable analyses indicated that older age, being female, using daily prednisolone equivalent to >7.5 mg, and bowel dysmotility treated with intravenous metoclopramide are associated with osteoporotic fracture (Lai et al, 2015). Therefore, osteoporosis in female patients should be a concern in SSc patients.

SSc related myopathy is frequent in SSc, involving up to 80% of SSc patients (Clements et al, 1978). This myopathy is often mild, non-progressive, with minor proximal weakness, and normal or slight elevation of creatine kinase (CK). The overlap between inflammatory myositis and SSc is less frequent, with a prevalence of about 5% (Tuffanelli 1962). This manifestation is characterized by proximal weakness, elevated CK typical EMG and histology of inflammatory myositis and presence of Anti-PmScl antibodies (Ranque et al, 2009).

V. Disease activity

In the assessment of SSc patients, the evaluation of different clinical features should be assessed, from diagnosis to clinical response to treatments. Defining disease activity in SSc could not be easily done using a single variable: i. patients may experience a heterogeneous course, from relative benign and indolent forms to rapidly progressive forms; ii. SSc flares can be difficult to separate from quiescent disease; iii. the two main morphological manifestations of the disease (interstitial fibrosis and vascular occlusion) may both reflect activity, which is still potentially reversible and/or damage, classically irreversible; iv. validated biological markers reflecting disease activity are still lacking. In 2001, 11 SSc disease activity variables were identified and a preliminary activity index was developed, which has been used to assess disease activity in subsequent studies. The validity of this activity index is supported by its correlation with the physician global assessment of activity of the Canadian Scleroderma Research Group, its association with anti-Scl70 titre and its role as the main predictor of the scleroderma phenotype of SSc skin fibroblasts (Valentini et al, 2011). However, it displayed some limitations mainly due to the procedure underlying its development such as most patients had long disease duration and the number of missing values was high. On these bases, more recently, a revised SSc activity index has been developed. Specifically, a weighted 10-point activity index was identified and validated: Δ -skin=1.5 (Δ =patient assessed worsening during the previous month), mRss >18 =1.5, presence of digital ulcers=1.5, presence of tendon friction rubs=2.25, CRP >1 mg/dL=2.25 and DLCO predicted $<70\%$ =1.0. A cut-off ≥ 2.5 was found to identify patients with active disease. To date, changes in the index paralleled those of Medsger severity score (Valentini et al, 2017). The revised EUSTAR index contains tendon friction rubs and increased serum CRP that have been associated with reduced survival and worsening of skin fibrosis (Avouac et al, 2016; Muangchan et al, 2012). Similarly, to the previous one, the revised EUSTAR index contains mRss, digital ulcers and DLCO. mRss reflects the degree of skin sclerosis and has long been considered a measure of disease activity in SSc (Walker et al, 2010). Nevertheless, the persistence of defined skin sclerosis is not

consistent with inactive disease. Digital ulcers are clearly related to vascular disease activity and have been recently found to predict the occurrence of new digital ulcers during follow-up and to be associated with cardiovascular morbidity and decreased survival (Mihai et al, 2016). A decreased DLCO can depend on both vascular and interstitial lung disease. In the absence of pulmonary hypertension, however, it has been found to provide the best overall estimate of HRCT-measured lung fibrosis (Valentini et al, 2017).

VI Treatment

VI.1 Overall treatment

Severe forms of the disease and rapidly progressive diffuse SSc in particular, are associated with significant mortality (estimated at 40%-50% in 5 years) secondary to pulmonary, cardiac, and renal involvement (Medsger et al, 1971 ; Altman et al, 1991). No proven effective therapy exists to prevent disease progression. The perceived failure of immunosuppressive treatments in the reversal of established fibrosis suggests that once initiated, the fibrotic process becomes independent of the immune drive and continues as an autonomous process.

Blinded randomized clinical trials of D-penicillamine failed to demonstrate a clinically significant effect (Clements et al, 1999). Low-dose oral methotrexate showed beneficial effects on skin thickening, but not on organ dysfunction, in a small placebo-controlled crossover study (Van den Hoogen et al, 1996).

Cyclophosphamide (Cyc) has been shown to improve skin thickening, stabilize pulmonary function, and increase survival in non-randomised trials (Akesson et al, 1994 ; White et al, 2000). Although the efficacy of Cyc is considered moderate, this is currently the only drug with proven efficacy in SSc interstitial lung disease and for that reason has been recommended as the drug of choice in progressive lung involvement (Avouac et al, 2009; Kowal-Bielecka et al, 2009).

Biologic therapies target molecules involved in the mechanisms of the immune system, such as cytokines (TNF- α , IL-6), immune cells (B cells) or co-stimulation molecules (CTLA4). Several of these pathways could contribute to SSc and the experience learned from other immune diseases promote the evaluation of biologics in SSc. Several trials are underway but some preliminary data highlight potential benefit. In a double-blind, placebo-controlled, phase 2, proof-of-concept study, the effect of tocilizumab (TCZ-162 mg SC weekly) was investigated in 87 DcSSc patients ≤ 5 years of disease duration, with modified Rodnan skin score (mRSS) 15-40, and elevated acute-phase reactants. At week 24, a favourable but not statistically significant effect of TCZ over PBO on mRSS was noted (-3.9 vs -1.2 ; adjusted mean difference, -2.7 [95% CI: -5.85 , 0.45], $p=0.09$). At week 48, a numerically larger change was noted in the TCZ vs PBO arm (-6.3 vs -2.8 ; adjusted mean difference, -3.6 [95% CI: -7.23 , 0.12], $p=0.06$). There were numerically greater improvements in the TCZ arm than in the PBO arm for patients reported outcomes (HAQ-DI, patient global assessment and FACIT-fatigue) at week 48. Of interest, fewer TCZ vs PBO patients showed a decline in forced vital capacity. Adverse events (AEs)/serious AEs occurred

in 98%/33% of TCZ and 91%/34% of PBO patients by week 48. One death occurred in the PBO arm and 3 deaths in TCZ patients by week 48; all were unrelated to study drug except for a fatal lung infection in one TCZ patient. Overall, the effect of TCZ on skin sclerosis, PROs, and pulmonary function and the observed safety profile suggest a positive risk/benefit profile for TCZ in SSc (Khanna et al, 2016).

An elegant study allowed by the EUSTAR database compared RTX treated versus untreated matched-control SSc patients. It demonstrated improvement of skin fibrosis and prevention of worsening lung fibrosis, supporting the therapeutic concept of B cell inhibition in SSc (Jordan et al, 2014). This supports the performance of a randomised trial to determine whether anti-CD20 therapy might be efficient against the fibrotic process in SSc.

A first double-blind placebo controlled randomized clinical trial evaluating IV immunoglobulins included 63 dcSSc patients. MRSS at 12 weeks showed no significant difference between the IVIg and placebo, but when re-administering IVIg to those patients who showed mRSS improvement ≥ 5 points, a significant difference in mRSS change was seen between double and single IVIg administrations. Therefore, although the primary endpoint was not achieved, repeated administration of IVIG may be effective for skin sclerosis (Takehara et al, 2013) and another trial is ongoing (NCT01785056).

In the past decade, intense immunosuppression followed by autologous stem cells transplantation (HSCT) has emerged as a new therapeutic procedure for patients affected by severe SSc that is refractory to conventional treatments (Tyndall et al, 2003). A phase I-II trial showed improvement in the skin score ($>25\%$ in 69% of the patients), stabilization of lung function and pulmonary pressure, and no occurrence of renal crisis after the treatment (Farge et al, 2002). The initial procedure-related mortality observed was particularly elevated (17%), probably owing to the already advanced organ damage of most participants (Farge et al, 2004). The results of the ASTIS trial, a randomized controlled trial of autologous HSCT vs. pulse monthly cyclophosphamide, showed from 156 early DcSSc patients better event-free survival and overall survival and clinically meaningful improvements (skin, forced vital capacity), although this is balanced by a high toxicity (in the HSCT arm, 8/79 patients died of treatment-related causes in the first year) (van Laar et al, 2014). Selection criteria for patients who might benefit from such procedure remain to be determined.

VI.2 Treatment of specific organ involvements

VI.2.1 Gastro-intestinal involvement

Treatment of oesophageal disease in SSc is based, first of all, on modifications in lifestyle. Gravity plays an important role in controlling reflux. To minimize the possibility of heartburn, it is recommended that an upright posture be maintained until a meal is digested and avoid exertion after a meal (Table 7). The medications prescribed to treat oesophagus dysmotility and reflux are promotility agents, H2 blockers, and

proton pump inhibitors. Despite the lack of specific RCT, PPI have been recommended for the prevention of SSc-related gastro-oesophageal reflux, oesophageal ulcers and strictures. Prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction) (Emmanuel et al, 2004 ; Tiev et al, 2011).

Because these agents work in different ways, combination therapy employing two or more of these drugs may be especially helpful in controlling symptoms (Table 7).

Malabsorption and enterocyte dysfunction further degrade the health of the gut by reducing local and systemic nutrition delivery. When bacterial overgrowth is caused by slow transit through the small bowel, broad-spectrum antibiotics are indicated for a few days per month, and patients should reduce or avoid fats and fibre in their diet in an effort to reduce abdominal symptoms such as constipation and distension. The bowel can remain atonic and nonpropulsive, causing fermentation and bacterial overgrowth. In early phases, treatment with octreotide can stimulate small bowel function, helping to reduce bacterial overgrowth.

Table 10: Treatments for gastro-intestinal involvement

GI	Intervention
Esophagus	Lifestyle modifications : avoiding taking food late, fat foods and chocolate (reduce LES pressure), spicy foods and alcohol (heartburn), cessation of smoking -> multiple small meals -> raising the head of bed Acid suppressive medication: proton pump inhibitors: reduce symptoms, improve Phmetry, heal oesophagitis
Stomach	Prokinetic agents (i.e., metoclopramide, domperidone, low-dose erythromycin) Percutaneous gastrostomy GAVE: iron replacement therapy and red blood cells transfusion, endoscopic ablation, exceptional surgical antrectomy
Intestine	Antibiotics Supportive nutrition Prokinetic agents: octreotide
Ano-rectal	Solidifying liquid feces, biofeedback and sacral nerve stimulation Surgical intervention to treat rectal prolapse or perforation

VI.2.2 Interstitial lung disease

At present, the pulmonary involvement is considered the main cause of mortality, in SSc patients. Currently, the management of SSc-ILD is related to immunomodulation. In fact, non-selective immunosuppressive drugs such as CYC and mycophenolate mofetil are still the most widely used medications (Iudici et al, 2015).

The effects of both pulses and oral Cyc on lung involvement in SSc have been reported in double-blinded placebo controlled randomized trials, where Cyc seems moderately helpful in stabilizing lung function. The

efficacy and safety of oral or pulse CYC in the treatment of SSc–ILD disease were shown in two randomized clinical trials (RCTs): the Scleroderma Lung Study (SLS) (Tashkin et al, 2006) and the Fibrosing Alveolitis in Scleroderma Trials (FAST), respectively (Hoyles et al, 2006). The SLS study showed that 1 year of oral CYC (≤ 2 mg/kg/day for 12 months followed for an additional 1 year) improved lung function, skin scores, dyspnea and health status/disability, and these effects may persist, for several months after CYC discontinuation. However, except for a sustained impact on dyspnea, all of these effects waned and were no longer apparent at 24 months. The FAST study did not show an improvement in the primary (FVC or DLCO) or secondary endpoints in the CYC group. However, for FVC, there was a trend toward statistical significance between the 2 groups. It must be pointed out that, despite of several studies support the effectiveness of CYC therapy in preventing a decline in lung function and premature death in SSc–ILD patients, recent systematic review and meta-analysis of RCTs and observational prospective cohort studies failed to confirm any clinically significant improvement in pulmonary function in SSc patients treated with CYC (Nannini et al, 2008; Poormoghim et al, 2012). Recently, SLS II, a study in which SSc–ILD patients were treated with mycophenolate mofetil for 2 years or CYC for 1 year, showed that both the treatment resulted in a significant improvement in the pre-specified measures of lung function over the 2-year course of the study. Mycophenolate mofetil was better tolerated and associated with less toxicity. However, the hypothesis that it would have higher efficacy at 24 months than CYC was not confirmed (Tashkin et al, 2016).

Although small case series and retrospective studies suggested the use of azathioprine as maintenance immunosuppressive treatment for SSc–ILD, a randomized unblinded clinical trial, comparing CYC and azathioprine (a purine analog), as first-line treatment, did not provide any evidence of efficacy for azathioprine in the treatment of SSc patients affected by ILD (Nadashkevich et al, 2006).

Pirfenidone is a pyridone showing both anti-inflammatory and anti-fibrotic effects, it has been approved for the management of patients with idiopathic pulmonary fibrosis. Pirfenidone was administered as a compassionate treatment in 8 patients with idiopathic pulmonary fibrosis and 2 patients with SSc–ILD. The drug was overall well tolerated, and although it did not improve survival, it stabilized the effects on progressive pulmonary fibrosis (Nagai et al 2002; Miura et al, 2014). Recently, the LOTUSS study, a phase II, open-label, randomized, 16-week study was designed to assess the safety and tolerability of pirfenidone in patients with SSc–ILD. The drug showed an acceptable tolerability profile that was not affected by concomitant treatment with MMF, but results about efficacy are still not available (Khanna et al 2015b).

Imatinib, a tyrosine kinase inhibitor, may be a therapeutic option for SSc patients. The open-label studies conducted to assess the safety and effectiveness of imatinib mesylate in the treatment of dcSSc showed a statistically significant improvement in FVC and also in skin thickening (Spiera et al 2011; Khanna et al, 2011; Fraticelli et al 2014).

Several alternative approaches may be considered in ILD-SSc, including B cell depletion therapies (rituximab; RTX), bosentan, anti-TGF- β antibody, anti-IL-6 antibody, anti-IL-13 antibody, and HSCT. Finally, lung transplantation may be considered but it is limited to those patients, with severe SSc-ILD, unresponsive to pharmacologic interventions and without significant comorbidities (Giacomelli et al, 2017).

VI.2.3 PAH Calcium channel blockers (such as nifedipine or diltiazem) can be effective in patients with a positive vasoreactivity test (Chaisson et al, 2013) but this is very unusual in SSc patients and therefore high dose of calcium channel blockers is exceptionally recommended.

Several endothelin antagonists are now on the market and although no trial was specifically performed in SSc-PAH, the post-hoc analyses coming from the large RCTs performed in PAH have shown some efficacy.

Bosentan, a mixed ETA and ETB endothelin receptor antagonist showed to reduce dyspnoea and improved ability to perform normal daily activities (Joglekar et al, 2006 ; Ahmadi-Simab et al, 2005). Macitentan is a dual endothelin antagonist characterized by sustained receptor binding and enhanced tissue penetration. It has demonstrated a reduction of morbidity and mortality among patients with pulmonary arterial hypertension (Pulido et al, 2013). Benefits were shown both for patients who had not received treatment previously and for those receiving therapy for pulmonary arterial hypertension at study entry. Data in SSc-PAH have not been analysed independently. Ambrisentan, a selective ETA blocker, has determined a significant improvement in exercise capacity and decrease in time to clinical worsening, along with evidence to support an improvement in WHO functional class and quality of life (Galie et al, 2005).

Other licensed therapies include PDE5 inhibitors. Sildenafil was shown to improve 6MWT, functional class and haemodynamics (mean PAP and PVR) and has been approved for the treatment of patients in NYHA class II, III and IV (Galie et al, 2005). Tadalafil, as a tablet with a recommended dose of 40 mg, is the first daily phosphodiesterase type 5 inhibitor approved to treat the disease. Tadalafil improved the walking distance, and patients receiving this drug experienced less clinical worsening, defined as death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, initiation of new PAH therapy, or worsening WHO functional class, compared to the placebo group (Oudiz et al, 2012).

Riociguat is a novel drug that stimulates soluble guanylate cyclase independently of nitric oxide and in synergy with nitric oxide. It is labelled and available in pulmonary arterial hypertension (Ghofrani et al, 2013) where it demonstrated efficacy on exercise capacity, pulmonary vascular resistance and time to clinical worsening and chronic thromboembolic pulmonary hypertension (Ghofrani et al, 2013) where it showed improvement in exercise capacity and pulmonary vascular resistance. Specific data in CTD-PAH (n=111) and SSc-PAH (n=66) suggested that the mean treatment difference between riociguat and placebo (+28 m) was lower than that observed in the overall PAH population (+36 m) (Humbert et al, 2017).

The antiproliferative agent and tyrosine kinase blocker Imatinib in patients did show in trials improvement in exercise capacity and haemodynamics in patients with advanced PAH, however, serious adverse events and study drug discontinuations were common, which did not allow the drug to be labelled in this indication.

Ventavis®, an inhaled-solution form of iloprost, is indicated for patients classified as having stage III or IV pulmonary hypertension (Olschewski et al, 2002). Severe cases still require intravenous prostacyclin analogues such as epoprostenol or iloprost. Beneficial hemodynamic effects of epoprostenol included a statistically significant decrease in pulmonary vascular resistance, mean pulmonary artery pressure and right atrial pressure, as well as a significant increase in cardiac index. However the way of administration (through a permanent indwelling central venous catheter) may favour adverse events such as infections, pneumothorax, and haemorrhage. Sudden disruption/withdrawal of i.v. epoprostenol (due to catheter/vein thrombosis and/or patient's decision) may lead to life-threatening PAH rebound. For that reason, on overall risk-to-benefit considerations, and in agreement with the current ACCP guidelines, intravenous epoprostenol is recommended for the treatment of severe, therapy resistant SSc-PAH (Badesch et al, 2000). Subcutaneous treprostinil has shown to improve the 6MWT, the dyspnoea score and hemodynamic parameters in a heterogeneous population of PAH patients. In a subgroup of connective tissue disease (50% SSc), treprostinil has shown to significantly improve the cardiac index and the fatigue-dyspnoea score and there was a trend towards improvement (Simonneau et al, 2002). Efficacy is dose related, and subcutaneous administration may be limited by infusion site reaction and pain (Simonneau et al, 2002). In a phase 3 event-driven trial, that enrolled 1156 patients with PAH in untreated patients or on top of a stable dose of an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both, selexipag (an oral selective IP prostacyclin-receptor agonist) did show its efficacy (Sitbon et al, 2015). A composite of death from any cause or a complication related to PAH occurred in 41.6% of those in the placebo group and 27.0% of those in the selexipag group. Disease progression and hospitalization accounted for 81.9% of the events. By the end of the study, 105 patients in the placebo group and 100 patients in the selexipag group had died from any cause (NS). The most common adverse events in the selexipag group were consistent with the known side effects of prostacyclin, including headache, diarrhoea, nausea, and jaw pain. SSc specific data are not available.

Combination therapy with agents that target different pathways may potentially increase the overall therapeutic effect on the mechanisms of this disease and provide additional clinical benefits. In an event-driven, double-blind study, including 500 patients in WHO classes class II or III, initial combination therapy with 10 mg of ambrisentan plus 40 mg of tadalafil (combination-therapy group) was compared to 10 mg of ambrisentan plus placebo (ambrisentan-monotherapy group), or 40 mg of tadalafil plus placebo (tadalafil-monotherapy group). The hazard ratio for the primary end point (time-to-event analysis) in the combination-therapy group versus the pooled-monotherapy group was 0.50 (95% confidence interval [CI], 0.35 to 0.72; $P < 0.001$) (Galie, et al, 2015). The adverse events that occurred more frequently in the combination-therapy

group than in either monotherapy group included peripheral oedema, headache, nasal congestion, and anaemia. This large controlled trial demonstrate that among participants who had not received previous treatment, initial combination therapy with ambrisentan and tadalafil resulted in a significantly lower risk of clinical-failure events than the risk with ambrisentan or tadalafil monotherapy. Within the participants, 187 had a connective tissue disease (118 SSc) and a similar benefit of the upfront combination therapy was observed (HR 0.432; 95% CI: 0.242, 0.771), with a reduction in hospitalisations primarily driving the treatment effect (Galie et al, 2015).

The UCLA team reported a historical cohort study to evaluate whether aggressive PAH-targeted therapy (the use of a prostanoid and prostanoid initiation within six months of the diagnostic catheterisation) could improve the outcomes of SSc-PAH. Among 251 SSc patients who underwent a RHC, 99 met RHC criteria for either SSc-PAH (n=28) or SSc-PH-ILD (n=71, defined by ILD >30% or if intermediate ILD on CT scan, associated with FVC<70%). It is of note that the initial PAH therapy was a PDE-5 inhibitor (43%) or an endothelin antagonist (45%) and that over 50% of the entire cohort was treated with at least two PH-specific therapies during the study period. Twenty-four percent of patients (1 [4%] SSc-PAH and 21 [32%] SSc-PH-ILD) started a prostanoid ≤6 months of the RHC, while an additional 24% (9 [36%] SSc-PAH and 13 [20%] SSc-PH-ILD) started a prostanoid >6 months after the diagnostic RHC. The 1-, 2-, and 3-year survival estimates were 82%, 66%, 60%, and 72%, 59%, 50% for the SSc-PAH and SSc-PH-ILD, respectively. After accounting for gender, PVR index, and ILD status, early prostanoid use remained significantly associated with improved survival (HR 1.4, p<0.01) (Volkman et al, 2014). This study confirms that survival in patients with SSc-PH-ILD is poor. This cohort suggests modestly improved survival in these patients compared with prior series and more data on early use of prostanoids such as for combination therapies are now needed.

It must be reminded that the very large majority of these data were obtained in trials including mainly idiopathic forms of PAH and that specific data on SSc-PAH patients are missing. It must also be reminded that supportive care must be offered to SSc-PAH patients (diuretics, oxygen delivery, anti-coagulants...

VI.2.4 Kidney involvement The outcome of scleroderma renal crisis is poor despite aggressive treatment for high blood pressure. SSc patients who develop high blood pressure should immediately receive ACE inhibitors to control blood pressure. ACE inhibitors can improve the prognosis, but it is still not known if they can prevent scleroderma renal crisis. Patients with loss of renal function require dialysis (Steen VD et al, 1990). It is noteworthy that four retrospective studies suggest that steroids are associated with a higher risk of scleroderma renal crisis. Patients on steroids should be carefully monitored for blood pressure and renal function (Steen et al, 1990).

VI.2.5 Digital vasculopathy Although vasculopathy is a key factor in the pathophysiology of SSc and the main cause for RP and its complications, available data suggest that SSc patients do not yet receive sufficient

vasoactive therapy. In a recent analysis of German Network for Systemic Scleroderma registry, patients were treated with vasoactive drugs in 61.1% of case mainly calcium channel inhibitors and angiotensin-converting enzyme inhibitors (Moinzadeh et al, 2016).

Nifedipine and i.v. iloprost have been shown to reduce the frequency and severity of SSc-related Raynaud's phenomenon attacks (Thompson et al, 2001). Dihydropyridine-type calcium channel blockers, usually oral nifedipine, should be considered for first-line therapy for SSc-related RP, and intravenous iloprost, or other available i.v. prostanoids, for severe SSc-related RP (Pope, 2007).

Digital ulcers, a complication of chronic tissue ischemia, need both topic and systemic treatment. Intravenous prostanoids (particularly i.v. iloprost) and nifedipine are efficacious in healing digital ulcers.

The use of Bosentan has determined fewer new digital ulcers in bosentan-treated SSc patients than in patients receiving placebo. The treatment effect was most marked in preventing the development of multiple ulcers. These encouraging results have been confirmed in a further randomised placebo-controlled clinical trial, in which bosentan demonstrated efficacy in the reduction of new digital ulcerations onset in SSc patients. In this trial bosentan appears more effective in patients with more than 3 active digital ulcers at treatment outset and this reduction is associated with improved hand function (eating and dressing). Bosentan does not appear to speed healing of digital ulcers, the cardinal ulcer persisted in 50% of all subjects for up to 24 weeks. These data suggest that chronic endothelin receptor antagonism has an important effect on peripheral vascular integrity and function in SSc (Korn et al, 2004; Matucci-Cerinic et al, 2011). Macitentan has been evaluated in 2 randomised controlled trials with 2 doses compared to placebo regarding the cumulative number of new DU at 16 weeks. Both trials failed to show efficacy. Among enrolled patients with SSc and active ischemic digital ulcers, treatment with macitentan did not reduce new digital ulcers over 16 weeks. These results do not support the use of macitentan for the treatment of digital ulcers in this patient population. It was remarkable that in this population with at least one current, or, in the past year DU, about 60% of the patients did not develop new DU during the follow-up (Khanna et al, 2016c).

The sildenafil that showed promises in observational studies failed to demonstrate its efficacy on DU healing in a randomized controlled study that involved 83 patients with a total of 192 DUs. The HR for DU healing was 1.33 (0.88 to 2.00) ($p=0.18$) and 1.27 (0.85 to 1.89) ($p=0.25$) when adjusted for the number of DUs at entry. An unexpectedly high healing rate was observed (66%) (Hachulla et al, 2015). However, a significant decrease in the number of DUs in favour of sildenafil compared with placebo was observed at W8 and W12, suggesting a sildenafil benefit.

In the treatment of SSc ulcers, a topical treatment is needed. Firstly a wash with sterile solution and disinfection of the lesion is required, then mechanical removal of fibrin, induction autolysis of necrotic tissue and induce repair is necessary in order to recreate an appropriate microenvironment (humidity). For that

reason any medication that will block the gas exchange and formation of humidity (greenhouse effect- restore the microclimate) should be avoided: “closing” the ulcers may facilitate infection that spread rapidly into the tissue, and the circulation (septicaemia). In case of infections it is necessary to identify the microbial agent through a biopsy, in order to establish a prompt systemic antibiotic treatment. Then a frequent follow-up should be considered to determine when the infection is solved, to go back to standard procedure.

VI.2.6 Musculoskeletal involvement The management of articular involvement is essentially supportive and symptomatic. For the most part, the minor rheumatic symptoms of SSc, such as arthralgias, will respond to simple non-steroidal anti-inflammatory drug treatment. Low dose corticosteroids (<10 mg/day) may also have some value for the symptomatic treatment of inflammatory arthritis or tenosynovitis. By analogy with RA, methotrexate is usually used for the treatment of inflammatory arthritis. Sub-cutaneous or intramuscular routes should be used to prevent reduced digestive absorption. Other immunosuppressive drugs may be used such as azathioprine. A pilot study performed on 7 women with SSc and severe and refractory inflammatory joint involvement has suggested the efficacy after 6 months of intravenous immunoglobulins therapy (Nacci et al, 2007). It seems reasonable to avoid TNF α inhibitors in SSc: cases of fatal exacerbation of fibrosing alveolitis have been reported in a SSc patient and also in RA patients (Allanore et al, 2006).

Very preliminary data showed in an observational study that both tocilizumab and abatacept could improve SSc-polyarthritis. Results on SSc-myopathy were less demonstrative. No trend for any change of fibrotic lesions was seen in these patients but this may relate to the exposure time and inclusion criteria (Elhai et al, 2013). Larger and randomised studies with longer follow-up are now warranted to further determine the safety and effectiveness of these drugs in SSc. Trial with tocilizumab targeting skin fibrosis in progressive patients will be finished in 2014 and trial with abatacept should start very soon.

No treatment has proven efficacy in calcinosis, which remains a critical complication to manage.

Surgery of the hand for SSc is generally considered for pain reduction, severe fixed deformities with functional limitations, ulceration and calcinosis. The goals of surgery are limited and include pain relief, repositioning the digits, providing a functional position of fusion, and in some cases modest mobilization through resection arthroplasty, to marginally improve finger function for patients with marked pre-existing limitations.

The treatment of tendon involvement is usually symptomatic and supportive, since their evolution is usually favourable after the first years of the disease course. For the most part, tenosynovitis will respond to NSAIDs and low dose of corticosteroids. Surgery may be required in the very rare cases of tendon rupture.

SSc related myopathy does not usually require any specific therapy. However, in the case of overlap between SSc and inflammatory myositis, high doses of corticosteroids and immunosuppressive may be added to the conventional treatment of SSc.

Conclusions

In the next future, the improvement of our knowledge regarding the genetic background of the disease and the molecular pathogenic pathways, involved in the susceptibility and pathophysiology of SSc, will allow us to better identify/classify patients, that are potentially good-responder to specific targeted therapies, in order to improve our skills in management of SSc patients.

SUMMARY POINTS

- In conclusion, there have been many advances over the past 10 years in management of SSc and controlled clinical trials are starting to confirm treatment effectiveness. This provides a strong platform for future advance.
- At present organ-based complications are generally more amenable to treatment than the underlying disease, in that way early detection is critical and systematic assessment mandatory
- Many controlled trials are ongoing looking primarily at skin or lung fibrosis and derive from the improvements in the understanding of the pathogenesis of the disease.

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EULAR on-line course on Rheumatic Diseases

Systemic sclerosis

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A previous version was co-authored by Jérôme Avouac, Yannick Allanore, Marco Matucci-Cerinic, Irene Miniati, Chris P. Denton

IN-DEPTH DISCUSSION I

Nailfold capillary microscopy

In systemic sclerosis (SSc), clinical and pathologic findings of vascular damage and endothelial cell activation strongly support the hypothesis of a unique vascular disease as an important and primary process. It is likely that prolonged endothelial cell perturbation and activation induced by ischemia and reperfusion may lead to dysfunction and irreversible loss of integrity, with cell detachment and persistent tissue injury. The earliest clinical symptoms of SSc are due to disturbances of the peripheral vascular system.

Nailfold capillary microscopy has an impressive cost/effectiveness ratio: it is simple, safe, non-invasive and inexpensive. In clinical practice, the skin capillaries are generally observed through an incident light microscope. However, nailfold capillary microscopy can be performed by means of a series of instruments, including the ophthalmoscope, the stereomicroscope, photomacrography and, more recently, videocapillaroscopic systems.

Videocapillaroscopic analysis is considered, at the present time, to be the most sophisticated and may also detect blood flow at the level of the microvessels.

Nailfold video-capillaroscopy (NVC) shows a variety of morphological changes including enlarged capillaries, bushy capillary formations, micro haemorrhages, and a variable loss of capillaries with or without avascular areas. Capillaroscopic patterns in SSc may vary according to the disease stage. Some studies have described the morphological aspects of vascular damage in patients with SSc by NVC, correlating these capillary abnormalities to selected characteristics of the disease. NVC is a non-invasive and safe technique that can be a diagnostic and potentially a follow-up parameter of microvascular modifications in SSc classified in the “early”, “active” and “late” NVC patterns. The principal alterations of each SSc pattern are reported in table I.

Before starting the exam patients are acclimatized for 30 min at comfortable temperature. NVC is performed using an optical probe videocapillaroscopy equipped with 100x and 200 x contact lenses and connected to image analyse software observed on a colour monitor and printed on a digital video printer.

The nailfolds of all 8 fingers are examined, (thumbs excluded), after a drop of immersion oil placed on the nailfold bed to improve the image resolution. Fingers affected by recent local trauma are not analysed. The following parameters have to be considered in SSc patients, according to previous classifications: presence of enlarged and giant capillaries, haemorrhages, loss of capillaries, and disorganization of the vascular array and ramified/bushy capillaries.

On the basis of the NVC abnormalities, SSc patients were distributed into the appropriate NVC pattern, as previously reported.

The three major NVC patterns seem to reflect the evolution of SSc microangiopathy and their recognition may be useful in assessing microvascular damage in individual patients, both at a single point and longitudinally in

time. In healthy subjects, capillary loops and capillary distribution do not change with time, and the same pattern is usually maintained.

In SSc patients the pattern of microangiopathy may change with time, but longitudinal data remain scarce so far. NVC abnormalities such as enlarged and giant capillaries are the first sign of SSc microangiopathy, but they become rare in patients with longer disease duration. On the contrary, capillary rarefaction and ramifications are rare in the early stage of SSc microangiopathy but are common in patients with longer SSc duration. Indeed, NVC patterns correlate with the duration of Raynaud's phenomenon and reflect the evolution of the disease process.

An increased vascular permeability and a reduced blood flow are observed in all NVC groups confirming previous studies. Furthermore, NVC allows, in SSc in particular, the observation of the prolonged phases of reduced or ceased capillary perfusion as a result of cold-induced peripheral vasospasm.

When SSc patients have been evaluated both with NVC and laser-Doppler Blood flowmetry (that is used to estimate cutaneous blood flow of microvessels), the blood flow changes observed with laser Doppler seem to correlate with the severity of microvascular damage in SSc as detected by NVC: when the probe was heated to 36 degrees induced a lower increase in peripheral blood flow in SSc patients with an advanced microvascular damage detected by NVC.

The NVC patterns have been correlated with different clinical aspects and manifestations of SSc, as well as with the effects of treatment, thus contributing to the overall study of the disease.

A recent study has highlighted the correlation of a quantitative videocapillaroscopic score with the development of digital skin ulcers in SSc patients through a retrospective analysis. According to the results, the total number of capillaries, the maximum diameter and the ratio between number of giant capillaries and the total number of capillaries correlated with the appearance of ischemic ulcers.

NVC has also been assessed, together with autoantibodies, as a predictor of SSc in a cohort of 586 patients with Raynaud's phenomenon and no definite connective tissue disease. Patients were evaluated for microvascular damage by nailfold capillaroscopy and for SSc-specific autoantibodies by specific assays, in order to identify markers predicting the evolution to definite SSc. Of these patients, 12.6% developed a definite SSc over the years. The results showed that, in patients with Raynaud's phenomenon, and abnormal capillaroscopy with scleroderma pattern together with an SSc-specific autoantibody at baseline, there was a good probability of 79.5% developing definite SSc after up to 9 years of observation.

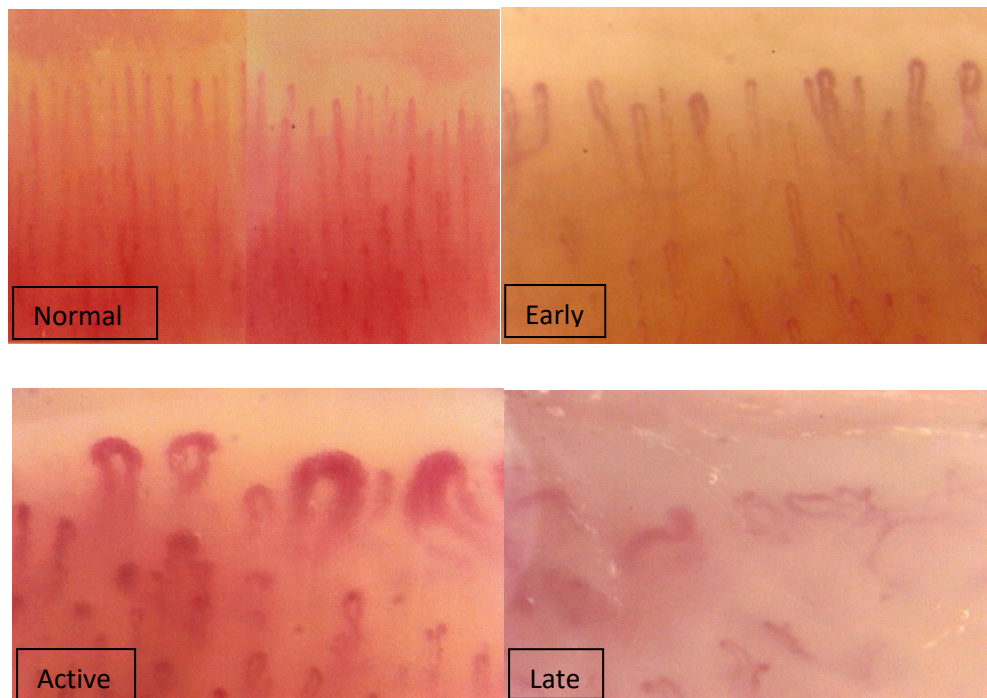
Very early diagnosis of SSc is an unmet clinical need. To increase the chance of accurately detecting very early SSc patients, experts from the EULAR Scleroderma Trials and Research (EUSTAR) recently identify through a Delphi consensus study a core set of preliminary items considered as important for the very early diagnosis of

SSc. While Raynaud's phenomenon, puffy fingers and antinuclear antibodies were considered by the whole assembly of EUSTAR as "red flags" for the general practitioner leading to the suspicion of very early SSc, NVC was considered, together with anticentromere and antitopoisomerase-I antibodies, as the preferred confirmatory diagnostic tool to diagnose a patient with very early SSc with a high probability. The further validation of these criteria, including NVC, is ongoing in the VEDOSS (Very Early Diagnosis Of Systemic Sclerosis) prospective observational cohort.

More recently, new EULAR/ACR classification criteria for the diagnosis of SSc have been elaborated in order to encompass a broader spectrum of SSc including patients whose disease is in the early stage, as well as those with the limited cutaneous subset. These criteria now include NVC, and the presence of an abnormal nailfold capillary pattern consistent with SSc, defined by enlarged capillaries and/or capillary loss with or without pericapillary haemorrhages at the nailfold, counts for 2 points (9 are required for a diagnosis of SSc). The presence of NVC in these new criteria strengthens the efforts of the clinician to reach an early diagnosis of SSc. Moreover, considering the value of magnified nailfold visualization in the diagnosis and management of SS, these new criteria may encourage acquisition of this skill by physicians caring for SSc patients.

Table 1 – SSc NVC patterns

early pattern	few (fewer than four altered capillaries per millimetre) enlarged/giant capillaries, few capillary haemorrhages, relatively well-preserved capillary distribution, no evident loss of capillaries;
active pattern	frequent (more than six altered capillaries per millimetre) giant capillaries, frequent capillary haemorrhages, moderate loss of capillaries, mild (between four and six altered capillaries per millimetre) disorganization of the capillary architecture, absent or mild ramified capillaries
late pattern	irregular enlargement of the capillaries, few or absent giant capillaries and haemorrhages, severe loss of capillaries with large avascular areas, disorganization of the normal capillary array and ramified/bushy capillaries.

Figure 1: SSc NVC patterns

Pictures provided courtesy of Pr Maurizio Cutolo (Genoa, Italy).

*To learn more: [Atlas of capillaroscopy in rheumatic diseases](#) by this author
(www.eular.org, education website)*

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IN-DEPTH DISCUSSION II

Pulmonary hypertension in systemic sclerosis

Pulmonary hypertension (PH) is a fatal disorder characterized by an increase in pulmonary vascular resistance, which leads ultimately to right ventricular failure. The interest in PH due to systemic sclerosis (SSc-PH) has recently increased, as SSc is the connective tissue disease most often associated with PH.

Epidemiology of PH and PAH

SSc-PH prevalence stands about 9% according to a recent meta-analysis, and incidence about 0.61 patient-years. Isolated pulmonary arterial hypertension (PAH) related to obstructive proliferative vasculopathy of the small and medium-sized pulmonary arterial circulation and PH secondary to chronic hypoxemia due to advanced lung disease are the two major causes of precapillary PH in SSc. Pulmonary veno-occlusive disease is also a recognized cause of PH, which is thought to be more common in connective tissue diseases but remains exceptional. In addition, left heart disease and thromboembolic disease may cause, respectively, post capillary/venous, and precapillary PH.

PH and PAH have been associated with significantly high mortality and morbidity rates. One- and three-years survival rates are 78-87% and 47-64% for patients with SSc-PAH. Survival is even worse for those with lung disease-associated SSc-PH (three-year survival 28-39%). Among SSc patients prospectively followed in the EUSTAR cohort, 26% of death was related to PAH. The outcomes of 76 SSc-PAH patients have been recently reported and prognostic factors investigated. In multivariate analyses, pulmonary vascular resistance, stroke volume index, pulmonary capacitance, pulmonary arterial oxygen saturation, estimated glomerular filtration correlated with prognosis. Therefore, this study correlates pulmonary vascular end-points with non-pulmonary conditions that may be of critical importance to explain the specific poor outcomes observed in SSc-PAH.

Definition of PAH

The gold standard for the diagnosis of PH is right heart catheterization (RHC). Precapillary PH is defined at RHC as a mean resting pulmonary artery pressure >25 mmHg in the presence of a pulmonary capillary wedge pressure ≤ 15 mmHg. The importance, when PH is suspected, to systematically proceed with RHC has been emphasized by several reports; indeed, in a series among 206 patients who had a RHC performed for a suspected PH, precapillary PH was confirmed only in 64 patients (31%); 123 patients (60%) had normal hemodynamic measurements, 17 (8%) had PH secondary to left heart disease and 2 (1%) pulmonary veno-occlusive disease.

Early diagnosis

Despite the proven association of PAH and lethality, this complication often remains undetected clinically until frank right heart failure occurs. In general, a substantial delay exists between the presentation of initial symptoms and the diagnosis of PAH. As a result, more than two-thirds of the patients exhibit functional class

(FC) III or IV symptoms at the time of diagnosis. This highlights the need for the early diagnosis of PAH to improve prognosis and to optimize therapy. Hence, screening for PAH in the high-risk scleroderma patient is of paramount importance.

According to the WHO guidelines, baseline and annual Doppler echocardiography is recommended. This practice is intended to identify most cases of PAH. However, the usefulness of ECHO is limited, as it cannot distinguish between the underlying causes of PAH. It may falsely indicate PH when it is actually not present, especially at the upper limits of normal pulmonary artery pressure (PAP in 35–40 mmHg range), and in rare cases, it may fail to detect elevated pulmonary pressure when present. Right heart catheterization (RHC) is therefore necessary for confirmatory diagnosis. The contribution of DLCO as a screening tool in addition to echocardiography has been highlighted: a decreased DLCO <50% identified in a recent series a subset of patients with confirmed PH despite normal sPAP. Increased levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) is also interesting in this context as it has been found as an accurate, reproducible and simple marker of PH.

Exercise echocardiography might also be very helpful to identify a subset of SSc patients with an inappropriate exercise-induced increase in PASP and early signs of right ventricular dysfunction that can relate to very early PAH. This tool is now under development in order to standardize the testing and determination normal values for controls.

Indications of RHC in case of suspected PH

An increase of systolic pulmonary artery pressure or volume of tricuspid regurgitation on echocardiography, reduced DLCO (without significant lung fibrosis), increased NT-proBNP levels, or unexplained dyspnoea have been previously used alone or in combination as indications to refer patients to RHC in case of suspected PAH.

Predictive factors of PH

The marked impact of PAH on the survival of patients suffering from SSc urgently mandates the identification of the subset of patients at highest risk, in order to implement an appropriate follow-up. PH may affect both genders at all ages, highlighting the need for a high index of suspicion and the routine screening of all patients. Although PAH was considered to be a late complication of limited cutaneous SSc, confirmed by reproducible studies, a recent French study showed that the incidence of PAH developing within 5 years after the diagnosis of SSc, was approximately 50% among patients with diffuse cutaneous SSc. Therefore, all patients should be screened for PH immediately after the diagnosis of SSc has been made and very regularly.

Previous retrospective works and some recent prospective ones have highlighted the critical input of pulmonary functional tests to predict the subsequent development of PAH and PH in SSc. In this context DLCO

is of very high value it must be used as a warning tool and patients with significant decrease of DLCO, notably in the absence of significant lung fibrosis, should be very scrupulously regularly followed for the risk of PAH. The combination of DLCO and increased NT-proBNP levels has been shown to highly predictive of the occurrence of PAH. Several attempts are ongoing to build predictive risk scores. Genetic might also be a promising approach to identify patients at risk to develop PAH, since several gene polymorphisms have been reported to be associated with the risk of SSc associated PAH.

Outcome measures of PH

SSc-PH patients require repeated assessments of either disease progression and/or treatment efficacy. Dyspnoea, functional classification, exercise capacity, hemodynamic changes and cardiac function are considered to be important for PH evaluation and prognosis. However, these outcome measures, especially the 6 min walk test, are only partially validated in PAH associated with SSc. The development of new tools, such as Tissular Doppler echocardiography, cardiac magnetic resonance imaging or new biomarkers might improve the evaluation of PH and better define the prognosis and response to therapy.

Treatment

In addition to the supportive care (oxygen, diuretics, anticoagulants), experts from EUSTAR recommended to consider the use of endothelin receptor antagonists, PDE5 inhibitors and prostanoids to improve exercise capacity, functional class and some hemodynamic measures in PH associated with SSc. Since disease worsening is inevitable for the majority of patients receiving monotherapy, there is increasing interest in the use of treatment combinations. A recent event-driven randomized controlled trial has shown that combination therapy with agents that target different pathways may potentially increase the overall therapeutic effect on the mechanisms of this disease and provide additional clinical benefits. Early treatment initiation and optimization following early detection could be the key to reducing the mortality associated with PH in SSc.

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EULAR on-line course on Rheumatic Diseases

Systemic sclerosis

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IN-DEPTH DISCUSSION III

Articular involvement in systemic sclerosis

While tethering of the skin is the clinical hallmark of systemic sclerosis (SSc), many patients develop musculoskeletal symptoms, during the course of their illness. Articular involvement contributes to disability and impaired quality of life in SSc.

CLINICAL PRESENTATIONS

Joint involvement eventually affects 46-97% of patients with SSc. The systematic cross-sectional examination of the EUSTAR registry identified clinical synovitis, defined by tender and swollen joints and tendon friction rubs (defined by a leathery, rubbing, “squeaking” sensation detected as the tendon is moved actively or passively) in 16 % (1191/7286) and 11% (802/7286) of SSc patients, respectively. Joint involvement may be an initial manifestation that precedes the onset of Raynaud’s phenomenon or arise concomitantly and therefore might be considered as an early indicator of SSc.

1/ Joint involvement

Generalized arthralgias with slight pain and stiffness are the usual presentations of articular involvement; however, true joint inflammation may occur and be a source of initial diagnostic confusion. The onset may be acute or insidious and oligoarticular or polyarticular in pattern. Virtually, all joints may be affected, although the fingers (in particular the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints), wrists and ankles predominate. As the disease progresses, there is tethering and contracture of the underlying joints with impairment of movement and function.

2/ Tendon involvement

Tendon abnormalities are described as “leathery crepitus” on palpation of the knees, wrists, fingers and ankles, related to fibrinous deposits on the surface of tendon sheaths and overlying fascia. In the forearm the source of this rub is usually the tendons of the flexor or extensor muscles immediately proximal to the wrist. Median nerve compression with carpal tunnel syndrome may occur, presumably from changes in the tendon sheaths beneath the transverse carpal ligament.

LABORATORY FINDINGS

Rheumatoid factor positivity occurs in up to 30% of SSc patients. This test seems non-specific and does not distinguish SSc patients with musculoskeletal manifestations from those not so affected. Rheumatoid factor may also be seen in patients with SSc associated secondary Sjögren’s syndrome. The search for anti-CCP antibodies might be of great help in the identification of the infrequent cases of true SSc-rheumatoid arthritis overlap. Analysis of the synovial fluid generally reveals normal or modestly increased leukocyte concentrations of less than 2000 cells/mm³ and a predominantly mononuclear infiltrate.

ARTICULAR INVOLVEMENT AS A CORRELATE OF PROGNOSIS AND DIAGNOSIS OF SSc

In the EUSTAR registry, patients with synovitis and early disease were more likely to experience diffuse cutaneous thickening. However, the likelihood of severe vascular (pulmonary hypertension) and muscular (muscle weakness) involvement was higher in patients with synovitis, regardless of their cutaneous subset or their disease duration. One study also identified an association between synovitis and elevated acute phase reactants, suggesting that joint involvement might be associated with systemic inflammation in SSc. Tendon involvement is more prevalent in patients with the diffuse cutaneous subset and early disease and tendon friction rubs is associated with poor outcomes including decreased survival.

Two recent prospective cohort studies including patients from the EUSTAR database have identified joint synovitis as a predictor of disease progression. The first study included 1,301 SSc patients with disease duration ≤ 3 years at inclusion and with a follow-up ≥ 2 years (mean follow-up: 4.5 ± 2.2 years). Joint synovitis, detected by clinical examination, was independently predictive of the worsening of the modified Rodnan skin score ($\geq 30\%$ and ≥ 5 points) and of the further occurrence of new ischemic digital ulcers and decreased left ventricular ejection fraction. The second study was performed on 637 SSc patients with the diffuse cutaneous subset. Joint synovitis was also identified in univariate and multivariate analysis as a predictor for progressive skin fibrosis. Using a second validation cohort of 188 dcSSc patients, joint synovitis were confirmed as independent predictors of progressive skin fibrosis within 1 year. Taken together, the results of these two studies support that synovitis, an easily detected clinical marker may be useful for the risk stratification of SSc patients.

The recent prospective analysis of the EUSTAR database has also confirmed that tenosynovitis was an independent predictor of skin progression and of the further occurrence of scleroderma renal crisis.

RADIOLOGIC FEATURES: STRUCTURAL OSTEOARTICULAR LESIONS

Articular lesions, from juxta-articular osteoporosis and joint space narrowing to frank erosions, have been reported throughout the MCP, PIP and DIP joints, as well as the wrist (figure 1). Patterns of SSc arthropathy range from that resembling erosive osteoarthritis or psoriatic arthritis with relative sparing of MCP joints to changes reminiscent of rheumatoid arthritis. The frequency of hand radiographic erosions is between 5% and 40%. Joint space narrowing prevalence on X-Ray is about 30%, with a predominant involvement of DIP joints. The detection of pencil-in-cup deformity in hands and feet has been reported. These articular features may be associated with non-articular abnormalities, in particular skin atrophy, subcutaneous calcinosis and digital tuft resorption, which are among the most distinctive radiographic findings in SSc.

In a prospective cohort involving 120 SSc patients, erosive arthritis defined as the occurrence of both erosions and joint space narrowing, was found in 18% of SSc patients. The five-year longitudinal follow-up of these

patients, with a systematic examination of dual time-point X-Rays, showed a total radiographic progression of erosive arthritis in 24 (23%) SSc patients. The presence of erosive arthritis was not associated with any SSc characteristics or auto-antibodies. This lack of any predictive factor for erosive arthritis might be related to the multifactorial aspects of SSc arthropathy. The possibility of erosive osteoarthritis should be considered; in our view, some patterns of erosive arthropathy can be directly related to SSc, however DIP involvement suggests coincident OA. The recent development of power Doppler ultrasonography, which allows the assessment of synovial vascularity, and magnetic resonance imaging as diagnostic tools and outcome criteria in rheumatoid arthritis has led to a substantial improvement in disease evaluation. The higher sensitivity of these non-invasive techniques to detect joint/tendon involvements has been demonstrated and several studies evaluating their input are ongoing.

TREATMENT

For the most part, arthralgias, but also tendonitis, will respond to simple non-steroidal anti-inflammatory drug treatment. Caution should be exercised, however, with this class of drugs because of the enhanced risk of gastro-oesophageal abnormalities or bleeding and impaired renal function in this group of patients. Low dose corticosteroids (<10 mg/day) may also be used, although the risk of renal crisis should be carefully considered (especially in diffuse SSc patient within the first 5 years of SSc onset and in case of positive anti-RNA pol III antibodies). Methotrexate may be used for the treatment of inflammatory arthritis and sub-cutaneous route may improve absorption. Other immunosuppressive drugs may be used, such as azathioprine, but cyclophosphamide did not show beneficial effects on joints in the secondary analyses of the Scleroderma lung Study. A pilot study suggested some interest in very selected severe and refractory SSc-arthritis cases of intravenous immunoglobulins therapy.

Biologics have been the starting point of a new era in the treatment of inflammatory rheumatic conditions. The efficacy of TNF α inhibitors on inflammatory joint symptoms has been suggested in a preliminary study, performed on 18 SSc patients treated with etanercept. However, no further trial has been performed probably because of the risk of exacerbation of fibrosing alveolitis, reported both in SSc and rheumatoid patients. Rituximab, a chimeric monoclonal antibody against the protein CD20 that demonstrated efficacy in RA, might also be potentially beneficial for the treatment of SSc arthritis. However, no study has yet assessed this drug for this specific indication. The EUSTAR group collected observations that revealed a tendency toward articular improvement in cases of polyarthritis under tocilizumab and abatacept during refractory SSc. Further randomized controlled trials are now expected to confirm these promising results.

The current literature on rehabilitation techniques in SSc consists of studies evaluating the effectiveness of paraffin wax treatment, hand and face stretching exercises connective tissue massage and joint manipulation, splints, aerobic exercise and resistance training. The data seem promising, except for splints, for the

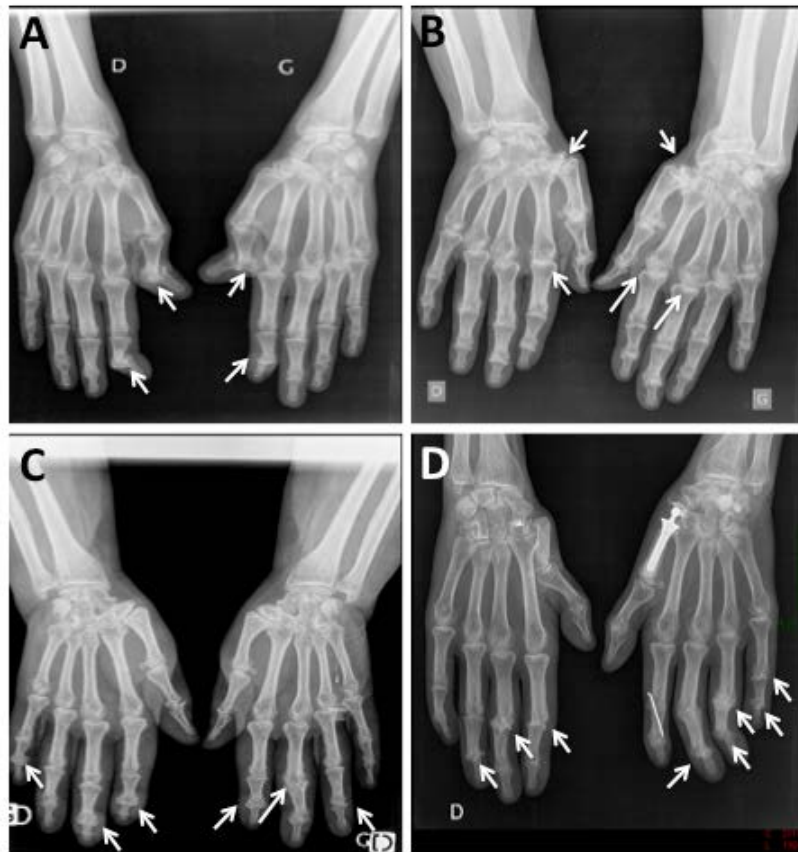
improvement in joint motion and hand function. However, larger randomized controlled studies are needed to fully determine the effectiveness of rehabilitation techniques for persons with SSc.

Surgery of the hand for SSc is used but the goals of surgery are limited. They include pain relief, repositioning the digits, providing a functional position of fusion, and in some cases modest mobilization through resection arthroplasty to marginally improve finger function for patients with marked pre-existing limitations. Surgery may also be required in the very rare cases of tendon rupture. In the case of carpal tunnel syndrome, corticosteroids injected under the retinaculum are frequently efficient, but surgical release may be needed in symptomatic and refractory patients. If surgery is contemplated then local or regional anaesthesia is preferred for patients, particularly in patients who have ongoing cardiac or pulmonary manifestations of SSc.

CONCLUSION AND PERSPECTIVES

Although the understanding of osteoarticular pathogenesis has significantly increased in the last few years, optimal treatments of inflammatory joint disease remain to be determined and appear as a major challenge for improving SSc morbidity and patients' quality of life. To that end, the study and validation of outcomes measures including new imaging techniques in this field must be put urgently on the research agenda of the SSc community. Thereafter, one may have the chance to perform rigorous randomized controlled trial assessing the potential input of the many relevant available and upcoming drugs and therefore offering some hope in a disease that remains devastating.

Figure 1: Several patterns of joint space narrowing and erosions in 4 different SSc patients



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Polymyositis, dermatomyositis

Inflammatory diseases of muscle and other myopathies

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LEARNING OBJECTIVES

- ➔ Know possible pathogenic mechanisms in inflammatory myopathies.
- ➔ Make an accurate diagnosis of idiopathic inflammatory myopathy.
 - Distinguish between inflammatory and non-inflammatory myopathies.
 - Describe cutaneous specific features of dermatomyositis.
 - Describe other extramuscular features of idiopathic inflammatory myopathies.
- ➔ Describe myositis-specific and myositis-associated autoantibodies and their associated clinical phenotypes.
- ➔ Use clinimetric measures for muscular and extra muscular features.
- ➔ Prescribe both pharmacological and non-pharmacological treatments.

1 Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of autoimmune, rare and heterogeneous muscle disorders characterized by the occurrence of proximal and symmetrical muscle weakness, which can result in impaired endurance and disability. Extra-muscular involvement and the overlap with other well-defined connective tissue diseases (CTDs) (eg Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease, systemic lupus erythematosus or rheumatoid arthritis) are not uncommon in IIMs. IIMs have traditionally been subclassified into three main types: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM) (Bohan and Peter, 1975). A classification of IIMs according to the presence of myositis-specific and myositis-associated autoantibodies (MSAs/MAAs) has also been proposed, since most MSAs, such as the antisynthetases (Cavagna et al, 2015*), and some MAAs, are associated with distinctive and characteristic clinical phenotypes (Trojanov et al, 2005*). In addition, different subtypes have been identified (necrotising myositis, chronic granulomatous myositis associated with sarcoidosis, orbital myositis, focal myositis and eosinophilic myositis) but they will be not treated in this course.

2 Epidemiology

IIMs are rare diseases, but data about prevalence and incidence are largely inhomogeneous. The variability is due to different methodologies used for patients' inclusion, genetic background and/or environmental factors exposure.

PM/DM prevalence ranges from 2.9 to 34 cases/100.000 inhabitants, with an annual incidence of 2–11 cases/1.000.000 inhabitants, (Svensson et al, 2017). The peak incidence is at the age of 50–60 years, but the onset is possible at any age. The female to male ratio is about 2:1. Juvenile-PM is much rarer than juvenile-DM. Interestingly, PM/DM distribution seems to have a latitudinal gradient, with DM occurring more frequently at latitudes closer to the equator, and PM at northern latitudes, potentially linked to the different UV-light irradiation exposure in these areas. The estimated prevalence of IBM is 3.3/100 000 (Molberg et al, 2016), the estimated annual incidence is 1–2/1.000.000 adults. IBM is more common in males. Mean age at onset is slightly higher in IBM than in PM/DM, and it rarely occurs before the age of 50. It should be noted that both sporadic- and hereditary- forms of IBM have been described.

3 Aetiopathogenesis

The aetiopathogenesis of IIMS is complex and not completely understood, involving both genetic and environmental factors. The interaction between these factors is crucial for the establishment of the autoimmune reaction leading to the occurrence of different manifestations of IIMs.

3.1 Genetic factors

IIMs susceptibility is closely associated with human leucocyte antigen (HLA) genes, in particular HLA class II alleles. In Caucasians, the strongest association is with HLA-DRB1*0301 and DQA1*0501, whereas in Asians it is with HLA-B7, with DQA1*01 acting as a protective factor. An even stronger association has been found between some subsets of myositis and specific autoantibody profiles (anti-Jo-1, HLA-DRB1*0301, DQA1*0501; anti-Mi-2, DRB1*07, DQA*0201). IBM has been associated with HLA-DRB1*0301, DRB1*0101, DRB1*1301, DQB1*0201 and DRw52. Patients with IBM and both DRB1*0101 and DRB1*0301 genes have an earlier onset and a rapid disease progression compared to those without this 'double-dose' of DRB1 genes, clearly suggesting the importance of gene–gene interaction in determining disease phenotype and severity. Recently, two variants of sequestosome 1 (SQSTM1) and valosin-containing protein (VCP) genes, the SQSTM1 p.G194R and the VCP p.R159C, have been found significantly overrepresented in sporadic IBM with respect to controls. These genes are also involved in the pathogenesis of some neurodegenerative disorders, thus a common nature between sporadic IBM and conditions such as amyotrophic lateral sclerosis and fronto temporal dementia is possible (Gang Q et al, 2016). Data on hereditary-IBM are scant, but different genetic transmissions and probably different genetic defects are possibly involved.

The above mentioned genetic associations support the role of T-cell driven immune response in IIMs pathogenesis, as the only known function of major-histocompatibility-complex (MHC) class II molecules is to present antigens to antigen-specific T-cell receptors.

Also non-HLA genes, such as those for proinflammatory cytokines (-308TNFA genotype), have been linked to IIMs. The -308TNFA gene is localised in a conserved haplotype (the ancestral haplotype) on chromosome 6, including also HLA-DR3 and other genes potentially relevant for the development of chronic inflammatory diseases. Whether the association between myositis and the HLA-DR3 gene or the tumour necrosis factor (TNF) gene depends on an association with a single gene or an extended haplotype is unclear. There are also reports of associations with a polymorphism in the interleukin-1 receptor antagonist (IL-1Ra) gene in juvenile-DM, where the IL-1RN A1 allele carries an increased risk for juvenile-DM.

Despite these evidences, it is clear that the genetic background in IIMs pathogenesis is complex and largely still to be defined. Furthermore, it is possible that environmental factors could interact with genetic

predisposition leading to IIMs occurrence. A single and relatively small study has tantalisingly suggested that smoking and HLA-DRB1*0301 (or DR3) may predispose to expression of the anti-Jo-1 antibody.

3.2 Environmental factors

3.2.1 Infections

Acute and self-limiting forms of myositis have been reported with Coxsackie, echo and influenza virus infections, in particular in children, but their role in chronic myositis is uncertain. Both clinical and histopathological features resembling PM have been seen in patients with retroviral infections, such as human T-cell leukaemia/lymphoma virus and human immunodeficiency virus. Also, *tripanozoma cruzi* infection has been associated with myositis. However, in the majority of patients with myositis, there is no proof of viral infection in involved muscles.

3.2.2 Exposure to UV light and vitamin D deficiency

The above-mentioned different latitudinal gradient of prevalence between PM and DM seems to indicate that UV light exposure may predispose to DM development. This link seems to be particularly evident in patients positive for anti-Mi-2 autoantibodies. The association between exposure to UV light and this specific myositis subset suggests that UV light may be an exogenous modifier that can differentially influence IIM clinical phenotype features, although with mechanisms that are still not defined.

Similarly to other CTDs, also vitamin D deficiency has been linked to IIMs (Azali et al, 2013), but the pathogenetic influence of this deficiency is still unclear.

3.2.3 Drugs

Among the different environmental factors linked to IIMs, the impact of drugs is not univocal. Several drugs may induce myopathies with muscle weakness and increased serum levels of creatine kinase (CK), that may resemble IIMs but that do not always belong to the IIMs spectrum. The most common drug-induced myopathy is caused by statins, but also other lipid-lowering agents (fibrates and nicotinic acid) may induce a myopathy. While statin use is very common, statin-induced myopathy is extremely rare. Predominant clinical features in statin-induced myopathy include generalised muscle pains and cramps and, sometimes, severe rhabdomyolysis, with a risk of renal failure due to the ensuing myoglobinuria. Muscle biopsy samples in statin-induced myopathy are usually normal without inflammatory cell infiltrates, though in more severe cases myonecrosis of fibres may occur (necrotizing myopathy), with or without inflammatory cell infiltration. The prognosis is usually favourable, with spontaneous recovery commonly occurring when the drug is stopped, though recent case series have reported that statin-induced myopathy may not regress after drug cessation. In persistent cases, the use of immunosuppressants such as methotrexate, or high dose intravenous immunoglobulins (IVIg) may induce disease remission (Trojanov et al, 2017).

However, if muscle symptoms persist after a lipid-lowering drug has been discontinued, the possibility of another underlying problem, such as a metabolic myopathy unmasked by the drug should be strongly considered.

The mechanism by which statins cause myopathy remains unknown, but may be associated with the fact that these drugs are 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (HMGCR) inhibitors, and such inhibition may interfere with energy production. This may lead to damage of muscle fibres and the overexpression of HMGCR by regenerating muscle fibres. The damage is mediated in some patients by anti-HMGCR antibodies, strongly associated with the HLA-DRB1*1101 gene. This autoimmune profile, reported also in non-statin users with myositis, together with clinical and therapeutic overlaps with PM/DM, could strengthen the hypothesis that some subsets of statins-related myopathy could be considered as IIMs (Albayda et al, 2014).

Other drugs that may rarely induce myopathies are cimetidine, (hydroxy)chloroquine, amiodarone and colchicine. In general, drug-induced myopathies can be distinguished from inflammatory myopathies by the history of drug usage, by an absence of inflammatory changes in muscle biopsy specimens and by the clinical improvements after drug withdrawal. Glucocorticoids may induce a myopathy, exclusively characterized by the histological occurrence of a non-specific atrophy of type II muscle fibres. In patients with IIMs on glucocorticoids treatment, the diagnosis of glucocorticoid-induced myopathy may only be established if muscle strength improves when the glucocorticoid dosage is reduced. Some cases of anti-TNF-alpha-induced myositis have been described in RA patients. By considering the frequent anti-Jo1 positivity since disease onset in these cases and recent advances on the clinical spectrum time-course in anti-Jo1 positive patients (*Cavagna et al, 2015), it is possible to speculate that myositis occurrence may be more likely related to the natural history of the disease rather than to the anti-TNF-alpha treatment. Alcohol and cocaine may rarely induce an acute rhabdomyolysis, but alcohol more commonly induces a chronic myopathy. Typically, although not specific, histopathological findings in alcohol-induced myopathy include an accumulation of fat in muscle fibres without inflammation.

4 Pathogenesis

4.1 Immune mechanisms

Both adaptive and innate immunity may play a role in the development of muscle inflammation in IIMs, in line with the occurrence of T-cells infiltrates in muscle tissue, HLA-DR associations, presence of myositis-specific and associated autoantibodies, hyperactivation of interferon (IFN) type I signature and pattern-recognition receptor-dependent pathways. Most targeted antigens in IIMs are ubiquitously expressed. Possibly, immature muscle precursors enhance local auto inflammation in muscles, linking innate and adaptive immune responses (Casciola-Rosen et al, 2005*; Tournadre and Miossec, 2013). Besides immune mechanisms, some non-immune mechanisms are emerging, which are likely to have a role in muscle damage (Vitadello et al, 2010).

4.1.1 Adaptive immunity

4.1.1.1 T-cells

T lymphocytes and macrophages dominate the inflammatory infiltrate in PM, often with a relatively high proportion of CD8 T-cells compared with CD4 T-cells in the endomysial infiltrates. In some cases, these infiltrates surround and seem to invade closer fibres with otherwise normal histology. In contrast, in DM infiltrating CD4 T-cells with a perivascular localisation, mainly in the perimysium, are predominant with respect to CD8 T-cells. Despite their widespread localisation, the precise role of T-cells in the pathogenesis of IIMs has not been clarified yet. T-cells display an activated phenotype, yet the driving antigen for T-cell activation has not been identified. It is interesting to note that restricted T-cell receptor (TCR) expression has been characterised in muscle tissue, suggesting homing or local proliferation of T-cells. Autoreactive T-cells in muscle tissue normally act both as antigen-presenting cells (APCs), (CD4), which can support B-cell proliferation and differentiation, and as cytotoxic effectors against muscle fibres overexpressing MHC I molecules (CD8). A new subset of T-cells, the CD28 null T lymphocytes, arising from a prolonged stimulation of T-cells, leading to CD28 exhaustion, is widely expressed in inflammatory infiltrates and in the peripheral blood of patients with IIMs. These cells are resistant to apoptosis and to immunosuppressive therapies and may persist in muscles for a long time. CD28 null T-cells have acquired cytotoxic properties and can secrete large amounts of inflammatory cytokines and cytotoxic molecules—for example, granzymes and perforins (Malström et al, 2012). By considering that regulatory T-cells are reduced and/or functionally deficient, proinflammatory T-cells—for example, Th17, increase in inflammatory infiltrates. T-cells seem to be target of a proinflammatory shifting of the immune balance in IIMs. IL-17 can then trigger the release of a number of proinflammatory Th1 cytokines—for example, IL-2, IL-1, IL-6 and IL-15—, and can induce an increase in MHC I expression on muscle fibres.

4.1.1.2 B-cells and plasma cells

B-cells infiltrates are less common in IIMs, more often with a perivascular localisation in DM, particularly in the subtype associated with calcinosis in children. However, microarray studies have shown the presence of Ig transcripts, dendritic cell (DC) transcripts and IFN type I (α and β) transcripts in muscle fibres of patients with IIM (Greenberg, 2007*), suggesting that plasma cells and DCs have a role in the development of muscle inflammation. Indeed, plasma cells (CD138+) have been found to infiltrate muscle fibres in PM to a greater extent than immature activated B-cells, and molecular characterisation of Ig variable region sequences showed isotype switching and somatic hypermutation in the presence of clonal expansion, suggesting that a local antigen-driven maturation of B-cells in inflamed muscle may occur. Effectiveness of anti-CD20 treatment in IIMs suggests that activated immature B-cells are also involved in the pathogenesis of muscle damage, but the driving antigen still remains unclear.

4.1.1.3 Autoantigens and autoantibodies

Autoantibody specificities and their usefulness in the clinical evaluation of IIMs are discussed in detail in section 6.5. From the pathogenetic point of view, it is possible that MSAs play a pathogenetic role, since their serum levels correlate with disease activity. Probably, autoantibody-mediated damage in IIMs results from well-characterised mechanisms—for example, antibody-dependent cellular cytotoxicity or complement fixation. The question is how ubiquitously expressed intracellular autoantigens drive damage to a particular muscle or specific disease phenotypes—eg the antisynthetase syndrome (ASSD).

The increased tissue- and muscle-specific antigen immunogenicity in IIMs, thereby shaping a dedicated immune response, has been linked to two different mechanisms: first, the increased expression of antigens in muscle tissue and second, the acquisition of adjuvant activity by autoantigens (Suber et al, 2008*). Regarding the first mechanism, it has been shown that myositis-specific autoantigens are overexpressed in inflamed muscle in IIMs, particularly by regenerating muscle cells, which can therefore emerge as preferred targets of the immune response. Moreover, most antigenic autoantigens have proinflammatory properties and can themselves exert a chemoattractant effect on immune and inflammatory cells; in this regard, it is interesting to note that the histidyl-tRNA synthetase (Jo-1) can attract leucocytes through chemokine receptor 5, while this does not apply to other non-immunogenic synthetases (e.g., aspartyl-tRNA synthetase). Regarding the second mechanism, self-antigens may become more immunogenic, as they are released in the extracellular space and undergo post apoptotic modifications. It is noteworthy that a common feature among myositis-specific antigens is their susceptibility to granzyme B-mediated cleavage, which is secreted by cytotoxic lymphocytes and CD28 null T-cells, thereby generating new antigen conformations and/or neo-epitopes that can trigger the positive selection of autoreactive T and B-cell clones. Interestingly, the initiating tissue in some cases may be far from the muscle itself. For example, a new conformation of the histidyl tRNA synthetase (e.g. the Jo-1) is found in the lungs of ASSD with interstitial lung disease (ILD) (Levine SM et al, 2007). Additionally, T-cells infiltrating muscle tissue were shown to express the same TCR as T-cells coming from bronchoalveolar lavage of such patients, showing a large expansion of the variable region TCR-V3b. This suggests that the triggering antigen of the primary immune response is localised in the lung, at least in anti-Jo1 positive patients. Finally, association of most myositis autoantigens with nucleic acids makes them likely to stimulate the IFN type I secretion pathways, which in turn can increase antigen availability and propagation of the immune response, as discussed later in this section.

4.1.1.4 Dendritic cells: DCs can link innate immunity with adaptive immunity; they function as sentinels of the immune system exposing a variety of pattern-recognition receptors (e.g., TLRs and C-type lectin receptors (CRLs)) by which they capture antigens in the periphery and then become activated mature professional APCs capable of priming and activating antigen-specific T-cells. Myeloid DCs mostly function as APCs, whereas plasmacytoid DCs are major producers of type I IFN. Both DC types have been found in inflammatory muscular

infiltrates of patients with IIMs (PM, DM, juvenile-DM and, to a lesser extent, IBM) at both immature (CD1a+) and mature stages (CD83 and DC-LAMP) (Greenberg, 2005). The presence of their ligand CCL20 together with the lack of the C-C motif chemokines CCL19 and CCL21 suggests that maturation of DCs can occur locally, leading to an abnormal accumulation of activated DCs in muscle.

4.1.2 Innate immunity

4.1.2.1 Interferon signature

Type I IFN is known to foster autoimmunity in several autoimmune systemic disorders including systemic lupus erythematosus (SLE). Growing evidence suggests that activation of IFN α/β pathways can also sustain autoimmunity in IIMs through enhancement of innate responses, induction of maturation of B-cells and DCs and stimulation of cytokine production by bystander cells (Greenberg, 2005). Patients with IIM show an increased expression of IFN-inducible genes in muscles and blood. Plasmacytoid DCs are probably the major local producers of IFN I as they can be stimulated by immune complexes containing RNA, similar to the process in SLE. Interestingly, recent data have shown that immature muscle precursors also act as a local source of IFN β in inflamed muscle. Recently, a high IFN score, potential trigger for type I IFN pathway activation in peripheral blood, has been associated with DM, IBM and with autoantibodies against RNA-binding proteins, such as the anti-Jo1 (Ekholm L et al, 2016).

4.1.2.2 Pattern-recognition receptor activation

Pattern-recognition receptors (Toll-like receptors, TLRs, and C-Type Lectin Receptors, CLRs) are usually activated by sensing microbial pathogen-associated molecular patterns, or they can be activated by endogenous ligands with concurrent nucleic acid-associated autoantigen recognition, leading to dysregulated activation of the immune cells on which they are expressed—for example, DCs. Interestingly, TLR3 and TLR7 are overexpressed in inflamed muscle tissue during IIM, whereas they are absent in non-inflammatory myopathies or healthy muscle (Cappelletti et al, 2011). Additionally, immature muscle precursors express high levels of TLR, the activation of which leads to increased IFN β release, which in turn can stimulate HLA-I expression on muscle cells. Upon TLR stimulation, immature muscle precursors can themselves release proinflammatory cytokines—for example, IL-6, or chemokines such as CCL20, which contribute to further T-cell recruitment and differentiation towards a proinflammatory Th17.

4.1.2.3 Cytokines

A high number of cytokines and chemokines has been detected in muscle tissue from patients with myositis and may play a role in the pathogenesis of myositis. The most frequently reported cytokines in all three traditional subsets of IIM are the proinflammatory cytokines IL-1 α , IL-1 β and TNF α . Recent clues have linked TNF α overexpression with muscle wasting. Indeed, cytokine expression on muscle specimens from patients with

myositis showed that myogenic miRNAs were reduced in comparison with healthy controls. Moreover, lower levels of myogenic miRNAs were coupled with higher levels of proinflammatory cytokines, including TNF α . Thus, it is suggested that TNF α might inhibit the differentiation of myoblasts into myocytes in the inflamed muscle (Georgantas et al, 2014). Recently, another proinflammatory molecule, the DNA-binding high-mobility group box 1 (HMGB1), was demonstrated with an extra nuclear and extracellular pattern in muscle tissue of patients with PM and DM. HMGB1 is ubiquitous and found in the nuclei of all cell types, but can be released from monocytes and macrophages on stimulation. Moreover, HMGB1 can be released from cells that undergo necrosis and is thus characterised as alarming. HMGB1 can induce production of other proinflammatory cytokines such as IL-1 and TNF. Thus, HMGB1 may be an endogenous factor that can induce and perpetuate inflammation by its release from injured cells, such as degenerating or necrotic muscle fibres or by active release from macrophages. Cytokines may induce upregulation of MHC class I and II molecules on muscle fibres but may also have a direct effect on muscle fibre function, as shown for TNF α and for HMGB1. IL-15 may induce the inflammatory infiltration of macrophages in PM patients through the NF- κ B pathway and MMP-9 expression level (Yan W et al, 2016). Furthermore, serum levels of IL-35 could act as a IIMs disease activity marker and as a risk factor for the occurrence of oesophageal involvement. Even if IL-35 may participate in the pathophysiological processes of IIMs, involved mechanisms are not known (Yin L et al, 2016). The importance of different cytokines and chemokines in the disease mechanisms of myositis is still uncertain but they constitute potential targets for development of new treatments.

4.2 Non-immune mechanisms

Recent studies highlighted the role of non-immune-mediated muscle damage in IIMs. The major mechanisms involved are endoplasmic reticulum (ER) stress, hypoxia and autophagy, which are thought to be tightly linked. Among these, the best characterised is ER stress. ER stress is generated after accumulation of misfolded or unfolded cellular proteins within the organelle. It can result in both the unfolded protein response or in the ER overload response, which are not mutually exclusive and lead to exaggerated gene expression of proinflammatory cytokines, adhesion molecules, HLA-I molecules and further fuelling of the ER feedback loop (Vitadello et al, 2010; Ghirardello et al, 2011). The overexpression of class MHC I molecules in muscle cells causes large amounts of MHC transcripts to accumulate within the ER, thereby enhancing a stress response which results in activation of the NF- κ B pathway via the ER, further ER flooding with induced gene transcripts and, eventually, cell death and autoantigen release in the extracellular space. Moreover, the sarcoplasmic reticulum is a specialised form of ER in muscle cells, which is responsible for calcium homeostasis; hence, perturbations of sarcoplasmic reticulum function due to overload may cause muscle cell disruption and further antigen release, which, in turn, can bind autoantibodies and activate IFN type I secretion, leading to a proinflammatory feedback loop.

4.3 A unifying hypothesis

How innate and adaptive immune responses together can generate and perpetuate inflammation in muscle is still a matter of debate; however, a unifying hypothesis has been proposed converging on the role of immature muscle precursors.

Immature muscle precursors are juvenile regenerating muscle fibres awakening in injured muscles. Previous findings have shown that regenerating muscle fibres express high levels of myositis-specific autoantigens, yet antigens are scarce on mature myotubes. Furthermore, mechanisms underlying activation and differentiation of myoblasts along the myogenic lineage are likely to resemble postnatal myogenesis. Thus, it is probable that on a predisposed genetic background any muscle damage induces repair pathways, during which myositis autoantigen expression and release are increased. Since autoantigens are mainly composed of protein–nucleic acid complexes they can induce TLR stimulation on their own or after ligation of cognate autoantibodies, thereby leading to type I IFN production, IL-6 and CCL20 release, DC stimulation and a self-perpetuating feedback loop resulting in lymphocyte activation and autoantibody production. These mechanisms are also likely to play a role in paraneoplastic IIM. Antigenic similarity with regenerating myoblasts and even expression of myositis autoantigens has been proved in cancer cells, which may result in cross-reactivity with muscle tissue (Casciola-Rosen et al, 2005*). Interestingly, muscle specimens of patients with cancer but without IIM showed histopathological features similar to those seen in IIM, with signs of muscle damage and regeneration. Possibly, inflammation evoked by the malignancy may injure muscle tissue, thus allowing antigen availability for the anti-tumour immune response, which would also affect muscle tissue (Ghirardello et al, 2011). Finally, damaged regenerating muscle fibres increase surface expression of HLA-I, which is also fostered by IFN β within an inflammatory microenvironment and as such become more susceptible to T-cell-mediated cytotoxicity and to ER stress responses, causing further autoantigen release. Thus, immature muscle precursors may serve as both targets and culprits of the autoimmune response, leading to muscle inflammation (Tournadre and Miossec, 2013).

5 Clinical features

5.1 Polymyositis and dermatomyositis

5.1.1 Muscle involvement

Muscle weakness with impaired muscle endurance and excessive muscle fatigue are common symptoms of PM/DM. The weakness is most pronounced in proximal muscle groups, usually with subacute or insidious onset and symmetrical distribution. Patients typically have difficulty in rising from chairs, and walking uphill or upstairs. In untreated cases muscle weakness progresses slowly, leading in most severe cases to wheelchair dependence. Patients may have difficulty in swallowing and eating owing to impaired contractility of the palatal and

pharyngeal muscles. This condition may put the patients at high risk of aspiration pneumonia, and so the airway may need temporary protection using tube-assisted feeding. In some patients, palatal and pharyngeal muscle weakness may also cause voice alterations. Breathing difficulties due to weakness of the diaphragm and/or the thoracic muscles are possible but they occur rarely. In severe cases, temporary assistance with mechanical ventilation is required.

5.1.2 Skin involvement

Cutaneous manifestations of DM are frequently pathognomonic. They may precede the muscle symptoms by months or years. Patients who have hallmark cutaneous manifestations of classic DM occurring for ≥ 6 months in the absence of clinical or laboratory evidence of myositis are classified as having a clinically amyopathic DM. This form of myositis may also be associated with malignancies, as is the case of classic DM. Other forms of DM are hypomyopathic DM, in which cutaneous manifestations of DM are associated with subclinical evidence of myositis; post-myopathic DM, in which patients with previous classic DM recover from myositis but the skin rashes remain active; and DM sine dermatitis, in which no rash is detected but histological features of the muscular biopsy sample are indicative of DM.

Gottron's papules (or plaques), which are about 1 mm thick, violaceous, pink or dusky red papules located over the dorsal side of metacarpal or interphalangeal joints (figure 1), are considered to be pathognomonic of DM. These papules may also occur over the extensor side of the wrist, elbow, knee or other joints. Macules located in the extensor site of joints are also described and are called 'Gottron's sign'. Another characteristic skin rash in DM is the heliotrope rash, a periorbital violaceous erythema of one or both eyelids often with oedema (figures 2 and 3). Red or violaceous erythemas may also be located over the shoulders, neck and chest (shawl sign, V-sign) (figures 4 and 5) or over the hips (holster sign) (figure 6). Other characteristic skin lesions are the periungual nailfold telangiectasias and/or cuticular haemorrhage, infarct and/or dystrophy (figure 7). Mechanic's hands consist of hyperkeratosis and scaling and fissuring of the skin, particularly of the radial side of the index finger; and it is more commonly associated with anti-Jo-1 autoantibodies as part of the ASSD (figure 8). A severe generalised erythema, or erythroderma (figure 9), occasionally with vesiculobullous lesions or ulcers (figure 10), may rarely occur. Other uncommon skin lesions are panniculitis, livedo reticularis (figure 11), non-scarring alopecia and vesiculobullous lesions. Cutaneous calcinosis, sometimes severe and painful, is occasionally seen in adults, being more common in juvenile-DM, (figure 12). Calcinosis predominantly occurs at sites that are subject to pressure or friction, such as the dorsal side of the elbows, it may be localised to the skin, subcutaneous fat, fascia and muscle, and it can be clearly visible in skin or muscle on X-ray/MRI examination. A DM skin rash may be precipitated or aggravated by UV light exposure. Patients with DM skin manifestations may complain of itching and pain. Histopathological skin features are non-specific and mostly overlap with those seen in patients with SLE. Thus, skin biopsy is an unhelpful diagnostic tool for DM.

Figure 1 Gottron's changes are defined as erythematous to violaceous papules and plaques (Gottron's papules), or macules (Gottron's sign), over extensor surfaces of joints, generally distributed symmetrically. The figure shows the most common distribution over the metacarpophalangeal and interphalangeal joints (A), occasionally with a hint of ulceration in a juvenile patient (B). An interarticular rash may occur at the same time in some patients (C). (Images courtesy of Dr J Vencovsky.)

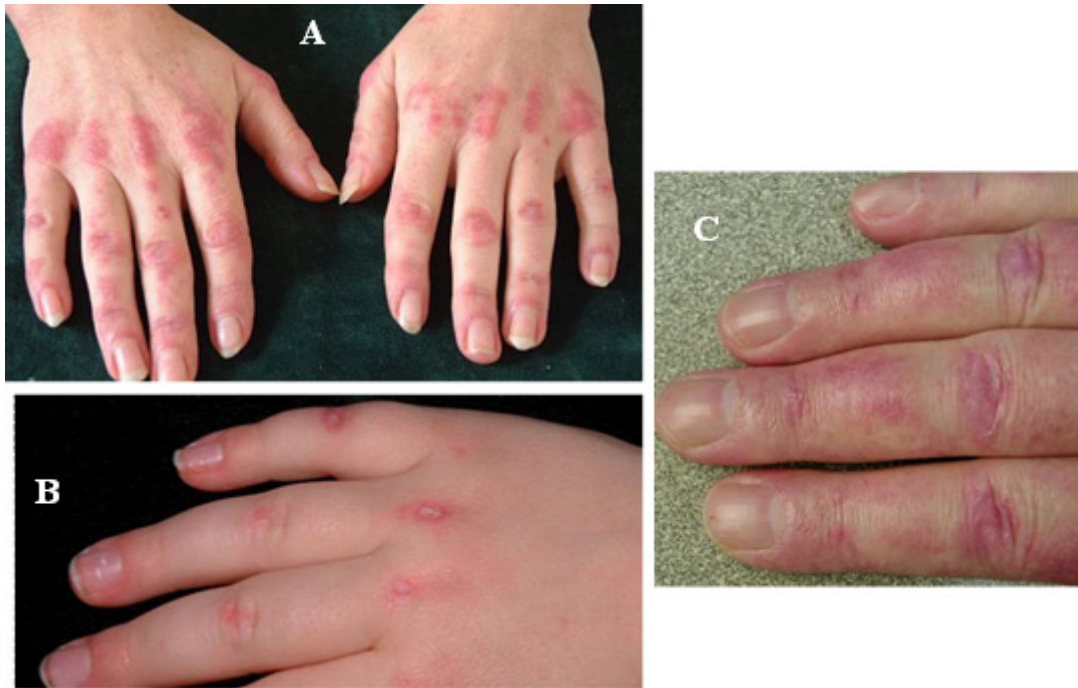


Figure 2 Cutaneous changes—heliotrope rash, periorbital oedema. This is a fairly typical rash on the upper and lower eyelids, often found together with oedema of the soft tissue around the eyes. It usually responds quickly to treatment. Reproduced with the patient's or parent's consent. (Images courtesy of Dr J Vencovsky.)



Figure 3 Relapse of rash around eyes (periorbital heliotrope rash) and in the face after this patient herself discontinued glucocorticoid treatment prematurely. Reproduced with the patient's consent. (Image courtesy of Dr J Vencovsky.)



Figure 4 Classic distribution of the rash in dermatomyositis. This is called the shawl sign, because it copies its distribution. (Images courtesy of Dr J Vencovsky.)



Figure 5 Rash in dermatomyositis often involves the face and chest in the shape of V. Note depigmentation on the chest which frequently occurs after some time during the course of the illness. Reproduced with the patient's consent. (Image courtesy of Dr J Vencovsky.)



Figure 6 Typical rash on the lateral part of the thigh (holster sign). (Images courtesy of Dr J Vencovsky.)



Figure 7 Periungual capillary changes. There is a dilatation of the nailfold capillaries, which may be accompanied by vessel dropout (A, B). In some severe and active cases, vasculitis and necrosis can be seen in the acral parts of fingers (B). This is more common in children but may occasionally be seen in adults also, as is in this case. (Images courtesy of Dr J Vencovsky.)

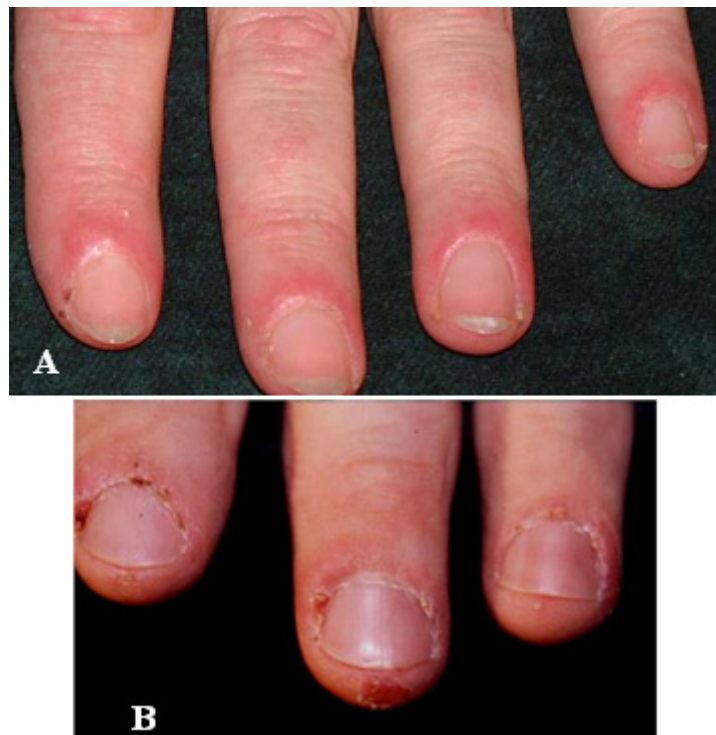


Figure 8 Mechanic's hands are defined as hyperkeratosis and scaling with frequent fissuring and cracking along the lateral and palmar aspects of the fingers. Usually the first and second fingers are affected most. Occasionally, the fissuring is deep and very painful. Sometimes the skin is just hard and looks dirty. Note also the Gottron's signs over the metacarpophalangeal joints. (Images courtesy of Dr J Vencovsky.)



Figure 9 Rash may occasionally be extensive—erythroderma, involving sun-exposed and non-sun-exposed skin. (Image courtesy of Dr J Vencovsky.)



Figure 10 Ulcers on the skin can appear in different locations. They originate from vascular changes to the epidermis and dermis and can be sometimes very deep and difficult to heal. Ulcers in two patients with dermatomyositis are shown. Ulcer (A) under the breast; (B) in the armpit. (Images courtesy of Dr J Vencovsky.)



Figure 11 *Livedo reticularis in a patient with dermatomyositis. (Image courtesy of Dr J Vencovsky.)*



Figure 12 *Calcinosis. Subcutaneous calcifications (usually not intramuscular) are more common in juvenile dermatomyositis than in adults. However, they can infrequently also be seen in adult polymyositis/dermatomyositis. It is a difficult condition to treat. When drug treatment fails, it is possible to remove some calcifications surgically (A). In some cases calcinosis is diffuse and no surgical removal is possible. Extensive calcinosis located under the skin of the torso in an adult patient with dermatomyositis led to problems with movement and with breathing (B). (Images courtesy of Dr J Vencovsky.)*



5.1.3 Lung involvement

The prevalence of lung involvement in IIMs varies from 5% to 90% depending on diagnostic methods used and population assessed. Dyspnoea and cough are the main suspect symptoms for lung involvement. Even if the most common pulmonary complication is ILD, also respiratory muscle weakness may aggravate dyspnoea. ILD can be detected by sensitive techniques such as lung high-resolution computed tomography (HRCT) (figures 13 and 14) and pulmonary function tests (PFTs) plus carbon monoxide transfer factor (DLCO). Lung HRCT may identify the underlying type and extension of interstitial involvement, occurring mainly in the form of Non Specific Interstitial Pneumonia (NSIP) (Kiely PD et al, 2013) and complicating in particular the clinical course of ASSD patients (Cavagna L et al, 2015*). Other less commonly observed patterns of interstitial involvement are organizing pneumonia (OP), usual interstitial pneumonia (UIP) and diffuse alveolar damage (DAD). PFTs may show a restrictive pattern and the DLCO is generally reduced since the early phases of lung involvement. In PM/DM, ILD onset may precede, be concomitant or follow the onset of myositis, whereas in ASSD it may occur also without myositis, with or without concomitant joint involvement (see paragraph 5.1.8)

ILD presentation is heterogenous. In the acute/subacute forms, dyspnoea begins acutely and progresses rapidly; an acute life-threatening onset is also possible. In chronic onset, dyspnoea begins insidiously and progresses slowly. Furthermore, lung involvement can be an instrumental finding only, without clinical correlates (asymptomatic onset), although the meaning of this form is uncertain. Responsiveness to immunosuppressive therapy varies between patients and according to different histopathological patterns and autoantibody profile.

Aspiration pneumonia is another serious lung manifestation that is related to an underlying oesophageal and deglutitory muscles involvement (see paragraph 5.1.6) and that may be worsened by the concomitant occurrence of a bacterial infection.

In patients with IIM who develop ILD, progressive pulmonary scarring and intrapulmonary hypoxia may ensue and over time leads to progressive pulmonary hypertension and right-heart strain. Right-heart failure and death may result, thus optimal treatment of myositis-associated ILD should be early and appropriately aggressive to prevent such complications. Lastly, growing attention is focusing on pulmonary arterial hypertension (PAH) in IIMs (Sanges S et al, 2016), a form of pulmonary hypertension not related to the extension of ILD, but related to the occurrence of a primitive vascular inflammation, such as in idiopathic PAH. This rare manifestation may respond to a combination of immunosuppressants and PAH specific treatments. The concomitant occurrence of ILD and PAH is another possibility, particularly in ASSD. This association dramatically worsens patients' prognosis (Hervier B et al, 2013).

Figure 13 CT scan of interstitial lung disease in a patient with polymyositis and antisynthetase syndrome. (Source: CRI (Club Rhumatismes et Inflammation, <http://www.cri-net.com>; image courtesy of Dr J Vencovsky.)

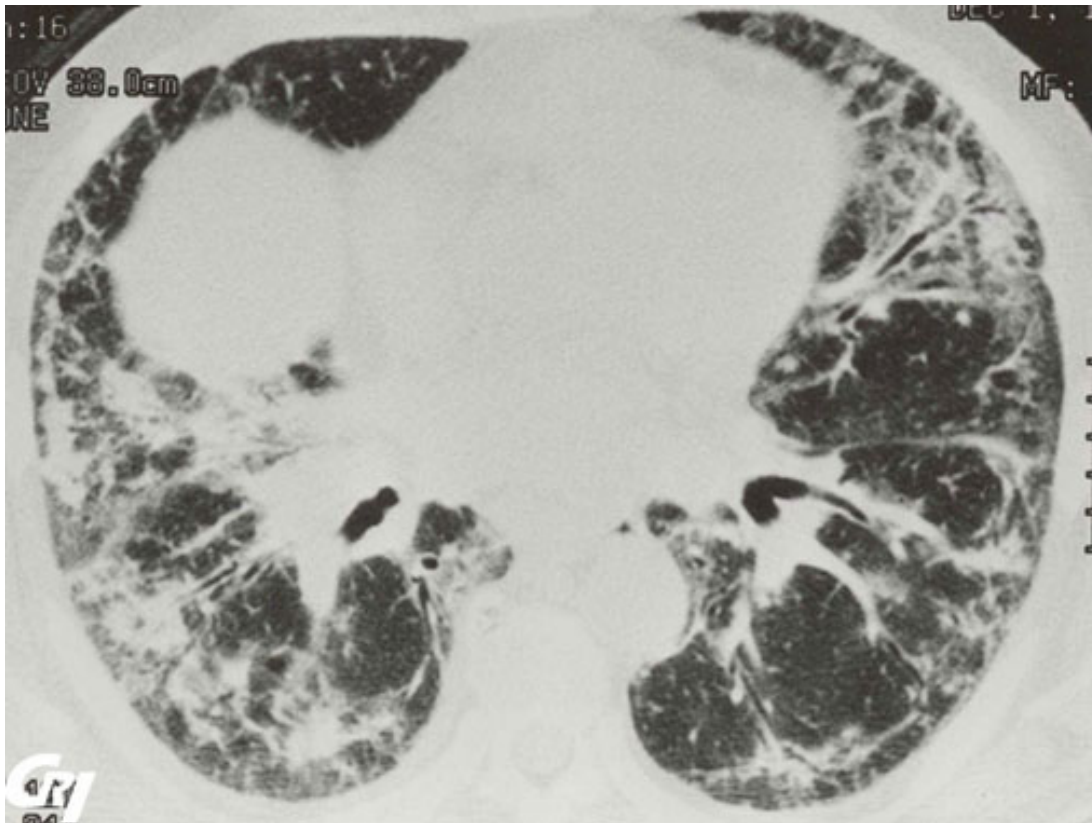
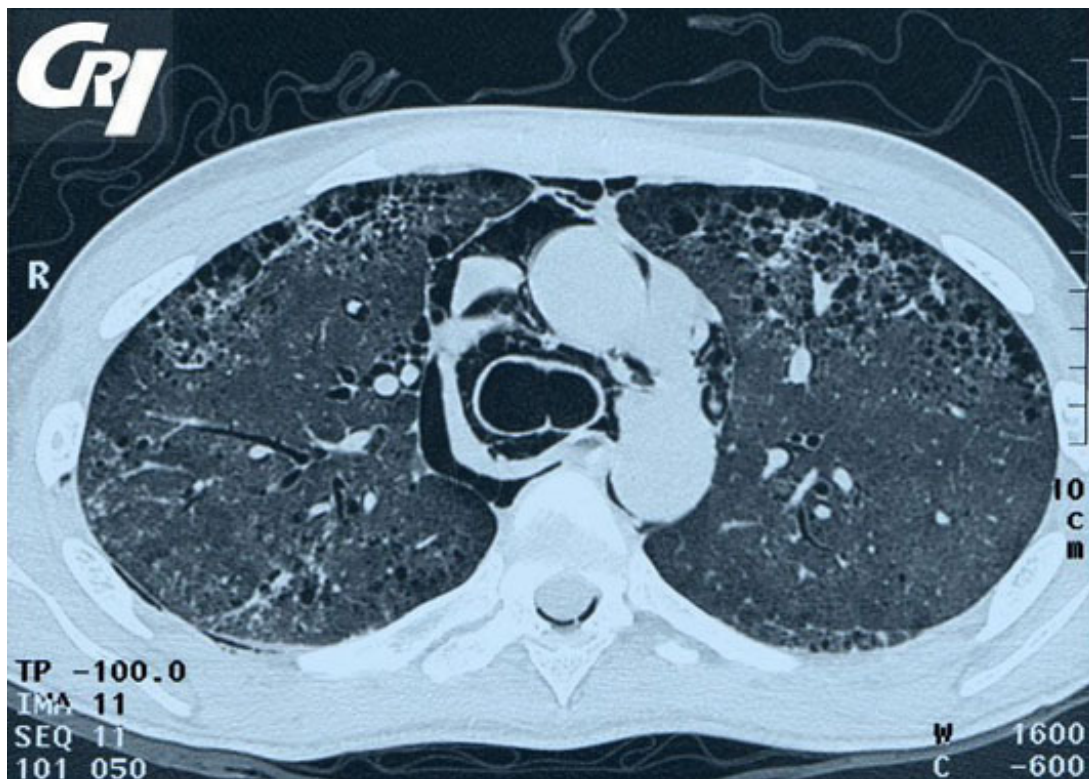


Figure 14 CT scan of severe diffuse alveolar disease in a patient with antisynthetase syndrome. (Source: CRI (Club Rhumatismes et Inflammation, <http://www.cri-net.com>; image courtesy of Dr J Vencovsky.)



5.1.4 Musculoskeletal findings

Arthralgias and arthritis are common in IIMs, particularly in patients with ASSD. In these patients, arthritis may be the first disease manifestation, often previously misdiagnosed as primary inflammatory arthritis (e.g. rheumatoid arthritis), at least until the subsequent occurrence of muscle or lung involvement becomes overt. In fact, when arthritis occurs in IIMs, it affects mainly small joints of the hands and feet, and in the subset of ASSD it may be very similar to rheumatoid arthritis (see In depth Discussion 3).

5.1.5 Heart manifestations

Although clinically significant heart involvement is rare, subclinical involvement in IIMs is common. Subclinical manifestations are dominated by conduction abnormalities, arrhythmias and heart rate variability detected by ECG, and by diastolic dysfunction detected by Doppler echocardiography. An inflammatory myocardial involvement is possible, since inflammation similar to that seen in the skeletal muscle can occur also in the myocardium. Furthermore, patients with PM/DM have an increased risk of developing atherosclerotic coronary artery disease (from twofold to fourfold), that, along with the increased prevalence of traditional cardiovascular risk factor, explains the prognostic impact of heart involvement in IIMs (Schwartz T et al, 2016).

5.1.6 Gastrointestinal involvement

Swallowing difficulties are often reported in PM/DM and, in particular, in IBM. In most severe cases, palatal and pharyngeal weakness may lead to aspiration pneumonia. The pathophysiology is related to weakness in the tongue, palate and pharyngeal muscles or sometimes also, in the lower oesophagus. Even if oesophageal dysfunction assessment techniques in IIMs are not standardized, electrodiagnostic tests, fibre-optic endoscopic evaluation of swallowing and oro-pharyngo- oesophageal scintigraphy could be considered useful tools. An underlying oesophageal dysfunction should be carefully considered in all IIMs patients. Gastro-oesophageal reflux is common and it may occur in 15–50% of patients. Constipation, diarrhoea and stomach pain are common symptoms and may result from disturbed motility of the gut or from gastrointestinal tract inflammation. Vasculitis in the blood vessels of the gastrointestinal tract is rare but it may be complicated by intestinal bleeding.

5.1.7 Malignancies

In comparison with the normal population, patients with IIMs have a higher risk of malignancy. This is mainly evident in DM (30% of cases), in particular if men, in old age (Zampieri et al, 2010*) and with dysphagia (Kang EH et al 2016). The risk of malignancy is particularly increased in the first years after disease diagnosis. The type of cancers associated with IIMs are lung, ovary, breast, colon and non-Hodgkin lymphoma (Kang EH et al, 2016). In some cases the association between DM and malignancies may be a paraneoplastic phenomenon, and thus, if the cancer is successfully treated, DM manifestations resolves. However, in other cases the development of

myositis is subsequent to malignancy or, despite treatment of the underlying cancer, the IIM does not improve. For PM and IBM the association with malignancy is less common.

Screening for cancer is recommended in patients with DM at diagnosis, possibly yearly thereafter, in case of relapse or of refractory disease (see in depth Discussion 2).

5.1.8 Antisynthetase syndrome

Antisynthetase syndrome (ASSD) is a clinically distinct IIM subset, affecting adults at any age, mainly females (F:M=3:1), positive for anti-aminoacyl-transfer RNA synthetase (ARS) antibodies and characterized by a highly variable clinical picture. The most frequent anti-ARS antibody is the anti Jo-1, directed against the histidyl-tRNA synthetase, whereas other specificities are less frequently identified (eg, anti-PL7, PL12, OJ, EJ, KS, Ha, Zo, see section 6.5.1). ILD, myositis and arthritis represent the classic clinical triad of the disease, with frequencies ranging from 60% to 95% of cases in different casuistries. Fever, Raynaud's phenomenon (RP) and mechanic's hands (MHs) are other important manifestations, even if less commonly observed (up to 50% of cases). It has been recently shown that in anti Jo-1 positive ASSD, the clinical triad of the disease is rarely observed at disease onset and frequently encountered at last follow-up, thus indicating that the ex-novo occurrence of triad findings lacking at disease onset is typical of this disease. This is particularly evident in patients presenting with an isolated triad finding (Cavagna L et al, 2015*), arthritis in particular (Cavagna L et al, 2016). The ex-novo occurrence of fever, MHs and RP during follow-up increases of four-fold the risk for the occurrence of triad findings lacking at disease onset (Bartoloni E et al, 2017). ILD is the main prognostic factor in ASSD. Similarly to PM/DM, NSIP is the most frequent ILD pattern. Joint involvement, that will be discussed in the in depth Discussion 3, ranges from simple polyarthralgias to a symmetrical, erosive, rheumatoid factor and anti-cyclic citrullinated peptide antibody positive polyarthritis. In ASSD muscle involvement is clinically similar to that previously described for PM/DM. Due to the lack of well-established classification criteria, several patients that are generally diagnosed with ASSD (eg an anti-Jo1 positive patient with ILD and with an oligoarthritis) could be classified as Interstitial Pneumonia with Autoimmune Features (IPAF) (Scire CA et al, 2017). Differences in clinical spectrum presentation and evolution between anti-Jo1 and non-anti-Jo1 positive ASSD should be assessed on large casuistries, even if an isolated ILD seems to be more common in non-anti-Jo1 positive patients. Non anti-Jo1 positivity impacts patients' survival (Hervier B, et al, 2012). It is important to remember that anti-Ro antibodies (mainly anti-Ro52 kDa) and anti-ARS antibodies co-occur in about 50% of cases (Cavagna L, et al 2015), and that a cytoplasmic positivity of ANA is commonly observed in ASSD (Aggarwal R et al, 2016).

6 Diagnosis

The diagnosis of IIMs is based on clinical, laboratory and histopathological findings. IIM should be suspected in adult patients with symmetrical, proximal skeletal muscle weakness or in cases of typical skin findings. Skin manifestations are easy to recognise by physical examination. Gottron's and heliotrope rashes are DM-specific

manifestations and usually do not require histological confirmation. When muscle involvement is suspected, muscle biopsy could be indicated. Biopsy is usually performed in an area with active muscle involvement in the proximal muscles of legs or arms.

A careful differential diagnosis in cases of myopathy or increase of serum creatine kinase levels should be performed (box-1).

Box-1 Conditions that might mimic inflammatory myopathies or induce Hyper-Creatine-Kinase-Emia and that should be considered in the differential diagnosis of IIMS

- A. Genetic muscle disorders
 - a. Muscle dystrophies: limb girdle, Becker's Emery–Dreifuss, facio-scapulo-humeral, dysferlinopathy, distal muscle dystrophy and ocular muscle dystrophy
 - b. Congenital myopathies: mitochondria myopathy, nemaline myopathy and central core myopathy
- B. Neuropathies
 - a. Denervation: spinal muscle atrophy, amyotrophic lateral sclerosis
 - b. Others: Eaton–Lambert syndrome, myasthenia gravis, Guillain–Barré, chronic demyelinating neuropathy
- C. Metabolic myopathies
 - a. Glycogen storage disease: McArdle, acid maltase deficiency
 - b. Lipid storage disease
- D. Endocrine disorders
 - a. Hyperthyroidism
 - b. Hypothyroidism
 - c. Acromegaly
 - d. Cushing syndrome
- E. Hydroelectrolytic disorders
 - a. Hyperpotassaemia
 - b. Hypomagnesemia
- F. Infections
 - a. Viral myopathy (parechovirus type 3, parvovirus B19, Coxsackievirus, human enterovirus, HIV, etc)
 - b. Trypanosoma cruzi
 - c. Bacteria (pyomyositis)
- G. Toxic agents and drugs
 - a. Alcohol
 - b. Cocaine
 - c. (Hydroxy)Chloroquine
 - d. Cimetidine
 - e. Colchicine
 - f. Statins
 - g. Amiodarone
 - h. Anaesthetics (used for general anaesthesia, such as the volatile aesthetic agents and succinylcholine, associated with malignant hyperthermia, life-threatening condition)
- H. Myosin-loss myopathy (in patients admitted to Intensive Care Units, deep impact on prognosis)
- I. Non disease related conditions
 - a. Injuries
 - b. Intense physical activity
 - c. Intramuscular injections
- J. Others: granulomatous diseases
 - a. Sarcoidosis

6.1 Classification Criteria

Up to now no validated classification criteria exists, but a shared ACR and EULAR initiative is currently working on the release of new validated classification criteria. The criteria proposed by Bohan and Peter (Bohan and Peter, 1975) are the most widely used ones, but they have several limitations: they do not clearly specify how to exclude other forms of myopathy, they may misclassify IBM as PM, and muscular dystrophies with inflammation as PM, and each included criterion is not defined explicitly, resulting in criteria with high sensitivity and low specificity. Other criteria have been suggested by Tanimoto (Tanimoto K et al, 1995), having high sensitivity and low specificity, by Dalakas and Hohlfeld (Dalakas and Hohlfeld, 2003), having low sensitivity and high specificity, and by Targoff (Targoff IN et al, 1997), having high sensitivity and specificity (Table 1). In 2005, a Canadian group proposed a classification based on overlap syndrome features and autoantibody profile (Trojanov et al, 2005*), thus opening the perspective in the definition of IIMs by including these new and clinically relevant aspects.

	Bohan and Peter ¹	Tanimoto ²	Targoff ³	Dalakas and Hohlfeld ⁴
Muscle findings	Symmetrical, usually progressive weakness	Pain on grasping or spontaneous	Symmetrical, usually progressive weakness	Weakness with subacute onset, rapid progression, prevalently proximal
Muscle biopsy	Necrosis of type I and type II muscle fibres, Phagocytosis, Degeneration and regeneration of myofibers with variation in myofiber size, Endomysial, perimysial, perivascular or interstitial mononuclear cells	Inflammatory infiltrate, degeneration or necrosis of muscle, active phagocytosis, central nuclei, active regeneration	Necrosis, phagocytosis, regeneration, mononuclear inflammatory infiltrate	Compatible findings for PM (DEFINITE: primary inflammation with the CD8/MHC-1 complex and no vacuoles; PROBABLE: ubiquitous MHC-1 expression) or DM (perifascicular, perimysial or perivascular infiltrates; perifascicular atrophy)
Serum muscle-associated enzymes	CK, aldolase, LDH, transaminases	CK, aldolase	CK, aldolase, LDH, transaminases	CK, aldolase, transaminases
Electromyography	Short, small, low amplitude,	Electromyographic triad of myopathy	Short, small, low amplitude,	Myopathic pattern

	polyphasic motor unit potentials or fibrillation potentials even at rest or bizarre high frequency repetitive discharges			polyphasic motor unit potentials or fibrillation potentials even at rest or bizarre high frequency repetitive discharges		
Cutaneous findings	Characteristics rashes of DM	Heliotrope rash, Gottron's linear extensor erythema		Heliotrope rash, Gottron's papules		Typical rash or calcinosis
Auto-antibodies	X	Anti Jo-1		Any proven IIM-associated antibody		X
Articular findings	X	Non-destructive arthritis or arthralgias		X		X
Systemic findings	X	Fever or elevated CRP or ESR		X		X

Table 1: mainly diagnostic and classification criteria available for idiopathic inflammatory myopathies (IIMs), eg polymyositis (PM) and dermatomyositis (DM).

1 Bohan and Peter: definite PM if 4 criteria (excluding skin findings); probable PM if 3 criteria (excluding skin findings); possible PM if 2 criteria (excluding skin findings). Definite DM if skin findings + 3 criteria; probable DM if skin findings + 2 criteria; possible DM if skin findings + 1 criteria.

2 Tanimoto: definite PM if 4 criteria (excluding skin findings). Definite DM if skin findings + 4 criteria.

3 Targoff: Definite IIM if 4 criteria; probable IIM if 3 criteria; possible IIM if 2 criteria; differentiation between PM and DM is made by presence or absence of skin findings.

4 Dalakas and Hohfeld (diagnostic criteria): definite IIM if 4 criteria. **FIRST EXCLUDE all other myopathies by state-of-the art methods (this will change over time)**

6.2 Laboratory abnormalities

Creatine-kinase (CK) is the most useful serum enzyme for diagnosis and assessment of IIMs, but an increased serum CK level is not specific for myositis, as it may be raised in several conditions (see Box-1). Furthermore, normal serum CK levels vary in healthy people; men have higher levels than women and African-Americans higher levels than Caucasian subjects. CK levels are not always increased in patients with myositis, and for instance, 10–20% have CK levels within normal range when first tested, particularly patients with DM and IBM.

A critical concern is the serum tests used to detect myocardial sufferance, as CK-MB can be released from damaged cardiomyocytes and also from regenerating skeletal muscle fibres. In patients with myositis, without cardiac involvement, the CK-MB/total CK ratio may be >3%, which is a threshold commonly used to determine myocardial damage. A more specific marker for myocardial damage in patients with myositis is increased serum levels of cardiac isoform troponin I (cTnI). Also high serum levels of cTnT (e.g., >100 ng/L) detected by high sensitivity assays may point towards myocardial involvement.

Myoglobin is a skeletal and cardiac muscle protein released after tissue injury. It is sensitive as CK in myositis and serum levels vary with disease activity, but it is usually less readily available than CK. Myoglobin is filtered through the kidneys, with an increased risk of renal failure in case of high levels of serum myoglobin. This condition requires a strong hydration in order to force the diuresis and reduce the risk of kidney damage.

Other circulating muscle enzymes are lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase. On this basis, it is important to remember that the increase of aminotransferase enzymes should not only be considered as a condition secondary to liver diseases. Although these other enzymes are not muscle specific, they often correlate with CK in patients with myositis. Isolated lactate dehydrogenase levels may be a sign of haemolysis or a malignancy. Aldolase is another enzyme that can be used to verify muscle injury, but it is less muscle-specific than CK.

6.3 Electromyography

Diagnostic electromyography (EMG) is an essential part of the investigation of patients with suspect IIMs. The myopathic changes include myopathic motor unit potentials with or without spontaneous discharges and fibrillations. A pathological electromyogram with changes compatible with myopathy supports a diagnosis of myositis, but changes are not completely specific. Conversely, a normal electromyogram pattern does not preclude myositis, as myositis, and consequently EMG changes, may be focal. An advantage of EMG, however, is that several muscles can be examined during the same test session. The sensitivity to changes of EMG is uncertain, thus EMG is not recommended as an outcome measure for monitoring treatment. Certain neurological conditions can cause weakness and CK elevations—for instance, some rare neuropathic conditions and anterior horn cell disease, and so might mimic PM. Thus, and as for muscle biopsy, EMG should also be considered as mandatory to preclude occasional myositis misdiagnoses.

6.4 Muscle imaging

Ultrasound (US) was the first imaging tool used for muscle evaluation. Affected muscles usually appear to be normal or have an increased size and have low echogenicity, and raised perfusion in cases of acute muscular involvement. Echogenicity is increased and muscle size and perfusion are reduced in the chronic stage (Weber et al, 2009). Even if potentially useful (Haber GE et al, 2015), ultrasonography is not routinely used in the daily assessment of IIMs.

Muscle magnetic resonance imaging (MRI) is considered the 'gold standard' for the study of muscles in patients with IIM, providing a detailed anatomical view of the extent of muscle involvement and of potential sites for muscle biopsy. Symmetrical muscular oedema, particularly in the musculature close to the limbs, which correlates well with disease activity, is clearly seen in T2-weighted images and short tau inversion recovery (STIR)

(figures 15 and 16) (Del Grande et al, 2011*). In T1-weighted images, fatty atrophy of the musculature reflects the chronic phase of the disease.

Figure 15 Examples of MR images. Thigh muscles from patients with idiopathic inflammatory myopathies. Inflammation causes oedema, which is seen on images that suppress the signal from fat (short tau inversion recovery or T2-weighted image with fat suppression) as white matter. (A) Symmetrical involvement of extensors; (B) fasciitis may occasionally be seen; (C) continuing active inflammation in the atrophic muscles during long-term disease; (D) limited symmetrical inflammation only in musculus quadriceps femoris. (Images courtesy of Dr J Vencovsky.)

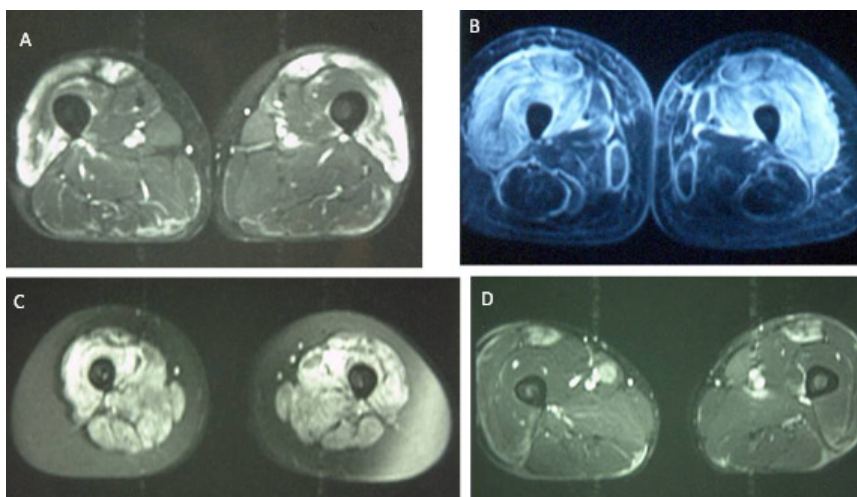
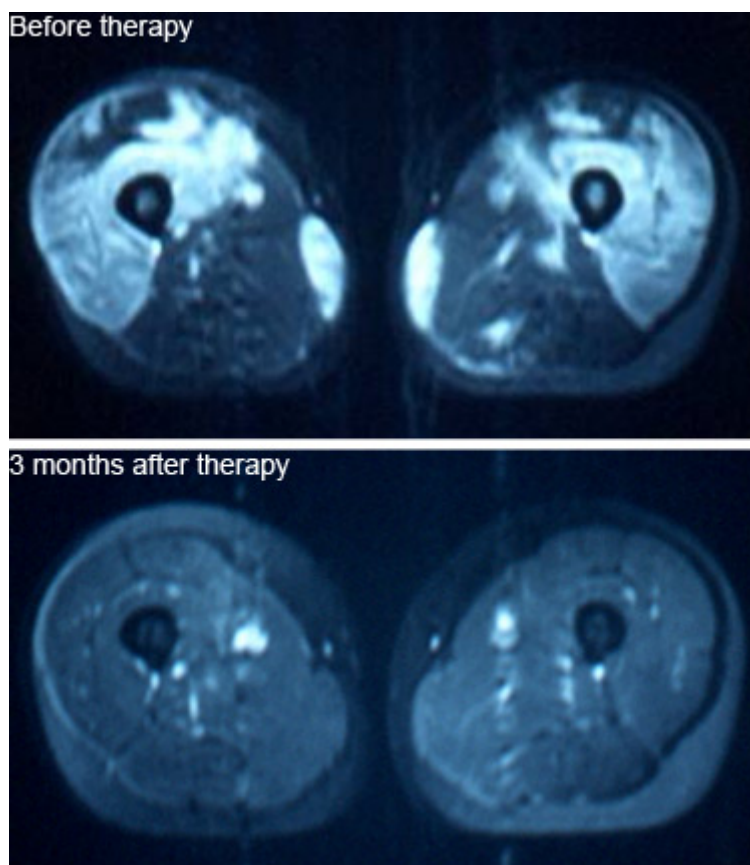


Figure 16 MR image (T2-weighted with fat suppression) in a patient with polymyositis who responded well to glucocorticoid treatment. (Images courtesy of Dr J Vencovsky.)



6.5 Muscle biopsy

Muscle biopsy in IIMs is useful for several reasons: (1) to confirm histologic muscle alterations of PM/DM; (2) to distinguish PM from IBM; (3) to exclude other myopathies such as dystrophies and metabolic myopathies, etc. A positive muscle biopsy is required for a definitive diagnosis of PM. In patients with skin changes characteristic of DM, the role of muscle biopsy in the diagnosis is questionable. A negative muscle biopsy does not exclude myositis, as inflammatory changes may be focal, and thus easily missed owing to sampling error.

To obtain optimal information from muscle biopsies, it is important to define: (1) the correct muscle biopsy site; (2) proper histological sampling; (3) proper handling of the biopsy specimen and (4) evaluation of the biopsy, which should be performed in a specialised laboratory with neuromuscular expertise.

1. The muscle selected for biopsy should preferably be symptomatic and not atrophic, as in muscles with severe atrophy it is more common to obtain samples with fibrosis and adipose tissue substitution. Muscle biopsy should be guided by imaging. MRI and US (if MRI is not available) can be used to localise areas with oedema suggestive of inflammation.
2. Several biopsy-sampling techniques are effective. A semi-open biopsy technique with conchotome, needle biopsy or open biopsy all give sufficiently sized biopsy specimens, as long as the operator is familiar with the technique. The advantage of the conchotome and needle biopsy techniques is that the trauma is minor allowing for repeated biopsies, if required during follow-up. Furthermore, several samples can be taken at the same time to ensure that an adequate amount of tissue is obtained for investigations. A drawback of the needle biopsy technique is that the cross-sectional area is smaller than for the other two techniques, and focal changes are more easily missed.
3. Proper handling of the biopsy specimens is essential to obtain optimal diagnostic information and to avoid artefacts, such as those due to ice crystal formation. The specimens should be frozen and the procedure should be agreed with the specialist neuromuscular laboratory where the samples are to be investigated. This is important as ice crystal artefacts preclude assessment of the biopsy. Frozen sections of muscle biopsy specimens are required for routine evaluations, both to identify the rimmed vacuoles seen in IBM and to carry out biochemistry and immunohistochemistry stainings, which must be performed routinely for several molecules depending on the clinical features and suspected diagnosis. More recently, immunoblot analyses have been introduced as a routine investigation to identify aberrations in proteins, such as those due to mutations in genes. They are also used to identify various muscular dystrophies that may clinically resemble myositis, such as limb girdle dystrophy and dysferlinopathy, which can sometimes have considerable inflammatory cell infiltrations in muscle tissue.

4. In view of the specialised nature of the analytical techniques required to assess muscle biopsy specimens, these should ideally be sent to a laboratory with specific expertise in myopathology and immunohistochemistry to obtain optimal information. For a clinician looking after myopathic patients, communication with a specialist neuropathologist is valuable to ensure that adequate investigations are performed on the biopsies. More recently, immunohistochemical staining for MHC class I antigens has been shown to be useful, adding information to the diagnostic procedure as a sensitive, although not specific, marker for myositis. Electron microscopy investigations require special fixation and are performed by the neuropathologist when clinically indicated. This technique is often required for identification of the tubular filamentous inclusions seen in patients with IBM.

6.5.1 Histopathology

The inflammation in myositis affects striated muscle but not smooth muscle. Occasionally, heart muscle may be involved. The cellular infiltrates of skeletal muscle are characterised by mononuclear inflammatory cells, mainly T lymphocytes and macrophages, but DCs, B lymphocytes and plasma cells can also be found. Other typical changes are degenerating, necrotic fibres and regenerating muscle fibres (figure 17). These are non-specific histopathological findings and may also occur in other muscle disorders. Atrophy of muscle fibres is a common and non-specific pathological finding, but if seen in a perifascicular distribution, it may be more specific, as this is predominantly seen in biopsy specimens from patients with DM, usually in a later phase of disease (figure 18). In patients with DM, the inflammatory infiltrates mainly have a perivascular and perimysial location and are dominated by CD4 T-cells and macrophages. Occasionally, B-cells are found. In PM the inflammatory infiltrates are mainly located in the endomysium surrounding muscle fibres. In these infiltrates there is a high prevalence of CD8 T-cells, but also CD4 T-cells and macrophages. The different localisation of the inflammatory infiltrates, perimysial versus endomysial, as well as the different predominating inflammatory cell types CD4 T-cells and CD8 T-cells, suggest that different disease mechanisms may cause myositis. These histopathological features are often confined to restricted muscle areas and in some cases a muscle biopsy specimen can result normal despite clinically evident muscle weakness. Furthermore, the extent of histopathological features does not correlate with the degree of muscle weakness. This observation is clinically important as a 'normal' looking biopsy specimen does not exclude a diagnosis of myositis. In addition, this raises the question regarding the mechanisms that cause muscle weakness in PM and DM, and what findings in the muscle correlate with symptoms. This will be discussed further below.

The histopathology of IBM resembles that of PM, with endomysial infiltrates with a predominance of CD8 T-cells and macrophages (figure 19). In addition, characteristic findings are rimmed vacuoles and intracellular amyloid deposits or 15–18 nm tubofilamentous inclusions found on electron microscopy. Early in the course of IBM, only the inflammatory infiltrates may be evident and the initial histopathology may be indistinguishable from that of

PM. If a patient labelled as having PM responds poorly to immunosuppressive treatment it is wise to consider a diagnosis of IBM, and to repeat the muscle biopsy.

Figure 17 Polymyositis muscle biopsy specimen, haematoxylin and eosin staining. Endomysial infiltrates surrounding muscle fibres and invading occasional muscle fibres. (Image courtesy of Dr Inger Nennesmo.)

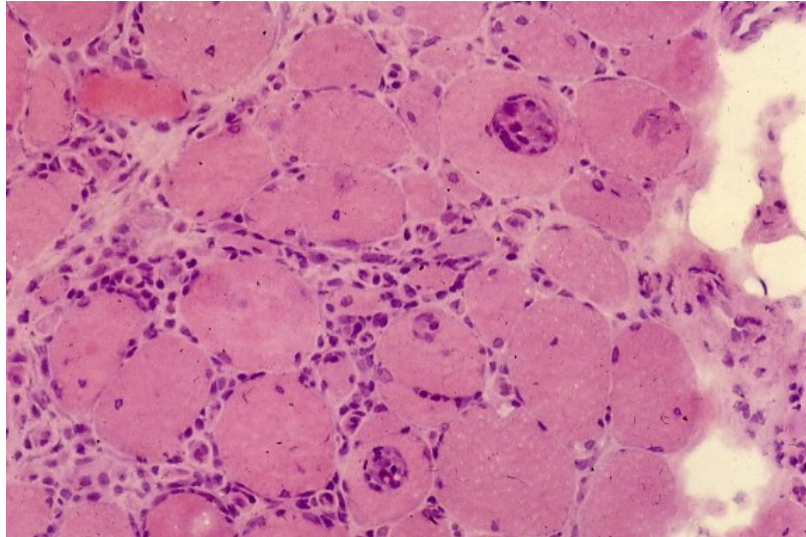


Figure 18 Dermatomyositis, muscle biopsy, haematoxylin and eosin staining. (A) Perivascular inflammatory infiltrate. (B) Perifascicular atrophy. (Images courtesy of Dr Inger Nennesmo.)

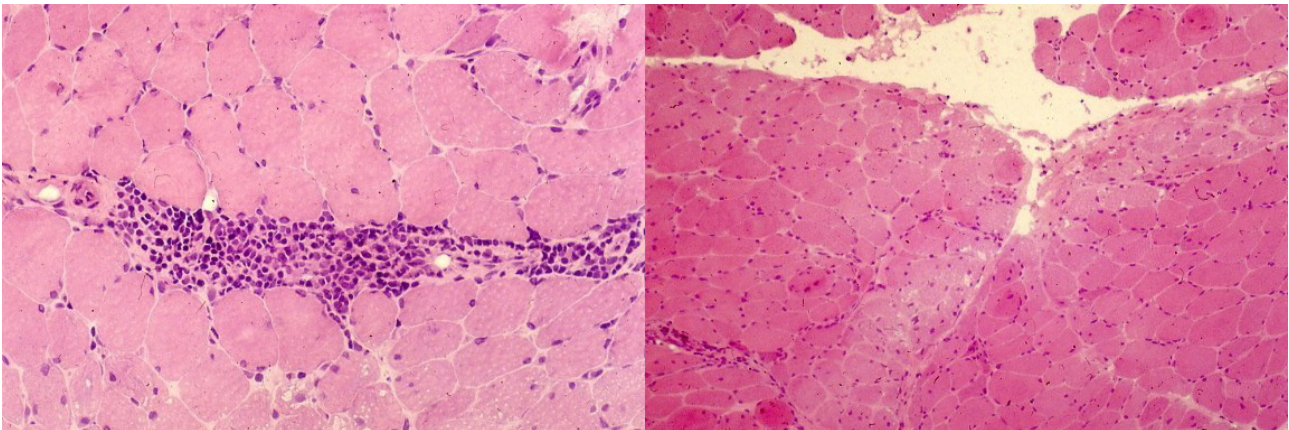
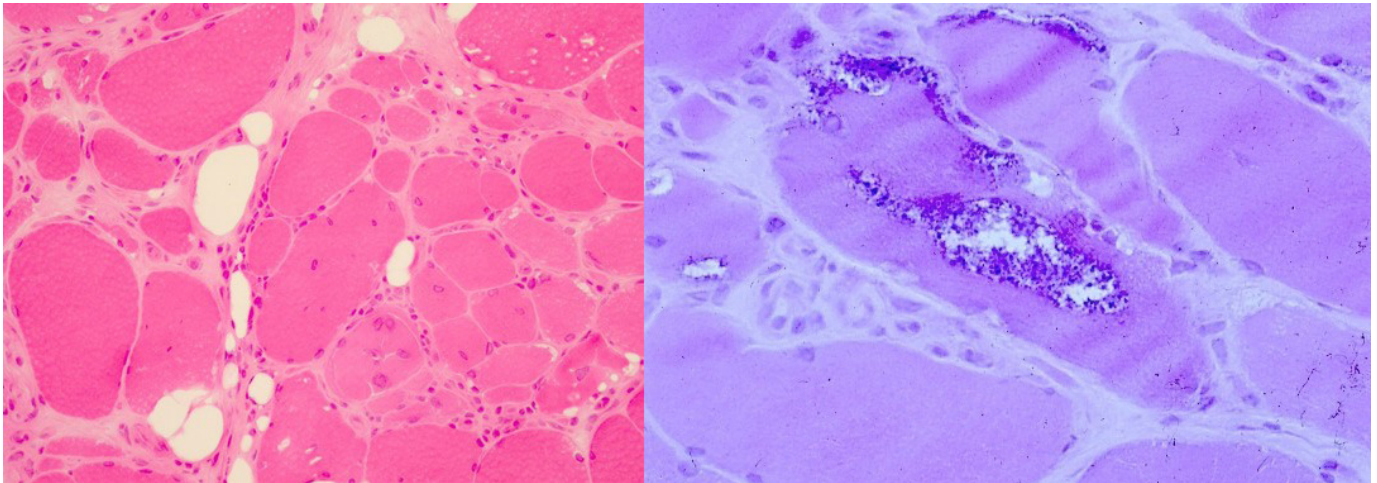


Figure 19 Muscle biopsy section from a patient with inclusion body myositis. (A) Haematoxylin and eosin staining, degenerating and regenerating fibres, infiltrates of mononuclear inflammatory cells. (B) Rimmed vacuoles. (Images courtesy of Dr Inger Nennesmo.)



6.6 Autoantibodies

Autoantibodies are a fundamental diagnostic tool, especially to confirm the diagnosis of IIM while contributing to the definition of disease subsets. Autoantibodies in IIMs are directed towards ubiquitous intracellular autoantigens. Autoantibodies are detected in about 60% of patients with myositis and are subdivided into two groups, based on their diagnostic accuracy: MSAs and MAAs, the latter mostly occurring in patients with myositis-overlap syndromes but also in connective tissue diseases without evidence of myositis (Ghirardello et al, 2013*).

6.6.1 Myositis-specific autoantibodies

MSAs are highly selective and mutually exclusive antibodies directed against cytoplasmic or nuclear components involved in the regulation of key processes, such as protein synthesis and translocation, gene transcription and viral recognition. The three best characterized antibodies target cytoplasmic enzymes (anti-ARS antibodies), the nuclear helicase protein Mi-2 and the cytoplasmic complex signal recognition particle (SRP). Moreover, several new MSAs have been recently described.

Anti-ARS antibodies are the most prevalent MSAs, found in 25–35% of cases and anti-Jo1 is the most common one (20–30% of myositis patients). Other less common specificities are represented by anti-PL7, PL12, OJ, EJ, KS, Zo and Ha (5% or less). All these antibodies are associated with a disease-related ILD, frequently isolated in anti-PL7 and PL12 positive patients (Hervier B et al, 2012). Casuistries addressed to non-anti-Jo1 anti-ARS antibodies are however, too little to allow firm conclusions. Anti-ARS antibodies positivity is associated with a reduced risk of concurrent neoplasm. Serum levels of anti-Jo1 (and of anti-Ro antibodies), correlates with disease activity levels of IIMs (Stone KB et al, 2007; Aggarwal R et al, 2016 b; Bauhammer J et al, 2016).

Anti-Mi-2 antibody, directed against a nuclear antigen with nucleosome remodelling activities, is an established serological marker of IIM, strongly associated with DM, in which it can be found in 10–30% of patients. Patients with anti-Mi-2 positivity usually have typical DM skin rashes such as Gottron's papules or sign, periorbital heliotrope rash, involvement of the neck and upper back ('V' and 'shawl' rashes) and cuticular dystrophies. These patients are less likely to develop cancer, ILD and polyarthritis and respond well to steroid treatment (Ghirardello et al, 2005; Hengstman et al, 2006b).

Anti-SRP autoantibody is reported in 4–8% of patients with IIM. There is evidence that the anti-SRP antibody identifies the so-called 'anti-SRP syndrome', a form of severe necrotising myopathy, clinically similar to PM, with rapidly progressive symptoms and poor response to treatment. Characteristic histopathological features consist of predominant muscle fibre necrosis and/or regeneration associated with scarce inflammation (Hengstman et al, 2006a*).

Anti-transcription intermediary factor 1 gamma (TIF1- γ) autoantibody is present in about one-fifth of DM patients with severe cutaneous involvement, and in ~50% of patients with cancer associated DM. Thus, if this antibody is present in a patient >65-year-old diagnosed with DM more thorough cancer screening is recommended. Anti-TIF1- γ is also found in about one-fifth of patients with juvenile-DM, where it is associated with aggressive skin ulceration without increased cancer risk (Fiorentino DF, et al 2013).

Anti-MDA5 (also known as the anti-CADM-140) antibody has been firstly described in Asiatic patients. It is associated with DM, mainly amyopathic, with cutaneous ulcers and rapidly progressive ILD (Narang NS et al, 2015).

Anti-NXP2 antibody is found in 25% of juvenile or adult DM, rarely in PM, and is associated with subcutaneous calcinosis, severe disease and muscle contractures. Juvenile-DM, severe cutaneous lesions, including calcinosis, and muscle contractures are the prominent features. An association with cancer has been observed in adults, especially in males (Fiorentino DF, et al 2013).

Anti-SAE antibody is directed against small ubiquitin-like modifier 1 activating enzyme A and B subunits, and is found in 8% of adult patients with DM characterised by severe skin disease, dysphagia and systemic features (Tarricone et al, 2012).

Anti-HMGCR (also known as anti-200/100 kDa) antibody was firstly described in a case series of patients with necrotising features at muscle biopsy. This antibody can be associated with statin use, but can also be found in patients who are not treated with statins (Musset L, et al 2015). The clinical phenotype of these patients resembles that found in patients with other forms of IIMs: proximal muscle weakness, markedly raised CK, myopathic features on EMG and good response to immunosuppressive therapy.

MSAs have a high specificity for IIM, and might thus be helpful for confirming the diagnosis, but their sensitivity is low. Most MSAs can be detected only by immunoprecipitation, which is time consuming and costly and only available in a small number of research laboratories. The recent availability of new tools (ELISA and Immunoblot assay) able to identify a large number of MSAs (and of MAAs) (Muro Y et al, 2013; Bundel C et al, 2016; Cavazzana I et al, 2016;) allows the detection of a large number of patients positive for MSAs, with a relevant diagnostic impact. Anti-Jo1 antibodies are the only anti-ARS antibodies tested in the majority of routinely available ENA screening tests.

Details of the MSAs detectable by immunoprecipitation are summarised in table 2.

Although it is well established that anti-ARS antibodies are significantly associated with the HLA-class II DRB1*0301-DQA1*0501-DQB1*0201 haplotype, and anti-Mi-2 antibodies are significantly associated with the HLA-class II DRB1*0701-DQA1*0201-DQB1*0201 haplotype, it has not been established yet whether the rarer MSAs described are also associated with specific HLA-class II haplotypes.

Table 2 Currently detectable myositis-specific autoantibodies, their target autoantigens and clinical associations. (Adapted from Betteridge et al, Arthritis Res Ther 2011;13:209)

Autoantibody	Target autoantigen	Clinical associations	Frequency	
			Adults (%)	JDM (%)
Anti-ARS	Aminoacyl-tRNA synthetase	Antisynthetase syndrome:	Overall: 30–40	Overall:
- Jo-1	Histidyl -	Myositis	Jo-1: 15–20	1–3
- PL7	Threonyl -	ILD	PL7: 2–5	
- PL12	Alanyl -	Raynaud's phenomenon	PL12: 2–5	
- OJ	Isoleucyl -	Arthritis	OJ: <2	
- EJ	Glycyl -	Mechanic's hands	EJ: 2–5	
- KS	Asparaginy -	Fever	KS: <2	
- Ha	Tyrosyl -		Ha: <1	
- Zo	Phenylalanyl -		Zo: <1	
Anti-Mi-2	Nucleosome remodelling deacetylase complex	DM with hallmark skin changes	10–15	<1
Anti-TIF-1γ	Transcriptional intermediary factor 1 gamma	JDM: DM and skin ulceration Adults: DM and malignancy	13–21	23
Anti-MJ/NXP2	Nuclear matrix protein 2	JDM: DM and calcinosis Adults: DM and malignancy	<5	25
Anti-SAE	Small ubiquitin-like modifier activating enzyme (SAE)	DM	8	<1
Anti-MDA5	Melanoma Differentiation Associated gene5 (MDA5)	JDM: DM and ILD Adults: CADM and ILD	<5 (50–70 in CADM)	7–38
Anti-SRP	Signal recognition particle (SRP)	Necrotising myopathy	4–8	<1
Anti-HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase (HMGCR)	Statin-induced necrotising myopathy	<10 Necrotising myopathy	Unknown

CAADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; ILD, interstitial lung disease; JDM, juvenile dermatomyositis.

6.6.2 Myositis-associated autoantibodies

MAAs are often found in patients with an overlap-myositis condition (eg, associated with other CTDs). The MAAs include anti-Ro52 kDa, anti-La (linked to anti-Ro), anti-PM-Scl (75 and 100 kDa), anti-RNP, and anti-Ku antibodies.

Anti-Ro52 kDa antibody is found in more than 30% of patients with myositis and, as previously stated, it is often associated with anti-ARS antibodies. This association suggests that (auto) antigenic Ro particles might participate in the priming/sustaining of muscle/lung tissue damage and, potentially, also of joint damage. Nevertheless, the clinical relevance of anti-Ro52 antibody in patients with myositis has not been fully elucidated, even if clinical presentation pattern and evolution, as well as survival were not influenced in a large casuistry of patients (*Cavagna L et al, 2015).

Anti-PM-Scl antibodies are frequently detected in adult patients whose myositis occurs in association with systemic sclerosis dermal and pulmonary features. In juvenile-DM, a proportion of cases will lose the characteristic DM rash found at disease onset, only to develop scleroderma features over time. These cases often prove positive for anti-PM-Scl antibodies, and the term, scleromyositis, has been invented for this differentiated phenotype. With respect to anti-PM/Scl-100 antibodies, the anti-PM/Scl-75 ones have been detected more frequently in younger and more active patients with joint contractures (Hanke K et al, 2011).

Patients with anti-RNP antibodies can have myositis as part of mixed connective tissue disease, while anti-Ku-positive patients can have myositis overlapping with systemic sclerosis or SLE.

7. Inclusion body myositis

IBM was identified as a subset of IIM in the 1960s based on specific histopathological findings, including sarcoplasmic and nuclear inclusions and rimmed vacuoles. Epidemiology has been reported in paragraph 2. The sporadic, non-familial, form of IBM is more common in men than in women and is mainly seen in people aged >50 years. Also hereditary forms of IBM have been detected, surely linked to a various and still to be established different genetic backgrounds (see paragraph 3.1). The characteristic clinical phenotype consists of muscle weakness with an insidious onset (over months to years) with an average diagnostic delay of 6 years. Weakness of knee extensors and of distal muscles, particularly of the forearms and of the hands, resulting in finger flexor weakness, are typical of IBM. The most common symptom is difficulty with walking, and the progressive weakness of knee extensors frequently causes falls during deambulation. IBM is not a painful disease. Creatine kinase levels can initially be elevated up to 10-fold, but they remain only slightly elevated as the disease progresses. The course of the disease is slowly progressive, leading to muscle atrophy that can be striking, particularly at the level of knee extensors and forearm muscles. Severe generalised weakness, including that of the swallowing muscles, may lead to premature death. Extra-muscular involvement is rare. Subsets of patients with IBM do not initially have the classic peripheral weakness of finger flexors and forearms and are often misdiagnosed as having PM. Initial biopsies in such cases often do not reveal the diagnostic inclusions; thus, multiple repeated biopsies over time are often required before these characteristic changes become apparent.

Autoantibodies are present in 30% of patients and in half of these, MSAs/MAAs can be detected. More recently, anti-NT5C1A antibodies, targeting the cytoplasmic 5' nucleotidase muscle specific protein, have been described at high levels in about 30-60% of patients with IBM. This antibody is rare in PM (5%), thus helping in the differential diagnosis. However, these antibodies can also be found in 14-20% of patients with DM, SLE or Sjögren's syndrome. Thus, the clinical relevance of this new antibody as a biomarker is still under investigation (Greenberg, 2013). IBM may be associated with inflammatory CTDs such as Sjögren's syndrome, SLE, systemic sclerosis or with interstitial pneumonitis.

IBM is generally refractory to immunosuppressants (see paragraph 9.5). Thus, a diagnosis of IBM should always be considered in treatment-resistant cases of PM. By considering this characteristic along with a common genetic background with some neurodegenerative disorders (see paragraph 3.1), it has been questioned whether IBM is an autoimmune disease or rather a degenerative muscle disease supported by abnormal accumulation of proteins, such as amyloid- β , in muscle fibres.

8 Clinometric measurements

A critical part of the clinical evaluation of IIMs patients is to distinguish the signs and symptoms due to disease activity or disease damage. Disease activity is reversible with treatment, whereas damage is often irreversible and cumulative.

Recently, two international collaborative groups, the International Myositis Assessment and Clinical Studies Group (IMACS) and the Paediatric Rheumatology International Trials Organisation (PRINTO) have defined a core set of measures to assess disease activity and disease damage in IIMs (box-3). Tools are posted in the free of charge IMACS website (<http://www.niehs.nih.gov/research/resources/imacs/diseaseactivity.cfm>) . Many of the core set measures are now used in randomised controlled trials and in clinical practice.

Box 3 Disease activity and damage: IMACS core set measurements

Disease activity

- Physician global activity – VAS/Likert
- Patient/parent global activity – VAS/Likert
- Muscle strength—manual muscle test (MMT)
- Physical function—[C] HAQ, CMAS
- Laboratory—muscle enzymes
- Extramuscular activity—MDAAT

Damage

- Myositis Damage Index (MDI)
- Physician global damage—VAS/Likert
- Physical function—[C] HAQ

[C], childhood; CMAS, Childhood Myositis Assessment Scale; HAQ, Health Assessment Questionnaire; IMACS, International Myositis Assessment and Clinical Studies Group; MDAAT, Myositis Disease Activity Assessment Tool; VAS, Visual Analogue Scale.

8.1 Disease activity assessment tools

8.1.1 Physician and patient/parent global activity

The physician and patient/parent global activity assessments are based on information available at clinical evaluation (subject's state, medical history, physical examination, laboratory testing and therapies). Adult patients or parents of children with myositis completing the patient/parent assessments are asked to take into account the active manifestations: muscles, skin, joints, heart, lungs or other parts of the body that can improve

with treatment. The score is recorded on a 10 cm Visual Analogue Scale (VAS) or a five-point Likert scale rating. For the VAS rating, a score of 0–10 (down to 1 decimal place) is used, and for the Likert scale, a grade of 0 (no disease activity), 1 (mild disease activity), 2 (moderate disease activity), 3 (severe disease activity) or 4 (extremely severe disease activity) is used. The 10 cm VAS may have higher sensitivity and specificity than the Likert scale. However, the two scales correlate highly. To reduce potential bias, this measure should be assessed by experienced clinicians.

8.1.2 Manual muscle testing

Manual muscle testing (MMT) considers and measures muscle strength as part of the physical examination. The MMT score has been reported as a sum of the scores for the total number of proximal, distal (tested bilaterally) and axial muscle groups. However, in IIMs the number of muscle groups tested has not been standardised. Recently, a subset of eight muscle groups, which includes a combination of proximal, distal and axial muscle groups, has been proposed and validated by the IMACS group: neck flexors, deltoids, biceps, wrist extensors, gluteus maximus and medius, quadriceps and ankle dorsiflexors are considered and separately scored. Both the modified Medical Research Council (MRC) Muscle Strength Scale and the Kendall Grading Scale are used. The Kendall grades are shown in table 3, and MMT execution is explained in figures 20–27. MMT is a valid measure of strength, that should be routinely performed in the evaluation of patients with myositis. However, it does not discriminate between activity and damage, resulting in less sensitivity and specificity for patients with accumulated damage and progressive muscle atrophy.

Table 3 Kendall's 10-point Strength Scale. (Modified from Kendall FP, McCreary EK, Provance PG. Muscle testing and function. 4th ed. Baltimore: Williams & Wilkins, 1993)

	Function of the muscle	Score
No movement	No contraction felt in the muscle	0
	Tendons becomes prominent or feeble contractions felt in the muscle, but not visible movement of the part	1
Movement in horizontal plane (gravity-eliminated position)	Moves through partial range of motion	1
	Moves through complete range of motion	2
Movement against gravity	Movement through partial range of motion	3
	Gradual release from test position	4
	Holds test position without added pressure	5
	Holds test position against slight pressure	6
	Holds test position against slight to moderate pressure	7
	Holds test position against moderate pressure	8
	Holds test position against strong to moderate pressure	9
	Holds test position against strong pressure	10

Figure 20 Manual muscle testing: evaluation of neck flexors. (A) Antigravity position. With the patient supine and their arms at their side, the head is supported on the table. The therapist stands next to the patient's head and the testing hand is placed on the patient's forehead. The patient lifts their head off the table by flexing the neck and tucking the chin. The tester applies resistance at the forehead in the direction of capital and cervical extension and may position a hand underneath the subject's head for protection, or offer additional stabilisation across the abdomen (if needed). **(B) Gravity-eliminated position.** With the patient lying on their side and their arms remaining at their side, the head is supported on the table. The tester will support the head to prevent cervical side bending, provide stabilisation at the anterior shoulder as needed. The patient flexes the head and neck; the therapist neither assists nor resists the patient's voluntary movement. Patient consent obtained.

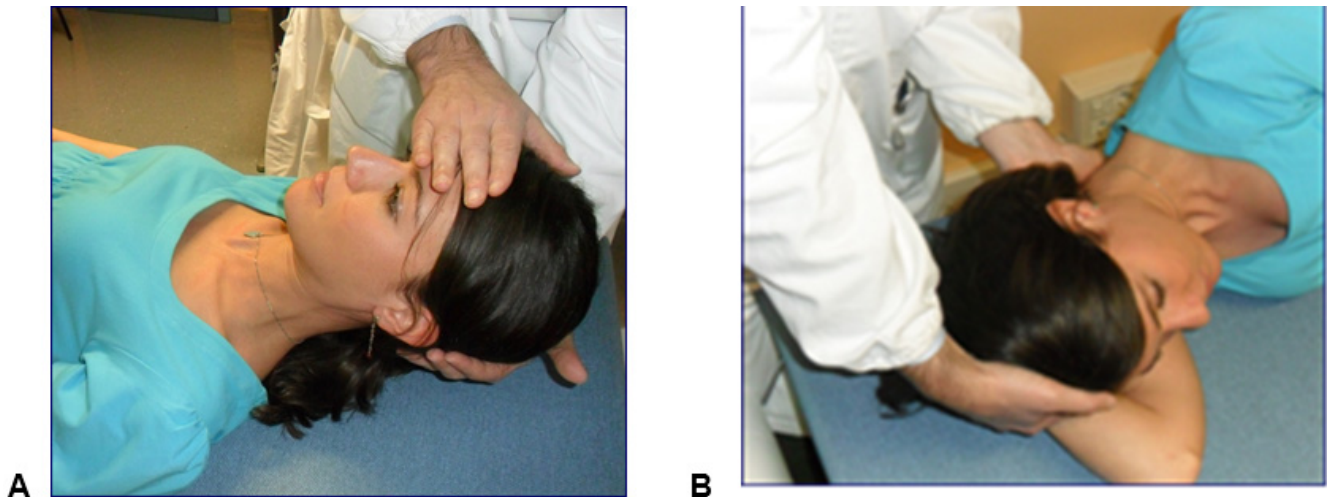


Figure 21 Manual muscle testing: evaluation of deltoid. (A) Antigravity position. With the patient sitting, the elbow should be flexed to indicate the neutral position of rotation. The therapist should stand at the test side of the patient and place pressure against the dorsal surface of the distal end of the humerus. The patient has to maintain the arm in abduction against gravity and tester pressure. **(B) Gravity-eliminated position.** With the patient supine, the arm is abducted to 90° but is supported on the table with the elbow slightly flexed. The patient attempts to abduct the shoulder by sliding the arm on the table without rotation at the shoulder. The tester will support the arm to minimise the friction between the arm and the testing surface, and provide stabilisation at the upper trapezius, if needed, and instruct the patient to fully abduct the arm; the therapist neither assists nor resists the patient's voluntary movement. Patient consent obtained.

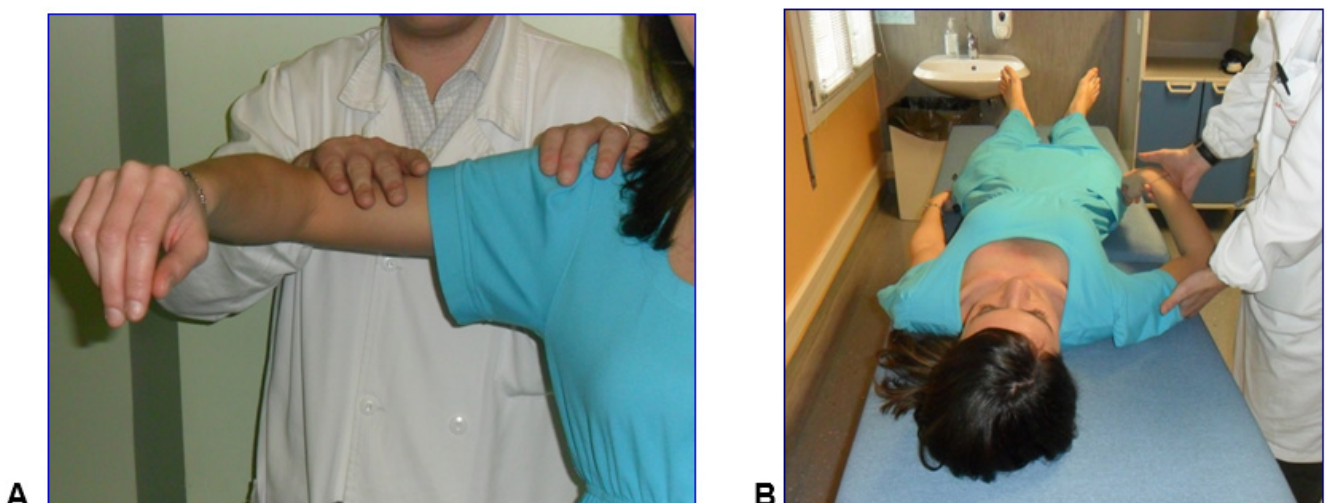


Figure 22 Manual muscle testing: evaluation of biceps. (A) Antigravity position. With the patient sitting the elbow is flexed at a right angle, with the forearm in supination. The therapist should stand in front of, and at the testing side of, the patient. The hand giving resistance is contoured over the flexor surface of the forearm just proximal to the wrist. The other hand is applied to the humerus to provide a counterforce. The patient flexes the elbow against the applied force. If the biceps/brachialis are weak the patient will pronate the forearm before flexing the elbow. **(B) Gravity-eliminated position.** With the patient sitting with 90° shoulder abduction or lying on the side, the elbow is fully extended. The therapist should stand at the test side of the patient and support the abducted arm under the elbow and wrist, if necessary. The patient attempts to bend the elbow with the hand supinated; the therapist neither assists nor resists the patient's voluntary movement. The side-lying position may be preferred for subjects with limited range of motion at the shoulder. Patient consent obtained.

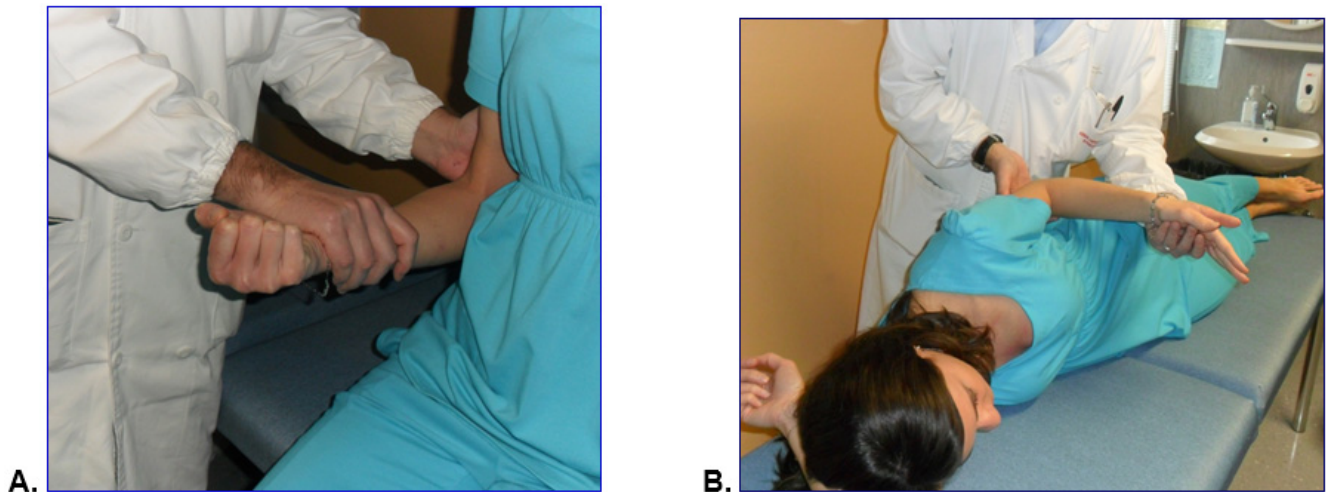


Figure 23 Manual muscle testing: evaluation of wrist extensors. (A) Antigravity position. With the patient sitting with the elbow and forearm supported, the forearm is in full pronation with the fingers flexed. The therapist should stand or sit in front of the patient and support the patient's forearm under the wrist while the other hand used for resistance is placed over the dorsal surface of the metacarpals. Full extension of the fingers is not allowed. **(B) Gravity-eliminated position.** With the patient sitting, the elbow and forearm are supported and the forearm is in a neutral position. The therapist should stand or sit at the test side of the patient and support the patient's wrist. This raises the hand from the table and removes friction. The patient extends the wrist; the therapist neither assists nor resists the patient's voluntary movement.

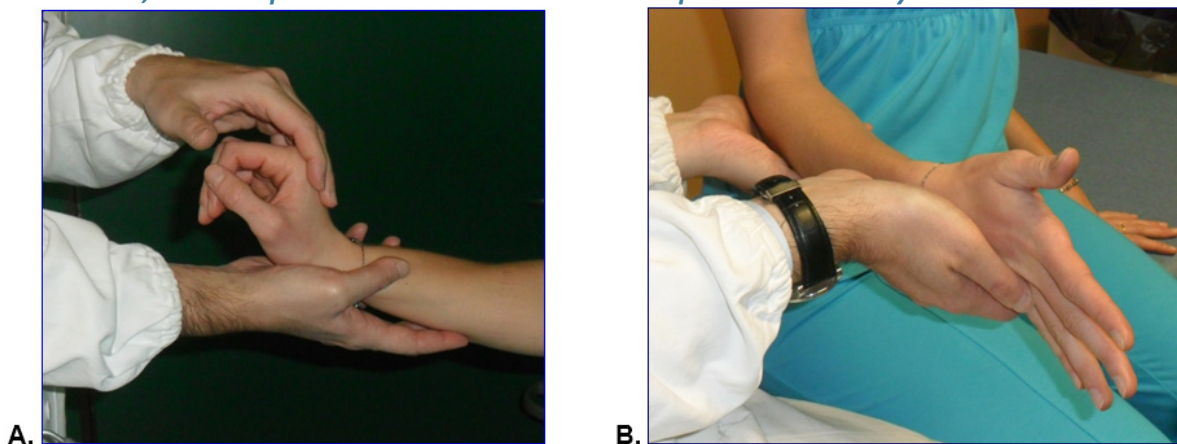


Figure 24 Manual muscle testing: evaluation of quadriceps. (A) Antigravity position. With the patient sitting with the trunk approximately perpendicular to the floor, the leg is extended—but not locked in extension at the knee. Trunk extension is allowed only if significant hamstring tightness precludes assuming the recommended testing position. The therapist stands at the side of the limb to be tested and the testing hand is placed over the anterior surface of the distal leg just above the ankle. The other hand is placed under the distal thigh. The patient extends the knee through the available range of motion. **(B) Gravity-eliminated position.** Side lying with the test limb superior to the supporting limb. The lower limb can be flexed for stability. Hold the test limb in about 90° of knee flexion with the hip in full extension. The therapist stands at knee level. One arm cradles the test limb around the thigh with the hand supporting the underside of the knee. The other hand holds the leg above the ankle. The patient extends the knee through the range of motion and the therapist neither assists nor resists the patient's voluntary movement.

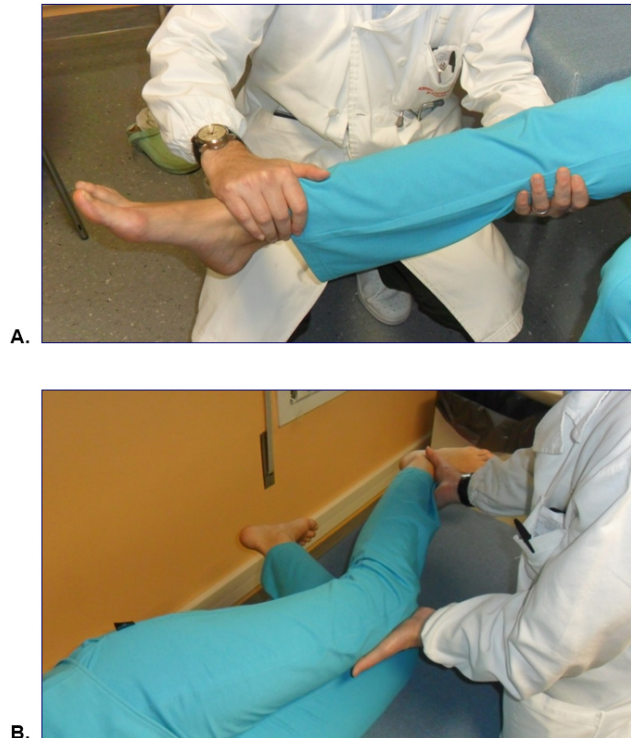


Figure 26 Manual muscle testing: evaluation of the gluteus medius. (A) Antigravity position. With the patient side lying, the test leg is superior to the supporting leg. The test limb is slightly extended beyond the midline and the pelvis is rotated slightly forward. The supporting leg is flexed for stability. The therapist stands behind the patient and the test hand is placed on the lateral surface of the knee (A1) or at the ankle (A2), and the other hand is just proximal to the greater trochanter of the femur. The patient abducts against the applied resistance without flexing or rotating the hip. Resistance by the examiner is straight and downward. (B) Gravity-eliminated position. With the patient supine the therapist stands on the side of the limb to be tested. One hand supports and lifts the limb by holding it under the ankle. The patient abducts the hip through the available range of motion; the therapist neither assists nor resists the patient's voluntary movement.

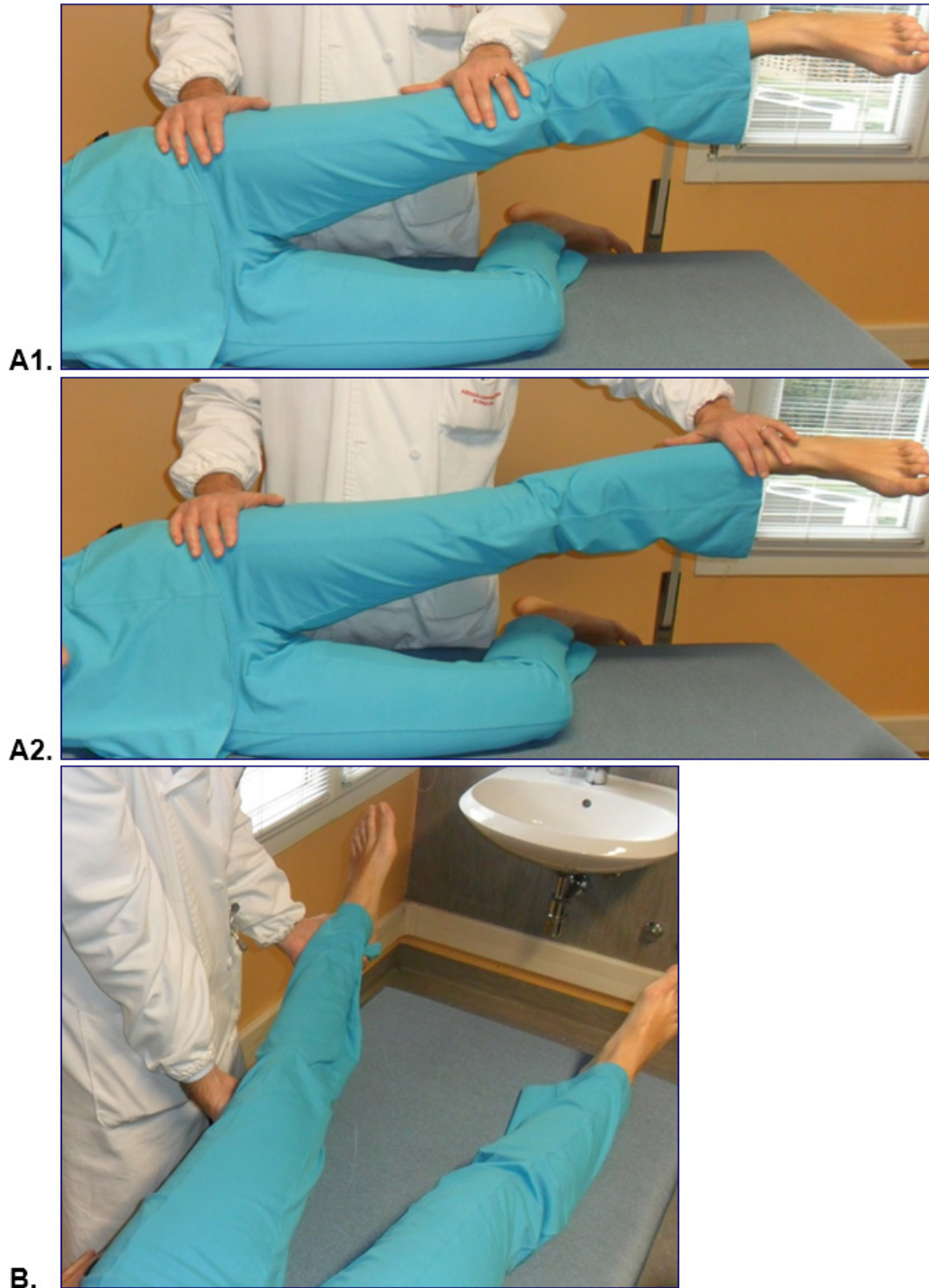


Figure 25 Manual muscle testing: evaluation of ankle dorsiflexors. (A) Antigravity position. With the patient sitting, the knee is flexed at 90°. The therapist sits at the side of the limb to be tested and supports the leg just above the ankle joint. The patient dorsiflexes the ankle joint foot without extending the great toe. Pressure is applied on the dorsum of the foot (in the direction of plantar flexion and eversion). (B) Gravity-eliminated position. Side lying with the test limb superior to the supporting limb. The lower limb can be flexed for stability. Hold the test limb in terminal knee extension with the hip in full extension. The therapist stands near the subject's feet and the supporting arm supports the test limb just proximal to the malleoli. The patient moves the foot from plantar flexion to dorsiflexion; the therapist neither assists nor resists the patient's voluntary movement.

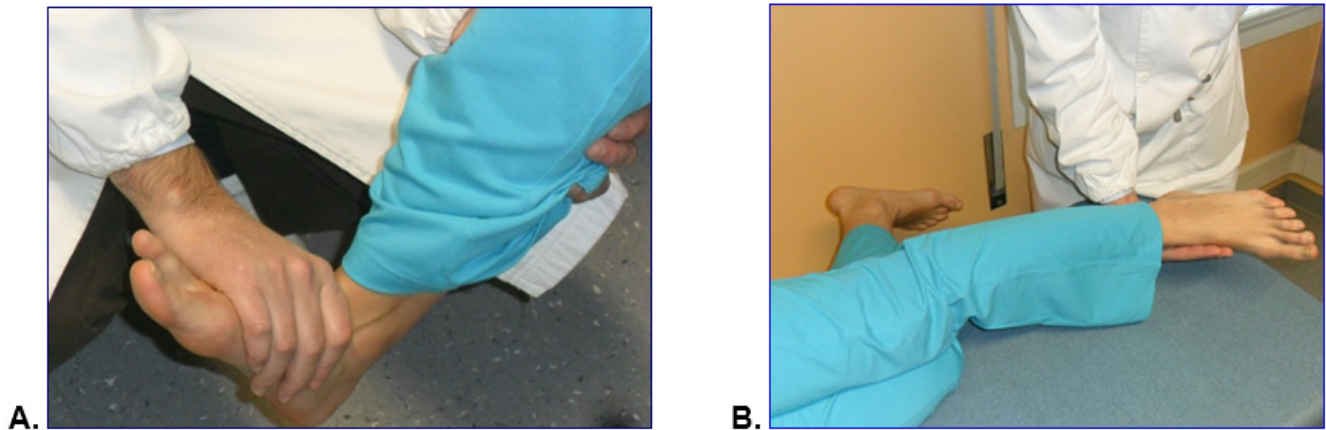
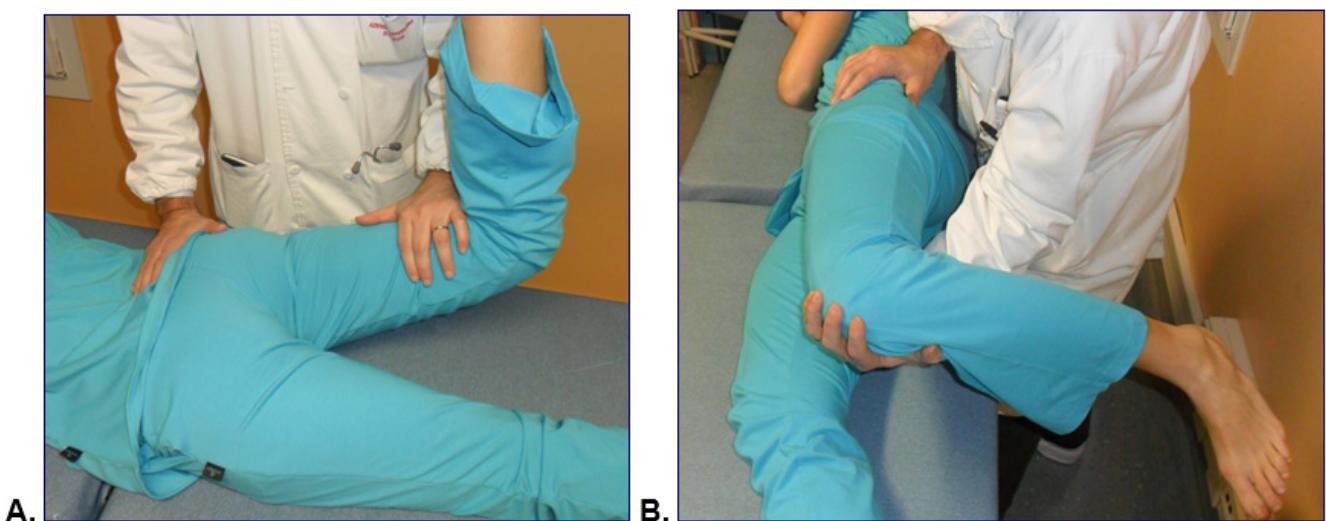


Figure 27 Manual muscle testing: evaluation of gluteus maximus. (A) Antigravity position. With the patient prone and the knee flexed to 90° the therapist stands on the side to be tested and the testing hand is placed over the posterior thigh just above the knee. The other hand may stabilise the pelvis at the upper buttocks. The patient extends the hip through the available range of motion maintaining knee flexion at 90°. Resistance is applied directly downward toward the floor. (B) Gravity-eliminated position. With the patient side lying and the testing limb superior to the supporting limb, the knee is flexed and supported by the examiner. The supporting limb is flexed for stability. The therapist stands behind the patient and cradles the limb to be tested with forearm and hand under the flexed knee. The other hand is on the pelvis to maintain alignment. The patient extends the hip with the supported knee remaining flexed; the therapist neither assists nor resists the patient's voluntary movement.



8.1.3 Myositis disease activity assessment tool

The Myositis Disease Activity Assessment Tool (MDAAT) is a combined tool that assesses disease activity in muscular and extra muscular organ systems. It is based on an intention-to-treat approach modified from the British Isles Lupus Assessment Group (BILAG) used for patients with SLE. The MDAAT records symptoms and compares them with those seen in the previous month. It consists of two subscales: the Myositis Disease Activity Assessment VAS (MYOACT) and the Myositis Intention to Treat Activities Index (MITAX). The MYOACT scores seven organs/systems, including constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiac and muscle disease activity using a 0–10 VAS scale. The MITAX scores each clinical feature in every organ or system using a scale of 0–4, where 0 = not present, 1 = improving, 2 = the same, 3 = worsening and 4 = new. After conversion through a specific scoring schema, the final score ranges from A to E for each system (table 4). The MDAAT is a difficult score and clinicians need specific training before using it.

Table 4 Final Myositis Intention to Treat Activities Index score

Score	Description
A	Very active disease requiring treatment with high-dose daily glucocorticoids or significant immunosuppressive therapy
B	Need for modest doses of glucocorticoids and/or continuing immunosuppression
C	Need for low-dose glucocorticoids or symptomatic drugs only
D	The system is no longer active
E	The system has never been active

8.1.4 Treatment response criteria

ACR/EULAR criteria for minimal, moderate, and major clinical response in PM/DM have been recently published. Previously validated IMACS myositis core set measures have been included in the assessment (physician and patient global activity on a 10-cm visual analogue scale, muscle strength measured by MMT, physical function measured by the Health Assessment Questionnaire (HAQ), extramuscular global activity measured by the physician on a 10-cm VAS, and the most abnormal serum muscle enzyme). Final myositis response criteria for are reported in Table 5.

Table 5 Final ACR/EULAR myositis response criteria

Included core set measures	Score of improvement
degree of improvement according to absolute percent changes	
Physician global activity	
Worsening to 5% improvement	0
>5–15% improvement	7,5
>15–25% improvement	15
>25–40% improvement	17,5
>40% improvement	20
Patient global activity	
Worsening to 5% improvement	0
>5–15% improvement	2,5
>15–25% improvement	5
>25–40% improvement	7,5
>40% improvement	10
Manual muscle testing	
Worsening to 2% improvement	0
>2–10% improvement	10
>10–20% improvement	20
>20–30% improvement	27,5
>30% improvement	32,5
Health Assessment Questionnaire	
Worsening to 5% improvement	0
>5–15% improvement	5
>15–25% improvement	7,5
>25–40% improvement	7,5
>40% improvement	10
Enzyme (most abnormal)	
Worsening to 5% improvement	0
>5–15% improvement	2,5
>15–25% improvement	5
>25–40% improvement	7,5
>40% improvement	7,5
Extramuscular activity	
Worsening to 5% improvement	0
>5–15% improvement	7,5
>15–25% improvement	12,5
>25–40% improvement	15
>40% improvement	20

In order to calculate the total **improvement score** it is necessary to sum the 6 scores obtained in every item included. **Minimal improvement**: scores from 20 to 39, **moderate improvement**: scores from 40 to 59, **major improvement**: scores ≥ 60 . Adapted from Aggarwal R, et al. Ann Rheum Dis 2017;76:792-801.

8.2 Disease damage assessment tools

8.2.1 Myositis Damage Index

The Myositis Damage Index (MDI) measures damage in 11 organ systems. It includes 11 separate VAS 0–10 ratings that constitute the MDI severity of damage scale; the physician scores 0 when damage is absent and 10 in cases of extremely severe damage. Each system has also 3–6 items to be scored as absent or present (0 or 1, respectively). To receive a positive score, each item must be present for at least 6 months (or the pathology leading to feature must have been present for at least 6 months) despite prior therapies. The MDI measures the severity and the extent of damage both disease and comorbidities-related.

9 Prognosis and treatment

9.1 Prognosis

Before glucocorticoids use, patients with myositis had a high risk of developing deep muscle weakness, severe disability and premature death, mainly owing to pulmonary complications, such as aspiration pneumonia or ILD. Corticosteroids first, then immunosuppressants and biological drugs have substantially improved survival, quality of life and disability of IIMs patients. Mortality in patients with IMMIs still remains two- to threefold higher than general population; most common causes of death are cancer, lung and cardiac complications, and infections. With immunosuppressive treatment, about 75% of patients improve, but only 20–40% of treated patients can achieve disease remission and very few recover full normal muscle function, even in the absence of muscle inflammation. Moreover, 60–80% of treated patients have a polycyclic or chronic disease course. Poor prognostic factors in IIMs are older age, male gender, non-Caucasian ethnicity, longer symptoms duration, ILD, cardiac involvement, dysphagia, cancer and some specific serological patterns (anti-SRP, anti-155/140, anti-TIF1- γ , anti-NXP2, and anti-CADM-140 antibodies).

9.2 Pharmacological treatment

The low incidence and prevalence of IIMs and the lack of validated criteria for disease definition and assessment have severely hampered randomised controlled trials in these diseases. Thus, the effect of treatment in patients with IIM has been generally evaluated in open-label studies and case series. Recently, IMACS defined a consensus core set of measures to assess disease activity, disease damage and response to treatment, to be used in randomised controlled trials and in clinical practice (see paragraph 8.1.3 and 8.2)

9.2.1 Glucocorticoids

No placebo-controlled trials with glucocorticoids are available and the optimal dose and duration of treatment for patients with myositis are not standardised. High initial doses of glucocorticoids are recommended in PM/DM. IBM is usually non-responsive to steroids. Patients with PM/DM treated earlier generally have better

responses and outcomes. A high dose of prednisone or its equivalent (0.75–1 mg/kg/day) is recommended as starting dose, and should be maintained for 4–12 weeks. This recommendation is based on the observation of a maximal improvement of muscle function after an average of 12 weeks. Dose tapering usually begins after 1 month and is guided by improvements in muscle function and CK reduction. The recommended reduction is about 10–20% of the daily dose every month until the lowest effective dosage. Glucocorticoids should be used carefully, since steroid-induced side effects are major causes of disability in patients with PM/DM. Preliminary results showed the possible effectiveness and safety of low glucocorticoids doses (prednisone 0.5–0.75 mg/kg/day), but results need to be confirmed. Long-term treatment with glucocorticoids can also lead to steroid myopathy, which may occasionally be difficult to distinguish from active inflammatory disease. Box-4 shows some suggestions that may help in the decisions. Furthermore, glucocorticoids can lead to hypokalaemia, that may be associated with muscle weakness and thus interpreted as myositis disease activity. Topical glucocorticoids may be useful in controlling cutaneous manifestations

Box-4 Key characteristics of steroid myopathy

- Worsening of proximal muscle weakness—predominantly in the lower extremities
- Creatine kinase levels improved or normal
- Improvement with reduction of glucocorticoid dose
- No signs of active myositis on electromyography or MRI
- Selective atrophy of type II muscle fibres
- Increased urinary creatinine excretion
- Obvious extra muscular signs of glucocorticoid use: Cushing features
- Worsening of neck flexor weakness is an indicator of active myositis

9.2.2 Immunosuppressive drugs

The addition of immunosuppressant drugs to glucocorticoid regimens is indicated for most patients with PM/DM. Many experts recommend the introduction of immunosuppressive agents early in order to facilitate glucocorticoid dose tapering, especially in severe cases with poor prognosis. This might help to reduce long-term side effects, such as glucocorticoid myopathy, osteoporosis, cataracts, aseptic necrosis, etc. The prognosis is worse if treatment is delayed and therefore long-term and insufficiently suppressed disease activity should be avoided. Only a limited number of double-blind randomised controlled trials in small cohorts of patients with PM/DM have been performed.

Methotrexate is commonly used in PM/DM. Available data of effectiveness come from open trials, small cohorts and case report series. Methotrexate is used in dosages similar to those used in rheumatoid arthritis, up to 25 mg weekly, although the use of higher doses has also been reported. Mild pulmonary involvement due to myositis does not seem to be a contraindication for methotrexate. Even if data are lacking, Methotrexate is currently used also in case of joint involvement in IIMs. Anecdotal reports suggested their possible effectiveness on calcinosis, whereas no data are available for cutaneous involvement.

Azathioprine is commonly used in IIMs. Even if a 3-month, double-blind, prospective clinical study showed no differences between patients receiving glucocorticoids alone and glucocorticoids + azathioprine, the open-label extension of this study showed that patients in the combination group had better functional abilities and required less prednisone after 1 and 3 years. No data are available for azathioprine effectiveness in joint and cutaneous involvement, whereas some reports showed their effectiveness in ILD.

In myositis with ILD, several small case series suggest that **Cyclophosphamide** in *combination with glucocorticoids* has a good effect on pulmonary function, although randomised controlled trials have never been carried out. Recently, major clinical benefit without any evidence of serious toxicity was reported in severe and refractory juvenile-DM. Only few reports of cyclophosphamide effectiveness on cutaneous involvement are available. Data on joint involvement are completely lacking. Cyclophosphamide (1–2 mg/kg/day orally or better 0.75–1 g/m² IV per month for 5–6 months) is usually reserved for more severe cases, due to the high frequency of side effects.

Calcineurin-inhibitors (Cyclosporine, tacrolimus and pimecrolimus). Cyclosporine has been used in several open-label studies, with good results on ILD in different IIMs subsets. Cyclosporine has been effective on muscle involvement in an open, randomised, prospective study performed in juvenile-DM, even if with a slight trend in favour of methotrexate (the comparator) in some clinical and laboratory findings. Cyclosporine is currently used also in case of joint involvement despite the lack of current evidences. A recent systematic literature review evidenced the effectiveness of tacrolimus for both muscle and lung involvement in IIMs (Ge Y et al, 2015). No data are available for systemic cyclosporine and tacrolimus effectiveness on cutaneous involvement, but several reports on the effectiveness of topical formulations of tacrolimus (and pimecrolimus) are available.

The efficacy of **mycophenolate mofetil** has been recently suggested in patients with IIMs. Its use allowed reduction in glucocorticoid dose with a good safety profile. In small series and case reports, mycophenolate mofetil was used to treat PM/DM at a dose of up to 3 g a day, orally; an improvement of muscle strength was reported in up to 91.7% of cases. Some case series showed also the effectiveness of mycophenolate mofetil on ILD and cutaneous involvement in different subsets of IIMs.

Hydroxychloroquine has been recently suggested as a first line therapy for cutaneous involvement in juvenile dermatomyositis. Hydroxychloroquine is currently used also in case of joint involvement, but without supporting data.

The use of a combination of immunosuppressant agents has also been reported. One study compared the use of glucocorticoids alone or in combination with either methotrexate or cyclosporine, or all three agents together; the results suggested that the addition of both the immunosuppressive agents did not improve the outcome. A combination of methotrexate and azathioprine was studied in a prospective, randomised, open-label crossover study, which compared two aggressive approaches in patients with refractory IIM. Patients were

randomised to begin with either weekly oral methotrexate together with daily azathioprine or intravenous methotrexate with leucovorine rescue every 2 weeks for 6 months. Some patients from both groups improved with treatment and the analysis showed a trend in favour of those patients who first received oral combination treatment. A combination of oral cyclosporine A and intravenous cyclophosphamide has been used successfully in a limited number of patients with acute interstitial pneumonia.

Few cases reports of patients with PM and DM successfully treated with autologous stem cell transplantation have been reported. The results from the French multicentre phase I–II study included three patients with myositis; however, after 36 months no patient had responded, and two patients died. Interestingly, PM can occur in chronic graft-versus-host disease after allogeneic stem cell transplantation with higher incidence than expected by chance.

9.2.3 Intravenous immunoglobulins and apheresis

A double-blind, placebo-controlled, crossover trial in 15 patients with DM showed a significant improvement in muscle strength and neuromuscular symptoms at the end of the 3-month treatment phase in patients receiving intravenous immunoglobulin (IVIg) compared with those receiving placebo (Dalakas 1993). However, to maintain the clinical benefit patients required IVIg infusions every 4–8 weeks subsequently. A concomitant improvement of cutaneous rash has been also observed. Two other randomised, double-blind placebo-controlled trials were performed using IVIg in a few patients with PM/DM, showing conflicting results. Moreover, an open-label study of 35 patients with PM showed a disease improvement in >70% of cases, but seven of the 25 patients who responded well to IVIg treatment relapsed after an average time of 17.1 months (range 4–23 months) from the discontinuation of IVIg (Cherin P, 2002). IVIg treatment is well tolerated, since side effects are usually mild. In the placebo-controlled trial a second muscle biopsy carried out in patients with DM showed an increase in muscle fibre diameter, mean number of capillaries and downregulation of MHC I, intercellular adhesion molecule-1 and transforming growth factor β expression in the group treated with IVIg compared to those treated with placebo. By contrast, no difference in terms of CK decrease and MMT improvement between treatment arm and placebo was found in another placebo-controlled trial on 26 patients with PM (16) and DM (10) (Myasaka 2012). In some reports, IVIg has been reported as effective on ILD and on calcinosis complicating IIMs (Anh-Tu HS et al, 2017). Thus, the effects of high-dose IVIg in PM/DM remain unclear and their modes of action have not been fully clarified. Recently, subcutaneous administration has been proposed, showing good efficacy and safety. It could be an alternative of IVIg in patients with difficult venous access and in patients preferring home care setting (Cherin P et al, 2016) However, owing to the high costs and the uncertain effects, high-dose IVIg is rarely recommended.

Plasma exchange is used only in case of severe life-threatening manifestations and treatment-resistant cases.

9.2.4 Biological agents

Observations of immunological changes in the muscles of patients with PM/DM have stimulated interest in the biological treatment of these diseases. As expected, a number of immunologically relevant molecules have been identified in the inflamed muscles, such as TNF α , IL-1, adhesion molecules and many others, suggesting an active role of these molecules in the development of inflammation.

The expression of TNF α in PM/DM muscle tissue, increased TNF α serum levels and the known effects of TNF α on muscle metabolism, which include accelerated catabolism, contractile dysfunction and disruption of myogenesis, were the rationale for the treatment of patients with PM/DM with TNF inhibitors. However, TNF α exerts biphasic effects on skeletal muscle, promoting early myogenesis in undifferentiated myocytes and stimulating catabolism in more mature myotubes. On this basis the effectiveness of TNF inhibitors in IIMs could be questionable and the results available up to now seem to conform this hypothesis. In fact, even if some patients improved, in the majority of cases, treatment was not effective and disease relapsed or worsened. Furthermore, as previously stated (see paragraph 3.2.3), anti-TNF inhibitors were not able to avoid the subsequent occurrence of myositis in some ASSD patients presenting with an exclusive joint involvement at disease onset (Cavagna I et al, 2015)

Infliximab was effective in three patients with myositis (two PM, one DM), but not in one with DM who later developed non-Hodgkin's lymphoma. Dastmalchi et al (2008) reported a 14-week open-label study with infliximab in 13 patients with refractory disease (five PM, four DM, four sporadic IBM). The treatment was not beneficial and there was a high incidence of adverse events. Although three patients were defined as responders according to a composite disease activity score (IMACS), none had improved muscle strength according to the MMT. Two patients had increased disease activity and three had an increased signal in muscle MRI. Activation of the type I IFN system was recorded in several cases, suggesting a mechanism for the disease flares seen in some patients.

Efthimiou et al (2006) retrospectively described six patients with refractory PM/DM effectively treated with **etanercept** (response in five out of six). The response was mainly based on CK levels, but the method used to assess clinical improvement was not clearly reported. A recent study reported five patients with DM who all experienced an exacerbation of the disease during treatment with etanercept. A randomised, double-blind, placebo-controlled pilot trial evaluated the efficacy of etanercept (50 mg subcutaneously every week for 52 weeks) in 16 patients with DM. The authors found improvement of skin manifestations in 5/11 patients treated with etanercept and in 0/5 patients on placebo; however, skin manifestations worsened in five etanercept-treated and one placebo-treated subject. A recent pilot trial carried out with the use of etanercept in IBM did not show differences between patients treated with the biological drug and the control group. Moreover, a small

but statistically significant improvement in handgrip at 12 months was seen, which prompted the authors to suggest a large placebo-controlled trial of etanercept in IBM.

Altogether, these studies suggest that anti-TNF α blockade should not be recommended in IIMs.

IL-1 is largely expressed in the muscle tissue of patients with myositis and the IL-1 receptor antagonist (IL-1Ra), **anakinra**, has been suggested as a therapeutic option. However, few reports on the efficacy of this drug in the treatment of patients with IIM have been published. Anakinra was not effective in one patient with overlap between SLE and myositis, but it was effective in one anti-Jo1-positive ASSD with refractory polyarthritis and fever and in one patient with refractory anti-MDA5 clinically amyopathic dermatomyopathy. In an open-label study of 12 months performed on 15 patients with refractory IIMs (6 PM, 4 DM and 6 IBM) (Zong M et al, 2014), anakinra showed a favourable IMACS positive response in six patients with PM/DM and in one with IBM. Anakinra was not effective in a small pilot study performed on 5 patients with biopsy proven sporadic IBM (Kosmidis ML et al, 2013).

Two randomised pilot trials of interferon β -1a (IFN β -1a) have been performed in patients with IBM (Muscle study group 2001 and 2004). The treatment was well-tolerated, but no significant differences in muscle strength and muscle mass between placebo and IFN β -1a groups were seen at 6 months. IFN β -1a was effective in one patient with corticosteroid resistant PM (Dressel A and Beuche W, 2002). However, a case of severe dermatomyositis triggered by IFN β -1a therapy and associated with enhanced type I interferon signalling has been reported. The rationale for using IFN β -1a includes inhibition of T-cell proliferation, downregulation of T-cell activity, inhibition of IFN γ , IL-12, IL-1 and TNF α , reduction of antigen presentation in B-cells, inhibition of some adhesion molecules and chemokines. The potential concern in myositis might be the ability of IFN β to upregulate MHC I molecules or to rescue memory T-cells.

Depletion of B-cells has emerged as a new strategy in autoimmune diseases. Several case reports, case series and open-label studies showed the efficacy of **rituximab** (monoclonal antibody against CD20) in PM/DM. Oddis et al (2013) in a large multicentre randomised, double-blind trial treated 200 patients with refractory PM (76 patients), DM (76 patients) and juvenile-DM (48 patients) with early or late use of rituximab. The primary end point was the time to reach the IMACS 'definition of improvement', the secondary end point was the time to achieve >20% improvement in muscle strength. No differences were observed between treatment arms in the primary end-points, but the 83% of patients reached the definition of improvement and the components of the IMACS score improved throughout the 44 weeks of follow-up. A recent literature revision (Fasano F et al, 2017) including 48 studies and 458 patients showed that the rate of response to RTX was 78.3%, and the effectiveness was particularly evident in patient positive for MSA. Rituximab has been shown effective also in the treatment of ILD and of cutaneous involvement in different subsets of IIMs.

9.3 Non-pharmacological treatment

Combining exercise and immunosuppressive therapy is safe and has clear beneficial effects on muscle function (Alexanderson, 2009). The exercise should be tailored to the individual and supervised by a physical therapist to avoid overuse of muscles. In patients with IIMs, the combination of a 4-week standardized rehabilitation programme and a personalized, home-based, self-managed rehabilitation programme was well tolerated and had a positive medium-term functional effect. A multicentre, randomized controlled trial performed on 21 PM patients has been recently published (Tiffreau V 2017, et al). The intervention group participated in a 4-week standardized, hospital-based rehabilitation programme followed by a personalized, self-managed, home-based rehabilitation programme. The control group received physiotherapy on an outpatient basis. At 12 months, the intervention group had better scores than the control group for Health Assessment Questionnaire Disability Index, SF-36 (General Health and Role Physical items) and pain levels. Exercise combined with creatine supplement may have an advantage over exercise alone in improving muscle strength.

In case of cutaneous involvement the use of sunscreens is recommended, in order to reduce the risk of flares that may be induced by sunlight exposition.

9.4 Focus of IBM treatment

9.4.1 Pharmacological approach

IBM is usually regarded as non-responsive to glucocorticoids. There are occasional reported cases of 'stabilisation' for a period of months but this probably reflects the natural history of the disease. Prolonged administration of glucocorticoids in patients with IBM may lead to worsening of clinical aspects of the disease, despite improvement in CK levels and reduction of T-cell infiltrates on biopsy samples. Prednisone treatment increases the number of amyloid-containing fibres. Most experts support a brief use glucocorticoids in patients with inflammatory infiltrates at muscle biopsy, with an early association of more aggressive immunosuppressive treatments—for example, methotrexate or azathioprine, in patients with a coexisting connective tissue disease. Moreover, no change in muscle strength was found in patients treated with etanercept and infliximab. Data on anakinra and on IFN β -1a are limited but not satisfactory, whereas positive results have been obtained with alemtuzumab infusions. A trend towards improvement in dysphagia associated with IBM was reported in a small trial and case series on the use of IVIg, but the results have not been confirmed in long-term studies. Very promising results have been obtained with Follistatin Gene Therapy for mild to moderately affected, ambulatory sporadic IBM patients, with improvement of 6 minutes walking test in treated patients compared to a decline in untreated patients (Mendell JR et al, 2017). Two trials on stem cell transplantation (<https://clinicaltrials.gov/ct2/results?term=stem+cell+transplantation+inclusion+body+myositis&Search=Search> and <https://clinicaltrials.gov/ct2/results?term=stem+cell+transplantation+inclusion+body+myositis&Search=Search>) and arimoclomol (<https://clinicaltrials.gov/ct2/results?term=arimoclomol+inclusion+body+myositis&Search=Search>) have been

completed but results are not yet available. Bimagrumab inhibits activin type II receptors in the myostatin pathway and its use is supposed to increase muscle size in patients with IBM. Some trials on bimagrumab in IBM are currently ongoing (<https://clinicaltrials.gov/ct2/results?term=bimagrumab+inclusion+body+myositis&Search=Search>).

9.4.2 Non-pharmacological approach

No large randomized-controlled trials evaluating the effect of exercise in IBM are available to date, however, data from several small studies have been published and reported the safety of a low-to-moderate resistance programme. Although limited by small sample sizes and relatively short follow-up periods these studies also reported prevention of loss of muscle strength over time, improvements in strength, function, and aerobic capacity. Thus, a low-to-moderate exercise appears to be safe and may produce the benefit of mild increases or maintenance of strength and function. However, implementation of any exercise regimen should be supervised by a trained physical therapist.

Since falls frequently occur in patients with IBM due to knee collapse or tripping due to foot drop or uneven surfaces, the beneficial use of orthosis has been hypothesized. A specific stance control orthosis used in a small cohort of patients with IBM resulted in more stability and fewer falls. However, it caused a walking velocity and cadence slow down, which can limit its widespread use (reviewed by Alfano LN, 2015).

9.5 Summary of currently available treatment

Only a few controlled studies with small numbers of patients have been performed in IIMs. These trials, together with open studies and clinical experience guide treatment approaches. With the exception of IBM, glucocorticoids are the basis of treatment and methotrexate and azathioprine, also in combination, are up to now the best treatment options available for patients refractory to glucocorticoids. Other useful drugs are IVIg, calcineurin inhibitors, mycophenolate mofetil and hydroxychloroquine. Among biological agents, rituximab has been shown effective in PM/DM, in particular when MAS are positive. However, before planning PM/DM treatment, extra-muscular involvement should be carefully considered since this deeply influences the final decisions of clinicians. For this purpose, we reported the currently available treatment options and the correspondent areas of effectiveness in table 6. Further efforts should be performed in order to identify the optimal medical treatment of IBM.

Finally, there are accumulating data to support active exercise, in combination with pharmacological immunosuppressive treatment for improving outcome, both as performance in daily life and as muscle strength, compared with non-exercising patients. Exercise could be introduced early but should preferentially be individualised and designed by a physical therapist, and adjusted with improvements.

Table 6: list of drugs currently used in idiopathic inflammatory myositis ad relative areas of effectiveness.
Adapted from Cavagna L et al, 2017. Autoimmunity Rev in press

	Myositis	Interstitial Lung Disease	Arthritis	Cutaneous involvement	Drug dosages
Corticosteroids	●●●	●●●	●●●	●●●	1 mg/kg/day or IV bolus (0.5-1 g/day for 3 days) then tapering
High doses Intravenous Immunoglobulins	●●●	●●	○	●●	2 g/kg divided in 2-5 days, every 4-8 weeks
Azathioprine	●●●	●●●	○	○	1-3 mg/kg/day
Methotrexate	●●●	!	●	●	7,5-25 mg/week
Cyclosporine*	●●●	●●	●	○	3 mg/kg/day
Cyclophosphamide	●●	●●●	○	●●	0,75-1 mg/m ² IV per month for 5-6 months
Mycophenolate	●●	●●●	○	●●	2-3 g/day
Hydroxychloroquine	!	○	●	●●●	200-400 mg/day
Rituximab	●●●	●●●	●	●●●	1 g intravenous repeated after 2 weeks, then after 6 months or 375 mg/m ² /week for 4 infusions

○ not supporting data

● currently used but without supporting data

●● small case series (<15 patients)

●●● large case series (≥ 15 patients), guidelines, other

! Warning

* Topical formulation of calcineurin inhibitors effective

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SUMMARY POINTS

- Idiopathic inflammatory myopathies (IIMs) are rare autoimmune diseases caused by inflammation in striated muscles, leading to muscle weakness as the main symptom.
- Extra muscular involvement can often be seen, affecting mainly skin, lungs, joints, oesophagus and heart.
- Diagnosis of disease is based on clinical assessment, muscle imaging, muscle biopsy, electromyography, muscle enzymes increase and autoantibodies.
- About 10–15% of cases are associated with malignancy, more often in patients with dermatomyositis (DM).
- Serum autoantibodies can be found in about 60% of patients. These antibodies are often myositis specific and are associated with differential and distinctive clinical phenotype subsets within the growing IIM disease spectrum.
- Characteristic findings in the histopathology of polymyositis (PM), DM and inclusion body myositis (IBM) differ, probably reflecting variances in the pathogenesis of each disease.
- Core set measures for disease activity, damage and improvement are available.
- The mainstay of treatment is the use of glucocorticoids. These should be combined with other immunosuppressive drugs to reduce the side effects of high doses of glucocorticoids and to enhance the efficacy of immunosuppressive treatment, which often has to be maintained for prolonged periods.
- No definitive data on the efficacy of biological treatment are available. The use of rituximab is supported by several evidences
- Active physical exercise should be introduced early, and in combination with immunosuppressive treatment, and be guided by a physical therapist, based on individual ability.
- Prognosis is variable with some patients acquiring full strength, but with a majority of them having chronic disease with relapses and accumulating damage.

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module

EULAR on-line course on Rheumatic Diseases

Polymyositis, dermatomyositis

Inflammatory diseases of muscle and other myopathies

Lorenzo Cavagna, Francesco Locatelli, Andrea Doria

A previous version was co-authored by Robert G. Cooper, Andrea Doria, Luca Iaccarino

IN-DEPTH DISCUSSION I

**Interstitial lung disease and idiopathic inflammatory
myopathies**

Introduction

Interstitial lung disease (ILD) is the major contributor to morbidity and mortality in IIMs. It may occur both at disease onset (up to 65% of cases, Fathi M et al, 2004), and during the follow-up (Cavagna L et al, 2015), for a final prevalence of up to 85% of cases in some subsets. ILD-associated-IIMs may be related to various factors (infectious agents, drugs and chemicals), but in recent years evidence linked ILD to Myositis Specific Antibodies/Myositis Associated Antibodies (MSAs/MAAs). In fact, the positivity of some MSAs/MAAs is strictly associated with ILD occurrence (eg the antisynthetase antibodies) and relevant evidences suggested their pathogenetic role (Levine SM et al, 2007). Because of the lack of established classification criteria in some of the conditions belonging to Myositis Spectrum Diseases (ASSD for example), the majority of MSAs/MAAs have been enclosed in the recently published classification criteria for Interstitial Pneumonia with autoimmune features (IPAF) (eg, the antisynthetase antibodies, anti-PM-Scl, anti-Ro 52kDa, anti-RNP, anti-MDA5 antibodies). ILD presentation severity ranges from an acute onset, with the clinical picture of the respiratory distress syndrome, to an asymptomatic onset, in which lung involvement is only instrumental. It is important to remember that dyspnoea in IIMs may be related to several factors, reported in Table 1. We will focus only on ILD.

Diagnosis

Some examinations should be included in the routine assessment of IIMs, as for example pulmonary function tests (PFTs) + DLCO and lung high resolution computed tomography (HRCT). In case of ILD, PFTs + DLCO evidence a restrictive pattern ($FVC \leq 80\%$, $FEV1/FVC \geq 70\%$, decreased or normal FEV1 and/or $> 20\%$ reduction in DLCO) and these changes are useful for both diagnosis and monitoring of ILD. However, a restrictive pattern may be observed in patients with respiratory muscle involvement and DLCO reduction in patients with concomitant pulmonary hypertension. Even if chest radiograph remains in the routine assessment of IIMs, lung HRCT is the most sensitive technique for ILD detection in early stages and for the definition of the underlying type of ILD (Omote N et al, 2015). Fibre-optic bronchoscopy for bronchoalveolar lavage (BAL) may be useful in some cases, in particular when it is necessary to rule-out infections, such as pneumocystis, mycobacterium, aspergillosis and cytomegalovirus, drug-induced pneumonitis (eg, amiodarone, etc) and sarcoidosis. The use of surgical biopsy in IIM-ILD (CT-guided needle biopsy, or open lung biopsy, or video-assisted thoracoscopy) is generally limited to patients with concomitant lesions suspected for neoplasia. This is a possibility to keep in mind in patients with higher smoking pack-year number (**SHOOT INFORMATION:** Rheumatologists should become confident with this calculation: <http://www.smokingpackyears.com/>) and HRCT findings of emphysema (Enomoto Y et al, 2016). In all cases, please remember: 1) the potential morbidity associated with open lung surgical biopsy (Tazelaar HD et al, 1990). 2) the variation in histopathological interpretation of biopsies. 3) that histopathological findings may be non-specific and therefore non-diagnostic. 4) that HRCT findings can predict the histological appearance of ILD in open lung biopsy specimens (Fathi M et al, 2005). Even if a large number of serum biomarkers of ILD-IIMs

have been described (eg the mucin-like glycoprotein KL-6, serum B-cell activating factor, serum LIGHT Levels), they are mainly used in the research setting and not in the daily clinical activity. Lung echography is a new promising methodology not yet standardized that will become surely relevant in next years.

Computed tomography correlates of ILD in IIMs

Lung lesions are predominantly sub pleural, and in lower dorsal lobes, with involvement of one or two slices of secondary pulmonary lobules, with subsequent extension of lesions in case of disease progression (Franquet T et al, 2001). Even if, in previous years, some ILD extent scores have been proposed and used (eg the Kazerooni score), their role in the evaluation of disease evolution is actually questioned. The main histopathological forms of IIMs-ILD are non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP), with NSIP the most common type (Kiely PD et al, 2013). The main characteristics of **NSIP** is the temporal homogeneity of lesions, with prevalence of alveolitis (Ground-glass opacification aspect, GGO), homogeneous septal thickening and maintenance of the normal lobular architecture. The occurrence of GGO surrounded by bronchioloectasis has the meaning of micro reticular fibrosis (eg, fibrosis involving lobules). It is important to remember that also a fibrotic variant of NSIP exists (and it is extremely frequent), in which interstitial thickening is more due to uniform dense or loose fibrosis and mild chronic inflammation, and in which lung structures are still preserved. Occasionally, focal honeycomb fibrosis may be observed. On the contrary, the main characteristic of **UIP** is the temporal heterogeneity of lesions, with a patchy craniocaudal gradient of (irregular) peripheral septal thickening, bronchiectasis, ground glass opacities, and honeycombing. Lung architectural distortion, reflecting fibrotic changes, is another relevant characteristic of UIP. Organising pneumonia (OP, formerly bronchiolitis obliterans organising pneumonia) is another type of ILD observed in IIMs. It is characterized by patchy consolidation (from 2 centimetres to the entire lobe) with a predominantly sub pleural and/or peribronchial distribution, in which air bronchograms and bronchiectasis are common. These consolidations are frequently migrant even without treatment. **OP** may occur concomitantly to an underlying GGO, bronchial wall thickening, bronchial dilatation, mediastinal lymphadenopathy and pleural effusion. The HRCT pattern of Diffuse Alveolar Damage (**DAD**) is characterised by a diffuse Ground Glass aspect and it is typical of acute onset ILD. Some lung HRCT scans (NSIP, UIP and COP) are enclosed at the end of the chapter.

Autoantibodies and ILD in patients with IIM

Several MSAs and MAAs have been associated with ILD, as for example the antisynthetase antibodies, the anti-Ro 52 kDa, the anti-PM-Scl (75 and 100 kDa), the anti-Ku and, recently, the anti-MDA5 antibodies. We will focus on antisynthetase antibodies and on anti-MDA5 antibodies.

Anti-aminoacyl-tRNA synthetases

ILD is a common manifestation of patients positive for antisynthetase antibodies. Anti-histidyl tRNA synthetase (anti-Jo1) antibody is the most common anti-synthetase. Patients with anti-synthetase syndrome typically present with a combination of active myositis, ILD, fever, Raynaud's phenomenon and mechanics' hands. Patients with non-anti-Jo-1 anti-synthetase antibodies (PL-7, PL-12, EJ, OJ, KS, YRS, Zo) are keener to present with an isolated ILD, even if the trend for the ex-novo occurrence of other manifestations should be still assessed (more stable disease?). Surely, these patients have a worst prognosis with respect to anti-Jo1 positive patients (Hervier B, et al, 2012). The association with anti-Ro antibodies is common (50% of cases) in both anti-Jo1 and non-anti-Jo1 positive patients.

Anti-MDA5 antibody

Recently a novel MSA with a strong association to ILD has been identified: the anti-Melanoma Differentiation-Associated Gene 5 (anti-MDA5). This autoantibody has been reported in adult Japanese patients with a rapidly progressive lung disease, frequently without manifest muscle or other accompanying findings (Sato S et al, 2009). Lung involvement related to anti-MDA5 antibody has been associated with poor survival in US Patients with Amyopathic and Myopathic Dermatomyositis (Moghadam-Kia S et al, 2016).

Treatment

Established and evidence-based protocols for the treatment of IIM-ILD are not currently forthcoming and thus treatment is based on case series and case reports. Corticosteroids tend to be the first line of treatment as is the case in treating IIM in the absence of ILD. The typical initial dose is 0.75-1 mg/kg per day for 6-8 weeks and tapering once normalisation of CK and clinical parameters have improved.

As is the case with other more common autoimmune inflammatory rheumatic conditions, the current practice is to introduce steroid sparing agents to avoid the side effects associated with long term steroid use. The most frequently used include azathioprine, cyclophosphamide and cyclosporine. Methotrexate should be used in selected cases (eg, the occurrence of an articular involvement in IIMs), because associated to a potential lung toxicity. However, to have an ILD is not a complete contraindication to Methotrexate use (it is better to treat patients with stable and non-diffuse ILD). Depending on the extension of the ILD, an induction therapy with steroids or cyclophosphamide IV pulses can be performed, although there are no specific protocols for IIM, followed by a therapy with steroid or steroid-sparing drugs. Other newer agents that may potentially be of benefit include tacrolimus, mycophenolate mofetil and rituximab. Recently, some authors (Morisset J et al, 2016) proposed a treatment algorithm based on existing literature, that despite some limits should be considered a good starting point for further guidelines (see enclosed flow-chart).

Table 1. Spectrum of pulmonary involvement in IIM

Extrinsic lung disease	Intrinsic lung disease
Aspiration pneumonia	Interstitial lung disease
Infectious pneumonia	Non-specific interstitial pneumonia
Hypoventilation due to respiratory muscle weakness	Organising pneumonia
Congestive cardiac failure	Usual interstitial pneumonia
Pulmonary arterial hypertension	Diffuse alveolar damage
Pleuritis	Pulmonary capillaritis

Adapted from Schnabel A, et al. Curr Rheumatol Rep 2005;7:99-105.

Figure 1: note the homogeneous ground glass aspect identifiable in every scan (surrounded by yellow lines), without evidences of architectural distortions. This is typical for Non Specific Interstitial Pneumonia. Not all areas of involvement and normality have been surrounded by correspondent lines (courtesy of dr Lorenzo Cavagna).

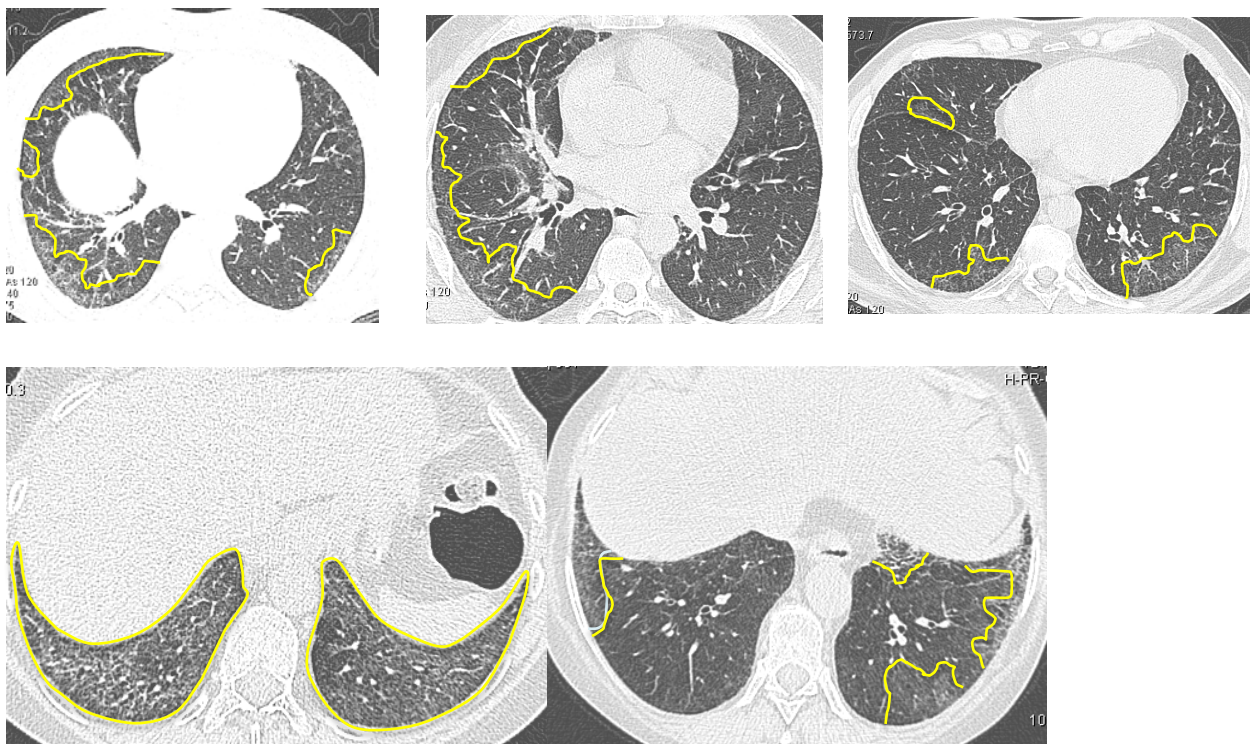


Figure 2: note the heterogeneity of lesions, with concomitant ground glass areas (surrounded by light yellow lines), honey-combing (surrounded by red lines) and totally normal parenchyma (surrounded by blue lines) as typically observed in usual Interstitial Pneumonia. Not all areas of involvement and normality have been surrounded by correspondent lines (courtesy of dr Lorenzo Cavagna).

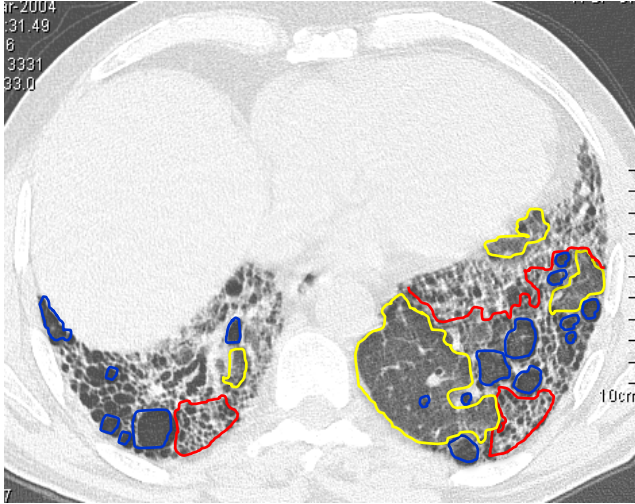
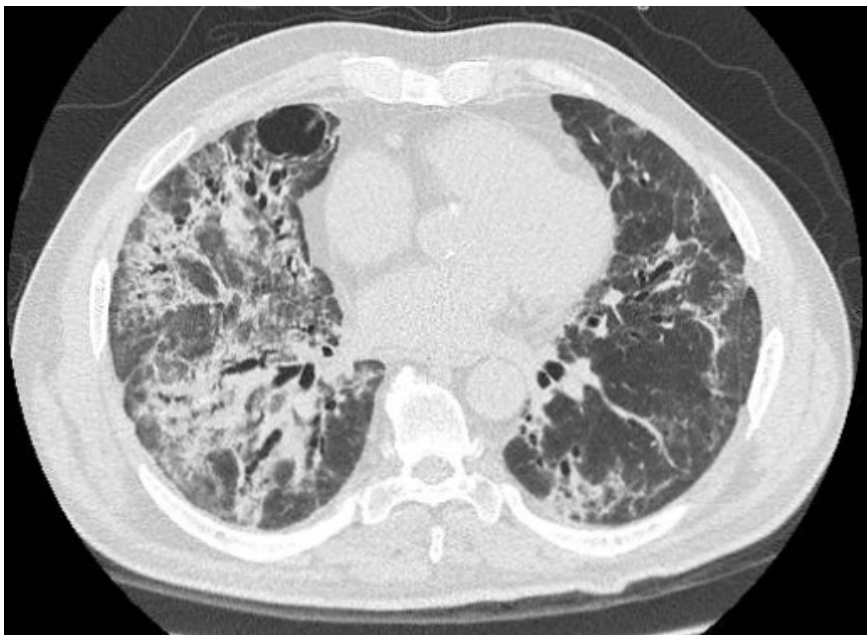
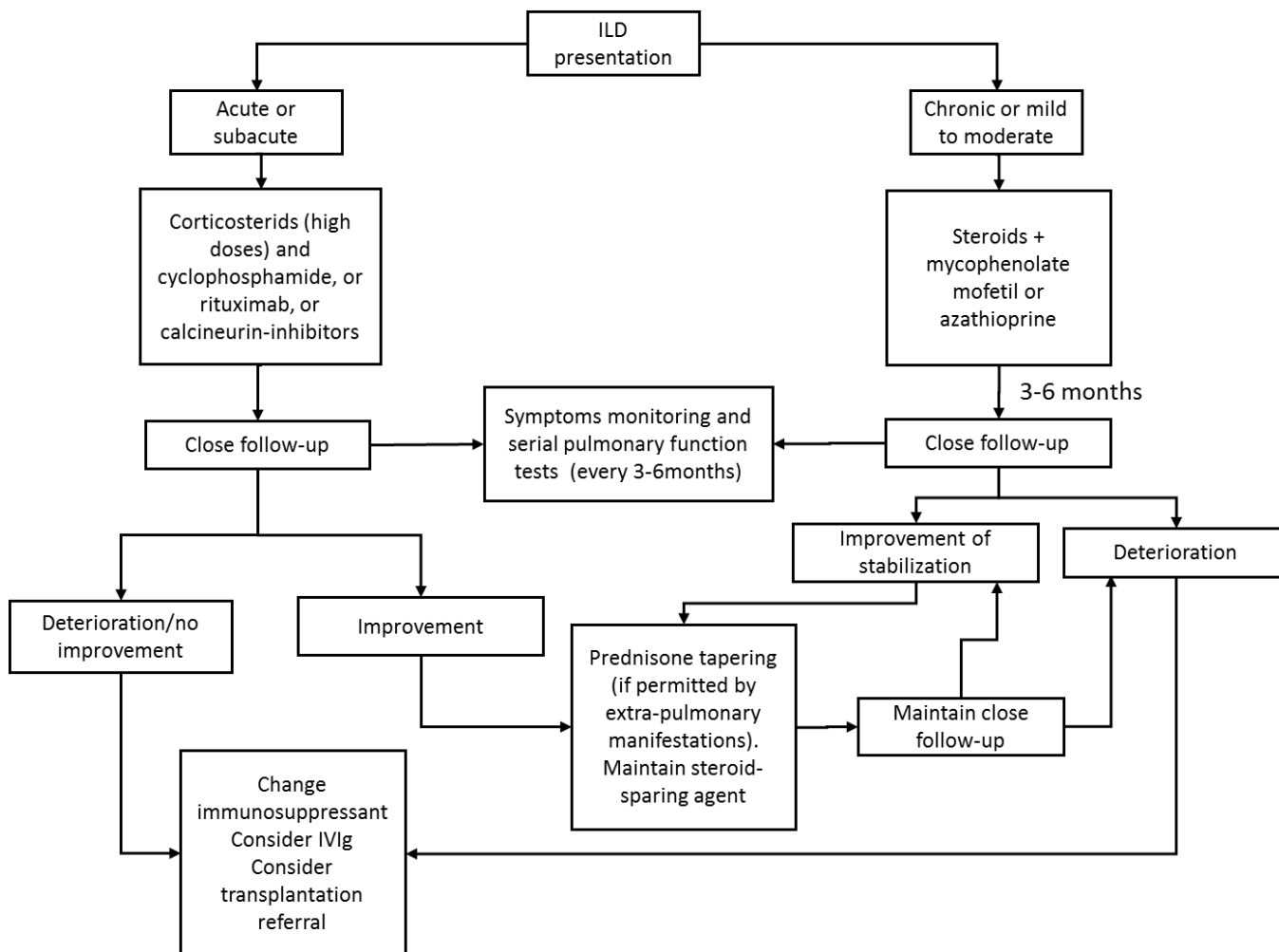


Figure 3: note the extended areas of consolidation in both lungs (courtesy of dr Lorenzo Cavagna)



Flow-Chart 1: proposed algorithm for ILD treatment in IIMs (Morisset J et al, 2016)



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module

EULAR on-line course on Rheumatic Diseases

Polymyositis, dermatomyositis

Inflammatory diseases of muscle
and other myopathies

Lorenzo Cavagna, Francesco Locatelli, Andrea Doria

A previous version was co-authored by Robert G. Cooper, Andrea Doria, Luca Iaccarino

IN-DEPTH DISCUSSION II

Myositis and Cancer

Introduction

Cancer together with ILD is the major determinant of prognosis in IIMs. Surely, cancer deeply impacts the survival of affected patients and also their quality of life. The association between myositis and malignancy has been reported since 1916. Myositis can sometimes be a paraneoplastic syndrome due mostly to a solid tumour or complicate disease course. Old-males with DM, and concomitant dysphagias are at increased risk of cancer. In the subset of DM, an underlying neoplasm could be observed in up to 30% of cases. PM, ASSD and IBM seem to have a weaker association with cancer with respect to DM, but in comparison with the normal population, patients with IIM have a higher risk of malignancy.

Type of cancer associated with idiopathic inflammatory myositis

There is no specific cancer form associated with Idiopathic Inflammatory Myopathies (IIM). The most frequent association is with solid tumours, in particular lung, ovary, breast, and colon cancer. This study found an association also with non-Hodgkin lymphoma. However, a large amount of cancer types has been linked to IIMs in literature: oesophageal cancer, stomach cancer, pancreatic cancer, Hodgkin's disease, kidney cancer, and prostate cancer. In Asian populations, nasopharyngeal cancer was reported in patients with DM, but this is also a common form of cancer in the general population in Asia.

Clinical picture and autoantibodies

The clinical signs of paraneoplastic DM are quite similar to the classical one, although in patients with DM sometimes the skin rash can be very severe. Often, MSAs/MAAs are negative and CK is not elevated. Often it is not easy at DM diagnosis to differentiate paraneoplastic DM from a classical DM, based only on clinical or laboratory data. One way of determining that we are not seeing a typical DM is a poor response to treatment, even if aggressive. Thus, treatment resistance should raise awareness of a possible underlying malignancy. Recently, two novel autoantibodies, anti-TIF1- γ and anti-NXP-2, have been proven to be independently associated with cancer in IIMs. These antibodies occur in more than 50% of otherwise "antibody negative" patients. Testing for such antibodies should be recommended in the diagnostic work-up of cancer-associated DM; anti-TIF1- γ antibody is currently detectable by commercially available line blot assays. In general, in patients positive for anti-TIF1- γ , the diagnosis of cancer is generally performed within 1 year from myositis diagnosis. However, these antibodies are not specific for cancer associated DM, because they are also found in other DM cases, both in adults and children. Another factor of suspect for an underlying occult neoplasia is the occurrence of an autoimmune necrotizing myopathy: in particular, malignancies are more common in seronegative forms and in HMGCR-positive patients compared to anti-SRP positive patients. No specific type of cancer was predominant. The occurrence of anti-TIF1- γ and of autoimmune necrotizing myopathy is mutually exclusive. Even if other MSAs and MAAs, such as the antisynthetase antibodies, did not increase the risk of a concomitant

neoplasm, the screening for an occult neoplasia is indicated in all IIMs patients. Finally, we should remember a peculiar form of dermatomyositis, the so-called Wong's dermatomyositis, in which keratotic follicular papules, that may mimic pityriasis rubra pilaris, are associated with the typical muscle involvement of IIMs. This variant is frequently paraneoplastic.

Time of cancer appearance in patients with idiopathic inflammatory myositis

Myositis symptoms can precede or follow a cancer diagnosis, but most of them are diagnosed within one year of each other. A late onset of malignant disease could also be a late effect of the disease or its treatment.

When myositis symptoms appear before the cancer symptoms, there is the risk that they mask them and cause a delay in cancer diagnosis. It is also possible that aggressive treatment of myositis may worsen the outcome of the cancer. It is therefore easy to understand why cancer screening in all myositis patients, particularly in DM cases, is imperative. Furthermore, when myositis symptoms and signs follow a cancer diagnosis these should raise awareness of a possible underlying relapse of the cancer, even if the cancer was some years back and seemingly removed or cured. This is particularly evident in patients first presenting with a paraneoplastic myositis, in which the relapse of neoplasia is quite always associated with the relapse of myositis. On the contrary, if a cancer did not manifest concomitantly with a paraneoplastic myositis before, the risk of an ex-novo paraneoplastic syndrome in case of relapse is quite low. However, despite that, cancer screening in IIMS and in DM in particular is always mandatory.

How should we investigate patients with idiopathic inflammatory myopathies for an underlying malignancy?

Based on the known association between idiopathic inflammatory myopathies and malignancy, male patients with DM aged more than 50 years, are at higher risk for having an underlying cancer. Thus, these patients should be investigated with a carefully taken history and clinical exam, screening with usual blood and urine tests, chest x-ray, mammogram and gynaecology check-up (for females), prostate palpation, PSA, PSA-free (for males), stool examination, abdominal and pelvic scan. If any tests are aberrant they should be followed by more in depth examinations. Subsequent steps may involve CT scans (total body), total-body Positron Emission Tomography and other laboratory tests, according to the underlying suspect. In case of need, also invasive procedures should be considered, for instance anaemia should cause attention to a possible bleeding source in the gastro-intestinal tract due to cancer. It is important that neoplasm screening should be regularly performed not only at disease onset, but also during the follow-up, for at least 5-10 years, even if risk neoplasia is particularly increased in the first year after diagnosis.

Treatment of cancer associated idiopathic inflammatory myositis

If a solid tumour is diagnosed and it is possible to remove it by surgery, this could give a prompt resolution of DM symptoms without need of any further treatment. Unfortunately, not in all cases elimination of the cancer leads to remission of the myositis. In cases in which the complete elimination of cancer is not possible, treatment of the myositis should be done in collaboration with the oncologist to determine how aggressive myositis therapy should be. Active physical exercise should also be considered in combination with pharmacological therapy in these patients.

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IN-DEPTH DISCUSSION III

Joint involvement in IIMs: available data

Even if joint involvement is a not rare finding in Idiopathic Inflammatory Myopathies (IIMs), no studies have been specifically aimed to arthritis pattern evaluation in these patients. Furthermore, joint involvement has been included exclusively in the Tanimoto Classification criteria for polymyositis/dermatomyositis (PM/DM), in term of non-destructive arthritis or arthralgias (see main document), but it is established that articular symptoms may range from simple arthralgias to destructive polyarthritis, also erosive, rheumatoid factor (RF) and anticyclic citrullinated peptide (ACPA) positive. In recent years, more attention has been put on joint involvement in antisynthetase syndrome (ASSD), in particular by the *French Club Rheumatisme et Inflammation* and by the *AENEAS collaborative group*. The results described by these two groups progressively changed the perspective of joint involvement in ASSD and suggested a more in depth analysis also in PM/DM, and in other Myositis specific antibodies (MSAs) and Myositis associated antibodies (MAAs) linked conditions (eg PM-Scl and scleromyositis). It is important now to focus on available data: in first reports on ASSD, joint involvement was considered mainly as a simple polyarthralgias, and joint erosions at plain X-rays were considered for long-time a rare finding. Only few reports suggested that RF test could had been occasionally positive in some ASSD patients, with subsequent troubles in the differential diagnosis with rheumatoid arthritis (RA). However, the first study specifically evaluating ACPA in ASSD patients and in IIMs in general, was published by Labrador-Horrillo et al in 2009. Even if positive test results were found in about 10% of patients, authors concluded that in the setting, ACPA may be considered as false-positive result and without clinical significance. However, in subsequent years, more reports described arthritis patients with RF and ACPA positive tests along with positive anti-synthetase antibodies (anti-ARS), with or without myositis or interstitial lung disease (ILD). In 2015, Lefèvre et al evidenced that ASSD may be revealed by a seronegative polyarthritis in 27% of cases. Of note, positive RF or ACPA, as well as the overlap with other connective tissue diseases was an exclusion criterion. Joint involvement pattern consisted mainly of a distal symmetrical polyarthralgia, with at least one joint with synovitis, or distal polyarthritis involving interphalangeal, metacarpophalangeal joints and wrists. Only 6% of patients had joint erosions at plain X-rays of hands and feet. Interestingly, Raynaud's phenomenon was observed in more than one third of patients and it was suggested as a red flag for the occurrence of ASSD in patients with seronegative and apparently isolated polyarthritis. Soon after this study, the same group evidenced that in ASSD, ACPA positive patients had a severe and erosive arthritis. The prevalence of ACPA in this study was 6% (17 out of 284 patients considered), but the occurrence of an isolated arthritis was one of the exclusion criteria identified by authors. All ACPA positive patients meet the 2010 ACR classification criteria for RA. In 2017, Cavagna L et al, described the characteristics of a large group of ASSD patients first presenting with an isolated arthritis. From the initial cohort of 243 anti-Jo1 positive ASSD, 58 (24%) were included in the study. Arthritis was mainly polyarticular (41 cases, 71%) and less frequently oligoarticular/asymmetrical (17, 29%). RF and ACPA were positive retrospectively in 39% and in 28% of evaluated patients, 35% had joint erosions at plain-X rays of hands and feet, and 47% showed the anti-Ro. Interestingly, the majority of patients (38, 65.5%) had arthritis as the only presenting clinical ASSD-related manifestation (no Raynaud's phenomenon, no fever, no mechanics hands)

and 22 (38%) were also anti-Ro negative. More than two third of patients satisfied the 1987 revised ACR classification criteria for RA, in particular all patients presenting with symmetrical polyarthritis. The first conclusion of the study was that the differential diagnosis between RA and ASSD is potentially troublesome because of several overlapping features, from the clinical, laboratory and radiographic point of view. But the most interesting finding observed was that quite all patients (with the exception of 5) developed myositis (65.5%) or Interstitial Lung Disease (ILD) (82%) or both (55%) during the follow-up, as confirmed in another subsequent study by Trallero-Araguas et al. These data showed the relevance of the early identification of antisynthetase antibodies and of ASSD in patients presenting with isolated arthritis, even when RA diagnosis is possible. Anti-Ro antibodies positivity (observed in 50% of ASSD patients), the cytoplasmic positivity of ANA test, and Raynaud's phenomenon occurrence, may be potential suspect findings for anti-ARS antibody positivity in patients with early arthritis. Furthermore, a multidisciplinary approach aimed at the early identification of muscle and lung involvement is mandatory in these patients. Based on this data, and as stated in the main text, it is possible that some cases of TNFi-induced anti Jo1 positive PM described in RA patients could be more related to the natural history of an ASSD rather than to TNF inhibitors (TNFi) therapy, as the anti-ARS positivity from arthritis onset suggest. In 2017, Gonzalez-Gay et al, evaluated if the timing of arthritis onset in ASSD (eg arthritis occurring at disease onset – Group 1, or developing during the follow-up- Group 2) could influence the presentation pattern of the manifestation. The study included 445 ASSD, mainly anti-Jo1 positive (366, 82%) but also non anti-Jo1 positive (79, 18%). The majority of these patients had arthritis from disease onset (367, 83%), whereas an ex-novo arthritis was less commonly observed (78, 17%). The data showed that arthritis characteristics are heterogeneous within the syndrome and influenced by the timing of onset. In particular, RA-like clinical, laboratory and radiologic features were more likely observed in patients presenting arthritis from disease onset and to a lesser extent in those presenting with an ex-novo arthritis during the follow-up. Conversely, fever, Raynaud's phenomenon and mechanic's hands were less common in patients with arthritis from disease onset when compared to patients with arthritis occurring after disease onset. On the other hand, the 1987 ACR revised classification criteria for RA were more commonly satisfied in Group 1 with respect to Group 2. From the serological point of view, anti-Ro antibodies were equally distributed among groups. According to these results and as recently suggested by the members of the French "Club Rheumatism and inflammation", it is possible to suggest that an overlap between RA and ASSD may occur in the first phases of the disease, whilst a "true" ASSD related arthritis manifests itself as a clinical feature during the follow-up. On this basis, it is evident that heterogeneity is the typical hallmark of arthritis in ASSD, that this heterogeneity may indicate different phenotypes of the disease with potentially different pathogenic mechanisms in various disease's phases. Of note, the final prevalence of arthritis in ASSD is about 70%. These results clearly showed how articular involvement in IIMs has been underrecognized and under evaluated for several years, even if potentially crucial in the assessment of these patients. More attention on articular involvement should be paid from now not only in ASSD, but also in IIMs in general.

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Sjögren's syndrome and lymphoproliferations in autoimmune diseases

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LEARNING OBJECTIVES

- ➔ Outline the diagnostic process and current classification criteria used to define primary Sjögren's syndrome (pSS)
- ➔ List and describe the clinical features and laboratory findings in pSS
- ➔ Describe and evaluate the diagnostic methods used in pSS
- ➔ Explain and evaluate the various pathophysiological causes that have been suggested for pSS
- ➔ Explain the relationship between pSS and other autoimmune diseases and the risk of lymphoma
- ➔ List, outline and evaluate the variety of treatments available for the treatment of pSS

1 Introduction and classification

Sjögren syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands. This leads to dryness of the main mucosal surfaces, such as the mouth, eyes, skin, nose, pharynx, larynx and vagina (Ramos-Casals et al, 2012a). The disease overwhelmingly affects middle-aged women, but it may also affect children, men and the elderly. The clinical spectrum of SS extends from dryness of the main mucosal surfaces to systemic involvement (extra glandular manifestations) and includes a large number of manifestations. The variability in the presentation of SS may partially explain delays in diagnosis of up to 10 years from the onset of symptoms. It is a disease that can appear in many guises depending on the specific epidemiological, clinical or immunological features. It may be a serious disease with excess mortality, mainly related to extra glandular (systemic) involvement and haematological cancer. The main characteristics of the disease are summarised in box 1.

Box 1 Main characteristics of Sjögren's syndrome

- Sjögren syndrome (SS) is a systemic autoimmune disease that presents with sicca symptomatology of mucosal surfaces.
- The main sicca features (xerophthalmia and xerostomia) are determined by specific ocular (Lissamine green fluorescein or Rose Bengal staining and Schirmer test) and oral (salivary flow measurement) tests.
- The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, determined by a biopsy of the minor labial salivary glands.
- The spectrum of the disease includes systemic features (extra glandular manifestations) in some patients, and may be complicated by the development of lymphoma.
- Patients with SS present a broad spectrum of analytical features (cytopenias, hypergammaglobulinaemia and high erythrocyte sedimentation rate) and autoantibodies, of which antinuclear antibodies are the most frequently detected, anti-Ro/SSA the most specific, and cryoglobulins and hypocomplementaemia the main prognostic markers.

When symptoms appear in a previously healthy person, the disease is classified as primary SS. When sicca features are found in association with another systemic autoimmune disease, most commonly rheumatoid arthritis (RA), systemic sclerosis (SSc) or systemic lupus erythematosus (SLE), it is classified as secondary SS; primary SS may also be associated with various organ-specific autoimmune diseases (box 2).

Box 2 Classification of Sjögren's syndrome (SS): primary and secondary SS**1. Primary SS****2. Secondary SS****2.1. Systemic autoimmune diseases**

Systemic lupus erythematosus
 Systemic sclerosis
 Rheumatoid arthritis
 Still's disease
 Sarcoidosis
 Inflammatory myopathies

2.2. Organ-specific autoimmune diseases/infections

Primary biliary cirrhosis
 Autoimmune Hepatitis
 Autoimmune thyroiditis
 Celiac disease
 Multiple sclerosis
 Diabetes mellitus
 Chronic viral infections
 Chronic HCV infection

 HTLV-I infection (Asian countries)
 HIV infection

2 Epidemiology

SS primarily affects white perimenopausal women, with a female:male ratio of at least 9:1. The disease may occur at all ages but typically has its onset in the fourth to sixth decades of life. An estimated 2–4 million people in the USA have SS, of whom about 1 million have established diagnoses (Helmick et al, 2008). Recent studies using the 2002 American–European Consensus Group (AECG) criteria have estimated a prevalence of 1–9 cases per 10 000 people in the general population of the greater Paris area (0.01–0.09%) (Maldini et al, 2014) and an annual incidence of 4.2 cases/100 000 people in the USA (Nannini et al, 2013).

A differentiated clinical and immunological expression has been reported for specific epidemiological subsets:

- Paediatric SS. SS might be diagnosed in children (Lieberman, 2013). More than 100 observations have been published, half of them concerning primary SS. In adults with primary SS, 5.5% of the patients reported

an onset of symptoms before the age of 16 years. In children, the average age of onset is 11 years. The female predominance is weaker than in adults, being between 73.5% and 80% (Cimaz et al, 2003). Parotid gland enlargement and recurrent parotiditis are the most common clinical features, whereas mouth and ocular dryness may appear later (Singer et al, 2008). The immunological pattern is identical to that of adults: antinuclear antibodies (ANAs) are detected in most cases and likewise anti-SSA antibodies are detected in 68–100% of children (Singer et al, 2008). Focal lymphocytic sialadenitis is not always present (Houghton et al, 2005). Thus these children will not always formally fulfil the AECG criteria developed for use in adult SS (Houghton et al, 2005; Singer et al, 2008). Lymphocytic infiltration of labial salivary glands and sialectasis are a consistent finding in all biopsies tested (Saad Magalhães et al, 2011).

- **Male patients.** Various studies have described a less pronounced clinical phenotype among male patients with SS than among female patients, including a lower frequency of abnormal ocular tests and a lower prevalence of positive ANAs, Raynaud's phenomenon and thyroiditis (Ramos-Casals et al, 2008). These findings are consistent with a generally accepted precept in autoimmunity—namely, that autoimmune diseases are more common in women, making diagnosis more difficult owing to this relatively muted presentation in men. IgG4-related disease (IgG4-RD) should always be considered in the differential diagnosis of male patients with sicca symptoms and salivary gland enlargement (Nocturne et al, 2011).
- **Elderly patients.** The prevalence of xerostomia increases with age and affects 30% of the population over 65 years of age. The presence of sicca syndrome is not necessarily associated with an autoimmune process and before performing other invasive or immunological tests, the first step is to discard the use of certain xerogenic drugs as the cause. Compared to younger patients, older patients have a lower frequency of serologic markers (anti-SSA, anti-SSB, Rheumatoid factor, hyperglobulinemia). Moreover, lung involvement and anaemia is more prevalent, whereas parotid enlargement, arthralgia and Raynaud phenomenon is less common (Baer et al. 2017)*.

3 Pathogenesis

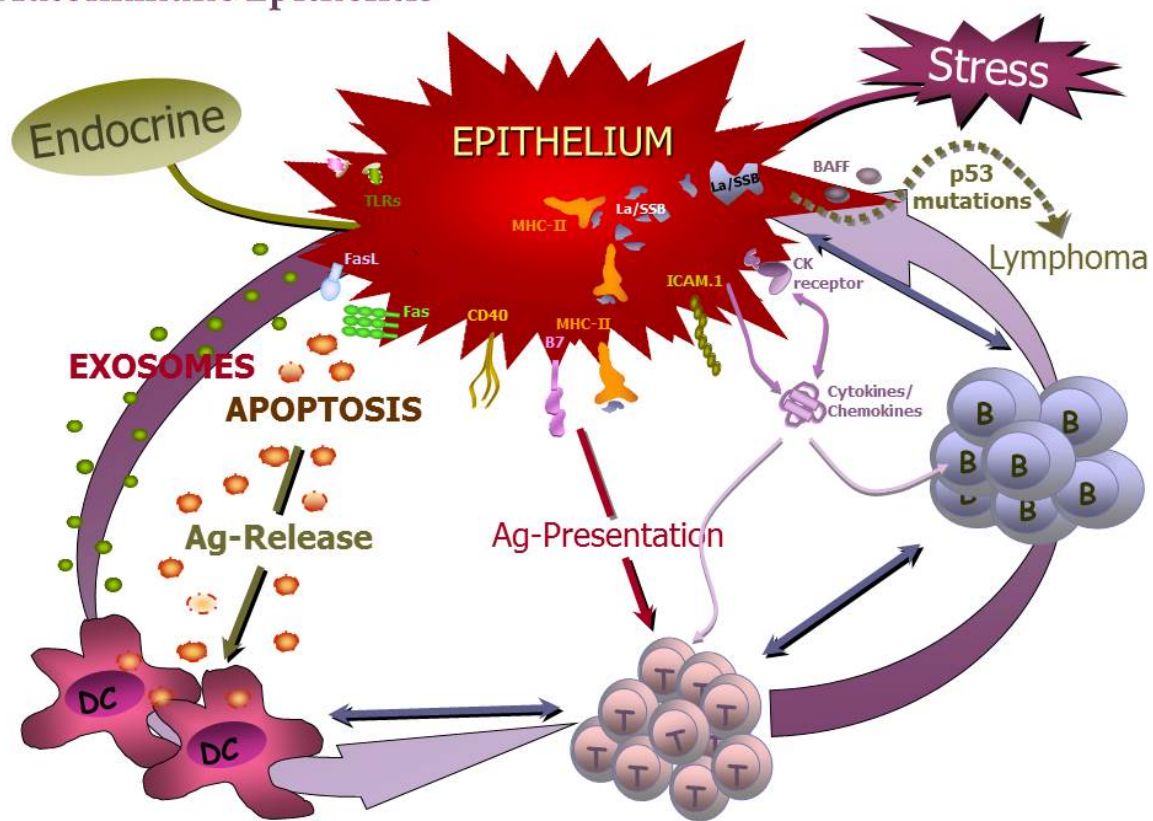
Primary SS is an excellent model for the study of autoimmune diseases since the targeted organs and cells (salivary gland epithelial cells and conjunctival epithelial cells) can be easily accessed and analysed (Voulgarelis and Tzioufas, 2010). Like all other autoimmune diseases, the origin of SS is unknown. Although, the interaction of genetic and environmental factors is being progressively unravelled (Fox, 2005) (figure 1).

Familial cases of primary SS are uncommon, but an aggregation of other autoimmune diseases is often seen. Polymorphisms of the early B cell factor 1, B cell lymphocyte kinase and tumour necrosis factor superfamily member 4 (TNFSF4) genes, all implicated in B cell differentiation and activation, have been recently associated with disease susceptibility (Nordmark et al, 2011; Ice et al, 2012). Interestingly, a gene polymorphism of interferon (IFN) regulatory factor-5, a transcription factor involved in IFN signalling pathway, is associated with

primary SS (Miceli-Richard et al, 2007) and additive effects of the major risk alleles of IFN regulatory factor-5 and STAT-4, both important mediators of type I IFN action, have been documented (Nordmark et al, 2009). Demonstration of the activation of the pathways of IFNs, potent antiviral proteins, sheds new light on the viral hypothesis; previous studies focused on the role of Epstein–Barr virus (EBV), herpesviruses, Cocksackie virus, retroviruses and hepatitis C virus (HCV). In addition, the epidemiological pattern of primary SS, overwhelmingly affecting women between the fourth and the sixth decade, strongly suggests the contributory role of hormonal factors.

Figure 1 Autoimmune epithelitis: pathogenesis of primary Sjögren's syndrome. (The figure is provided by Professor H M Moutsopoulos.)

Autoimmune Epithelitis



The epithelial cells play a central role in the pathogenesis of the immunopathological lesions. It appears that these cells are activated, producing a variety of cytokines and chemokines, as well as molecules able to prime local immune responses (HLA class II, costimulatory molecules and altered cellular distribution of autoantigen) (Tzioufas et al, 2012). Based on these observations, the term autoimmune epithelitis has been proposed (Moutsopoulos, 1994; Moutsopoulos, 2007).

Lymphocytes play a key role in the pathogenesis of SS. In mild lesions CD4+ T lymphocytes constitute the major cell population of invading cells (70–80%); whereas in more advanced lesions B cells predominate (Christodoulou et al, 2010). B cells in the lesions contain intracytoplasmic immunoglobulins with anti-Ro (SSA)

and/or anti-La (SSB) reactivity (Youinou et al, 2010). Oligoclonal B lymphocytes and germinal centre formation in salivary infiltrates (Theander et al, 2011; Risselada et al, 2013a) may represent a predisposing factor for lymphoma.

Macrophages and plasmacytoid dendritic cells, the professional type I IFN producers, have also been detected in minor salivary gland biopsy specimens from patients with SS. They are characterised by the presence of Toll-like receptors 7 and 9 (sensed by exogenous or endogenous nucleic acids), implying the presence of a viral or viral-like trigger at the level of salivary gland tissue. IFNs induce the expression of BAFF (B cell activating factor of the TNF family, or B lymphocyte stimulator (BLyS), see below) by monocytes, dendritic cells and salivary gland epithelial cells (Mavragani and Crow, 2010). T and B cell-attracting chemokines together with BAFF create a microenvironment supportive of B cell aggregation and differentiation, and local production of anti-SSA/SSB antibodies, with structural features remarkably similar to the germinal centre seen in lymph nodes (Ogawa et al, 2002; Salomonsson et al, 2003; Barone et al, 2005). B cells are overstimulated and produce excessive amounts of immunoglobulins and various autoantibodies. Peripheral blood and salivary gland B cell subset distribution is altered, leading to the constitution of ectopic germinal centres where autoreactive clones may escape tolerance checkpoints. Several B cell-specific cytokines, such as BAFF or FMS-like tyrosine kinase 3 ligand (Flt-3L), are instrumental in the occurrence of B cell dysfunction. Chronic and excessive stimulation of B cells may lead to the development of lymphoma in patients with SS.

In summary, a plausible pathophysiological scenario that might account for the complex immunopathology seen in SS would implicate a genetically determined exaggerated innate immune response against inappropriately overexpressed endogenous or exogenous danger signals. More specifically, transient or persistent infection of the epithelial cells by a putative virus may lead to genetically determined exaggerated induction of type I IFN production (Mariette and Gottenberg, 2010; Wahren-Herlenius and Dörner, 2013) by locally recruited plasmacytoid dendritic cells. This can lead to further activation of epithelial salivary cells through upregulation of the major histocompatibility complex and costimulatory molecules and to apoptotic events resulting in exposure of autoantigens such as Ro/SSA and La/SSB and generation of disease-specific anti-Ro/SSA and La/SSB autoreactivities (Kyriakidis et al, 2014). Recent data suggest that the glandular dysfunction may involve inhibitory operating mechanisms in the secretory process, including inhibition of neurotransmitter release by cytokines (interleukin 1, TNF α) (Zoukhri and Kublin, 2001), enhanced breakdown of acetylcholine by increased levels of cholinesterase in primary SS (Dawson et al, 2005), blockade of M3 receptors by antimuscarinic autoantibodies (Lee et al, 2013; Sumida et al, 2014), altered production and intracellular calcium mobilisation and altered fluid movement due to abnormal distribution of aquaporins.

4 Clinical findings

4.1 Signs and symptoms

4.1.1 Sicca features

Sicca features are symptoms that usually receive little attention and may be considered trivial by both doctor and patient. They progress slowly in time, and often patients do not consult timely at symptoms onset due to lack of awareness. Not all patients present the whole sicca spectrum, and likewise, sicca symptoms intensity may vary from patient to patient. Although often elusive, an early, accurate diagnosis of SS can help prevent, or ensure timely treatment of, many of the complications associated with chronic/severe dryness.

- **Dry mouth.** The subjective feeling of oral dryness is a key feature in the diagnosis of SS, occurring in >95% of patients. Other oral symptoms may include soreness, adherence of food to the mucosa and dysphagia, with subjective difficulty in swallowing (more common to solid food than liquids). Reduced salivary volume interferes with basic functions such as speaking or eating. The lack of salivary antimicrobial functions may accelerate local infection, tooth decay and periodontal disease. Xerostomia can lead to difficulty with dentures and the need for expensive dental restoration, particularly in elderly patients. Various oral signs may be seen in patients with SS. In the early stages, the mouth may appear moist, but as the disease progresses the usual pooling of saliva in the floor of the mouth disappears. Typically the surface of the tongue becomes red and lobulated, with partial or complete depapillation (figure 2). In advanced disease, the oral mucosa appears dry and glazed and tends to form fine wrinkles. Angular cheilitis, erythematous changes of the hard palate and a red tongue with atrophic papillae strongly suggest Candida infection.
- **Dry eyes.** The subjective feeling of ocular dryness produces sensations of itching, grittiness, soreness and dryness, although the eyes might look normal. Other ocular complaints include photosensitivity, erythema, eye fatigue or decreased visual acuity. Environmental irritants such as smoke, wind, air conditioning and low humidity may exacerbate ocular symptoms. Diminished tear secretion may lead to chronic irritation and destruction of corneal and bulbar conjunctival epithelium (keratoconjunctivitis sicca). Tears also have inherent antimicrobial activity and patients with SS are more susceptible to ocular infections, such as blepharitis, bacterial keratitis and conjunctivitis. Severe ocular complications may include corneal ulceration, vascularisation and opacification.
- **Other dryness.** Reduction or absence of respiratory tract glandular secretions can lead to dryness of the nose, throat and trachea, resulting in persistent hoarseness and chronic, non-productive cough (Ramos-Casals et al, 2009). Involvement of the exocrine glands of the skin leads to cutaneous dryness with pruritus. In female patients with SS, dryness of the vagina and vulva may result in dyspareunia, pruritus urinary urgency dysuria and recurrent urinary tract infection, affecting their quality of life.

Figure 2 Oral dryness and red tongue in a patient with primary Sjögren's syndrome. (Source: CRI (Club Rhumatismes et Inflammation), <http://www.cri-net.com>)



4.1.2 Glandular swelling

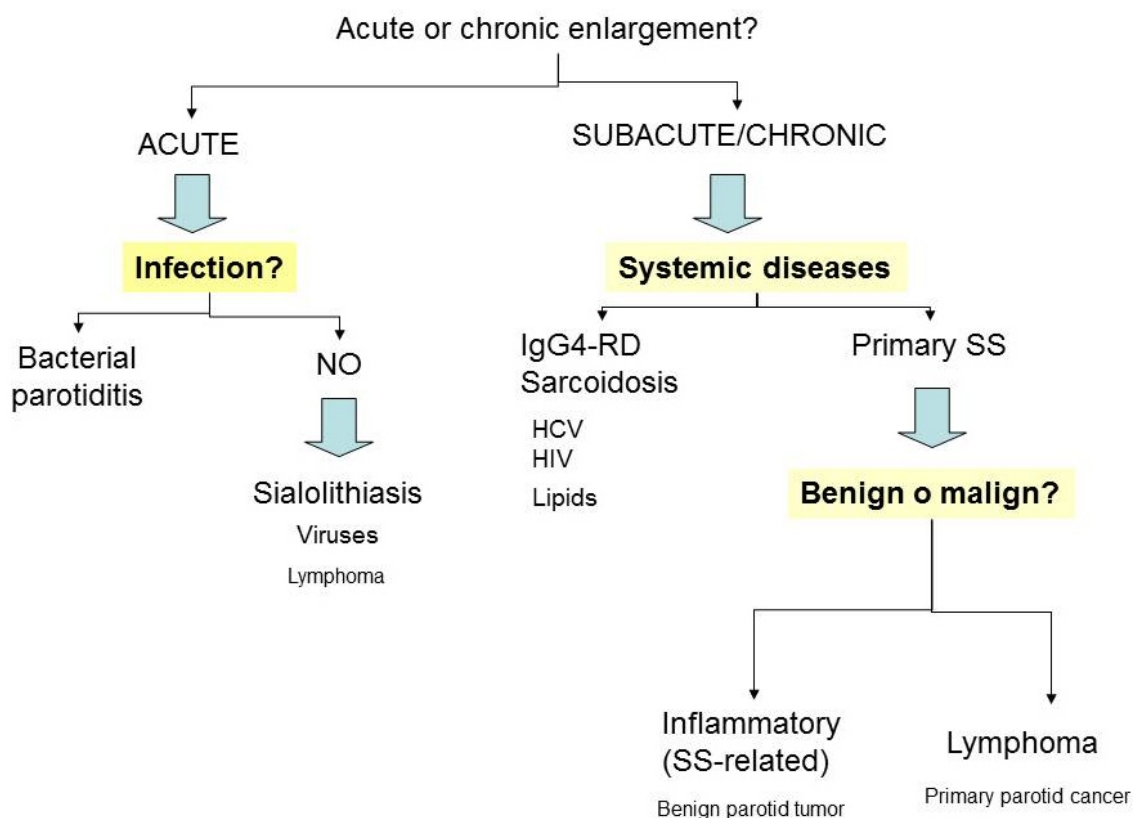
Chronic or episodic swelling of the major salivary glands is reported in 10–20% of patients and may start unilaterally, but often becomes bilateral (figure 3), affecting mainly the parotid glands but also the submandibular and sublingual glands. However, isolated submandibular gland enlargement is an atypical finding in SS that should make one consider other disorders, principally IgG4-RD (see online in-depth discussion). Differential diagnosis of unilateral salivary gland enlargement should include lymphoma, lithiasis and infections.

Figure 3 Bilateral parotid enlargement. Patient consent obtained. (Source: CRI (Club Rhumatismes et Inflammation), <http://www.cri-net.com>)



The course of glandular enlargement in SS varies from patient to patient. Enlarged salivary glands are usually bilateral, firm to palpation, either symmetrical or asymmetrical in size and have minimal symptoms. Enlargement can be episodic, with gradual waxing and waning, or chronic, with gradual progression over months or years. Although nearly 90% of patients with primary SS present inflammatory, benign parotid enlargement, B cell lymphoma should be always suspected, especially in patients with persistent enlargement. A rapid increase in the size of an enlarged gland associated with symptoms and signs of acute inflammation suggests a superimposed bacterial sialoadenitis and calls for systemic antibiotic treatment (figure 4).

Figure 4 Differential diagnosis of parotid enlargement. HCV, hepatitis C virus; HIV, human immune deficiency virus; IgG4-RD, IgG4-related disease; SS, Sjögren's syndrome.



4.1.3 General symptomatology

Patients with primary SS often present with general symptoms, which may have a much greater effect on the quality of life than sicca features. Low-grade, self-limiting fevers may occur in SS, usually in young patients with marked hypergammaglobulinaemia and positive immunological markers. Fatigue, generalised pain, fibromyalgia, and weakness are among the most debilitating clinical features of primary SS (Ng and Bowman, 2010*; Westhoff et al, 2012). Other non-specific symptoms closely associated with fatigue are sleep disturbances, anxiety and depression, with a prevalence according to recent studies of nearly 15%, 20% and 40% of patients with primary SS, respectively (Theander et al, 2010; Segal, 2012; Westhoff et al, 2012). Chronic pain is often associated with polyarthralgia/myalgia, which is reported by more than 50% of patients. Careful

assessment is essential, as this set of symptoms is also characteristic of other conditions (menopause, hypothyroidism, neoplasia, primary depression and, above all, fibromyalgia). The environment plays a key role in exacerbating these symptoms.

4.1.4 Organ-specific signs and symptoms

Patients may develop a large number of organ-specific signs and symptoms, either at presentation or during evolution of the disease, detailed as follows.

4.2 Systemic involvement

A long list of extra glandular features, including all the main organs and systems, is reported in patients with primary SS, the majority of whom are characterised by a 'Janus-faced' pattern of involvement (figure 5; table 1).

Figure 5 The 'Janus-faced' pattern of systemic involvement in primary Sjögren's syndrome.

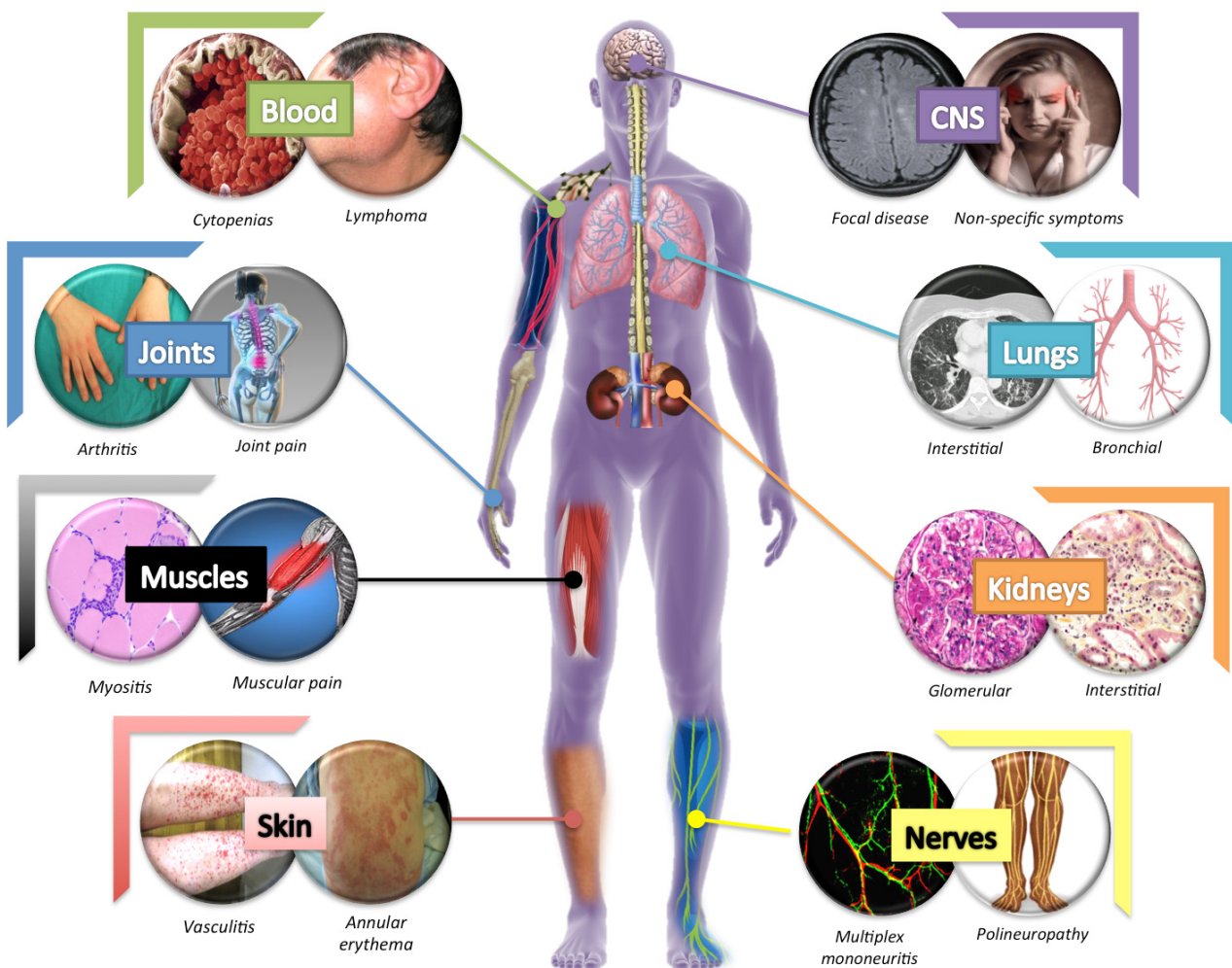


Table 1 Major systemic manifestations of Sjögren's syndrome: percentage of overt clinical involvement in different large case series (Adapted from Ramos-Casals et al, BMJ 2012b;344:e3821*)

Organ	Manifestation
Skin	Purpura (10–15%) often related to cryoglobulinaemia Annular erythema (photosensitive erythematous lesions with indurated borders; 5–10%)
Joints	Non-erosive symmetrical arthritis (15–30%)
Lungs	Chronic obstructive lung disease (10%) Bronchiectasis (8%) Interstitial lung disease (5%)
Cardiovascular	Raynaud's phenomenon (18–37%) Pericarditis (<5%) Symptoms of autonomic dysfunction
Liver	Primary biliary cirrhosis (3–8%) Autoimmune hepatitis (<5%)
Pancreas	Recurrent pancreatitis (<5%)
Nephro-urological	Renal tubular acidosis (11%) Glomerulonephritis (<5%) Interstitial cystitis (<5%) Nephrolithiasis (<5%)
Peripheral nerves	Mixed polyneuropathy (5–10%) Pure sensory neuronopathy (5%) Mononeuritis multiplex (5%) Small-fibre neuropathy* (<5%) Myoclonus
Central nervous system	White matter lesions (MS-like disease) (<5%) Cranial nerve involvement (V, VIII and VII) (7%) Myelitis (<5%)
Thyroid	Autoimmune thyroiditis (14–33%)
Haematological	Autoimmune haemolytic anaemia (<5%) Severe thrombocytopenia <10 000/mm ³ (<5%) B cell lymphoma (5–10%)

**Patients with small-fibre neuropathy often present with painful burning dysaesthesia of the distal limbs. Because electromyographic studies may be normal, a skin biopsy often confirms the diagnosis. MS, multiple sclerosis.*

4.2.1 Joint and muscular involvement

Joint involvement (including either arthralgia or arthritis) was reported in 53% of patients included in retrospective/cross-sectional studies. The arthropathy is usually symmetrical, non-erosive and intermittent. The most commonly affected joints are the knees, wrists, interphalangeal and metacarpophalangeal joints (Fauchais et al, 2010). Joint deformity is rare, except when associated with RA or SS-related Jaccoud arthropathy.

A mild inflammatory myopathy has been reported in 2-47% of SS patients, being either subclinical or characterized by the insidious onset of proximal muscles weakness. Inclusion body myositis has been reported in rare cases and should be suspected in patients with muscles weakness and relatively low muscles enzymes elevation (Kanellopoulos et al, 2002) .

4.2.2 Skin

The main cutaneous manifestation in patients with primary SS is xerosis, present in 23-67%. It is characterized by dry, scaly skin, affecting mainly the lower extremities, and patients complain of pruritus. Hyperpigmented lesion may arise secondary to scratched skin. However, a wide spectrum of cutaneous lesions may be seen, the most common of which is a small-vessel vasculitis (Ramos-Casals et al, 2004a).

Vasculitis is reported in 10% of patients with primary SS included in retrospective studies, overwhelmingly presenting with cutaneous purpura (88%) (figure 6), with other cutaneous lesions such as nodules, digital lesions or maculopapular rash being rarely reported; cutaneous ulcers are reported in 8% of patients. Cryoglobulins are positive in one-third of cases and vasculitis is confirmed by biopsy in nearly half; 90% disclose leukocytoclastic vasculitis.

Figure 6 Cutaneous purpura.



Patients with primary SS may also present with non-vasculitic cutaneous lesions. Some patients with anti-Ro/SSA antibodies may present with polycyclic, photosensitive cutaneous lesions (figure 7), clinically identical to the so-called annular erythema (AE) described in Asian patients with SS and subacute cutaneous lupus. Recently, AE was reported as one of the most common cutaneous lesions found in European patients (Brito-Zerón et al, 2014). Subacute cutaneous lupus (idiopathic, drug-induced or related to SLE), AE and neonatal cutaneous lupus should be considered as a clinical spectrum of the same immune-mediated disease, which may have a common pathogenic basis, mainly related to anti-Ro antibodies.

Figure 7 Annular erythema.



Other skin lesions are erythema nodosum, livedo reticularis, lichen planus, cutaneous amyloidosis, vitiligo, eyelid dermatitis and angular cheilitis. Some lesions may arise due to treatment such as the hyperpigmentation seen in patients receiving hydroxychloroquine.

Figure 8 a. Cutaneous amyloidosis



Figure 8 b. Cutaneous amyloidosis histopathology

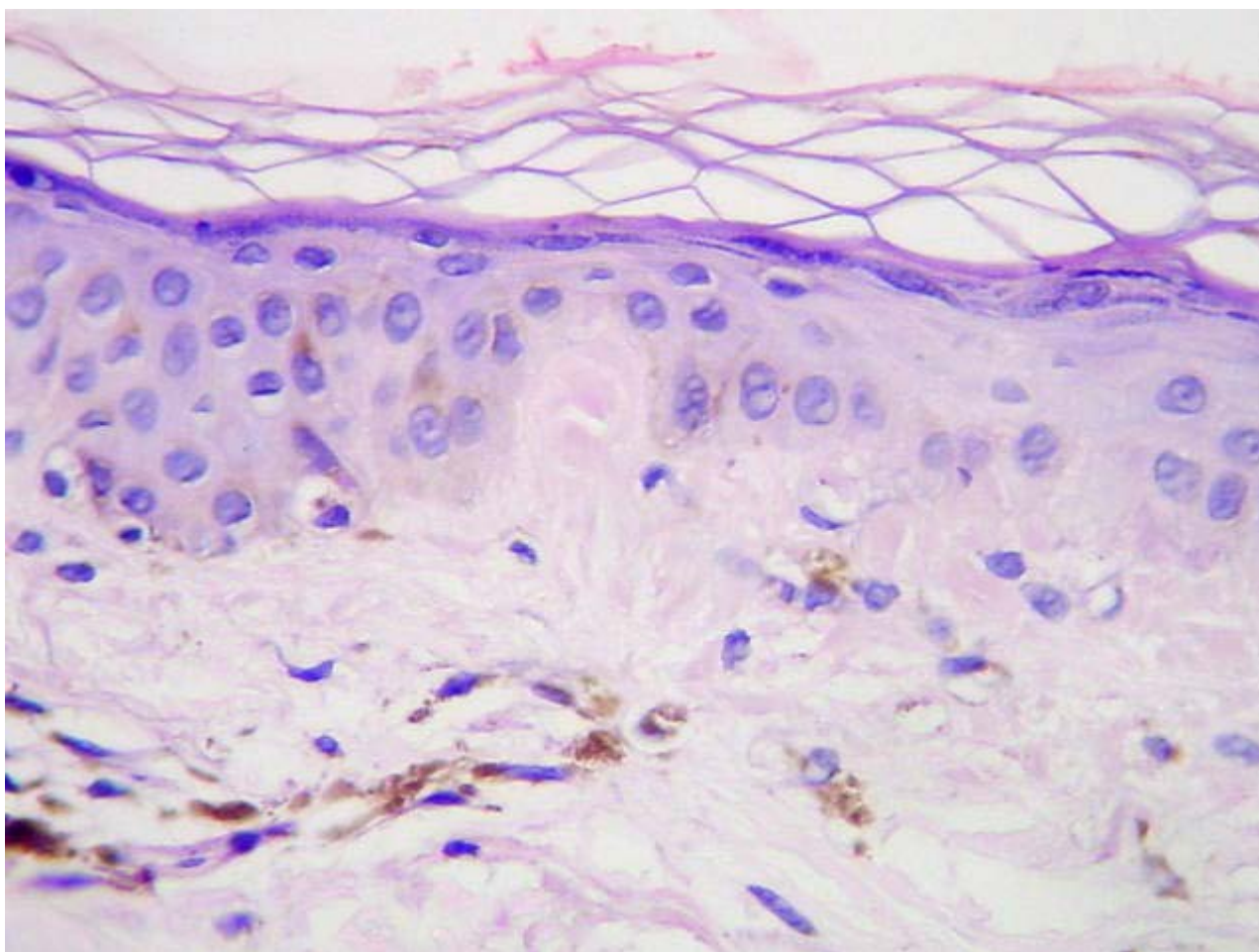
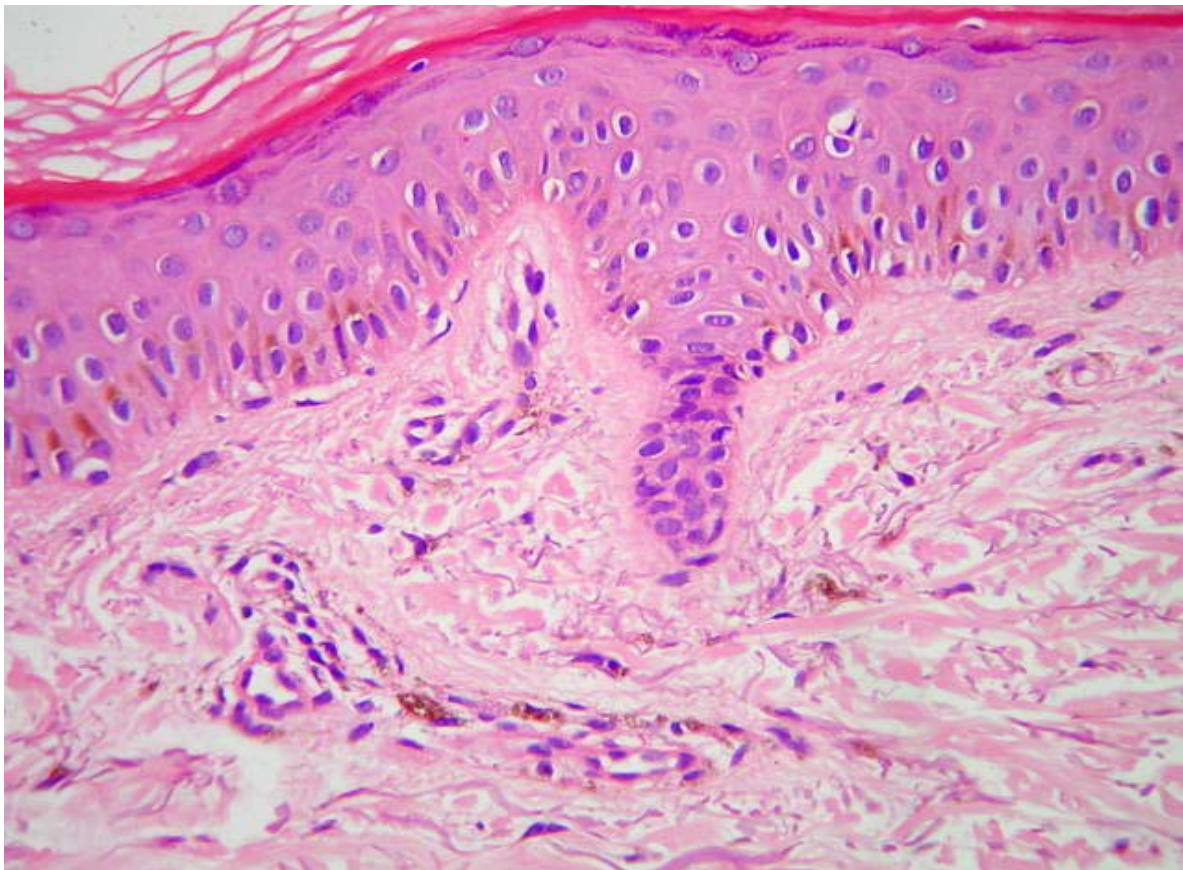


Figure 9 a. Hydroxychloroquine hyperpigmentation



Figure 9 b. Hydroxychloroquine hyperpigmentation histopathology

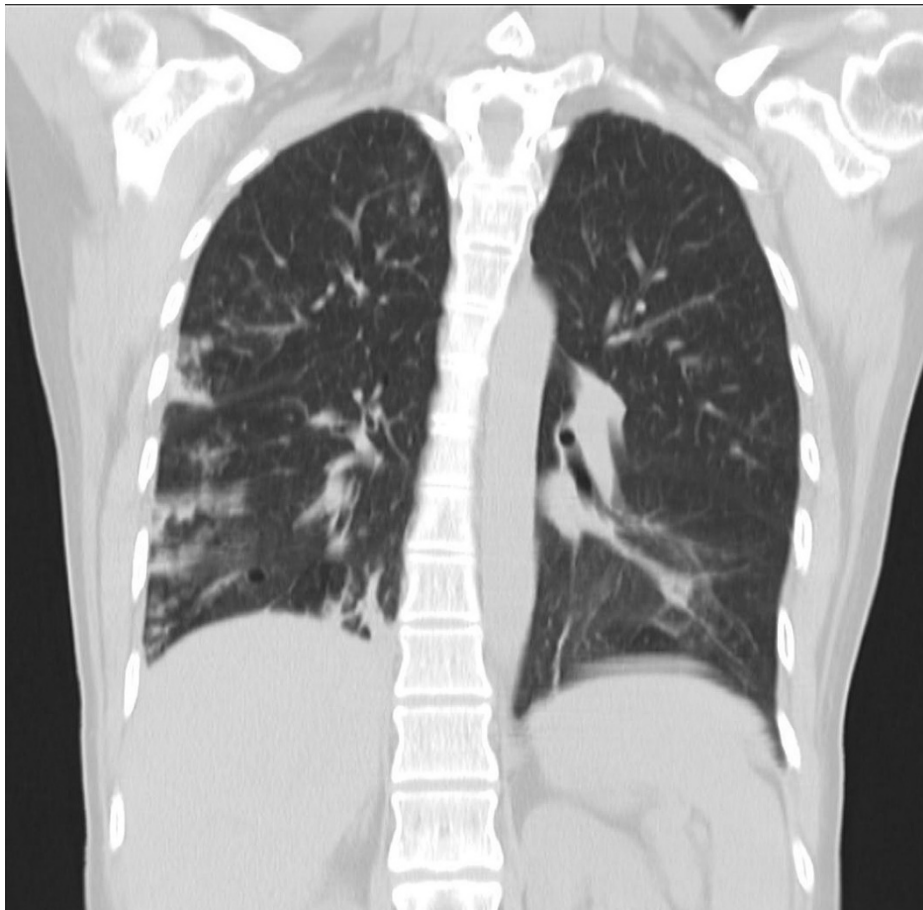


4.2.3 Lungs

Overall analysis of studies including unselected patients with SS found pulmonary involvement in 16%; one study focused on bronchial involvement and found bronchiectasis in 8% of patients. Clinical features included dyspnoea (62%), cough (54%), sputum/rales (14%), chest pain (5%) and fever (2%).

Two types of pulmonary involvement are predominant in primary SS (bronchial and interstitial), although most investigators have reported a predominance of bronchial/bronchiolar involvement rather than pulmonary fibrosis; the main underlying pathology in these patients is peribronchial infiltrates that leads to small airway disease (Papiris et al, 1999). CT findings found bronchiectasis/bronchiolar abnormalities (50%) and ground-glass opacities/interstitial changes (49%) to be the most common abnormalities. The most common histopathological diagnoses were non-specific interstitial pneumonia (NSIP) (45%), bronchiolitis (25%), usual interstitial pneumonia (UIP) (16%) and lymphocytic interstitial pneumonia (LIP) (figure 8) (15%). LIP has a strong association with primary SS, it is described as lymphoplasmocytic infiltrates within the interstitium, often forming nodular lymphoid aggregates, and lymphocytes within the alveolar spaces. These patients commonly also present polyclonal or monoclonal gammopathy.

Figure 8 Lymphocytic interstitial pneumonia in a 33-year-old woman with primary Sjögren's syndrome.



The typical symptoms of patients with bronchial or bronchiolar disease are cough, dyspnoea and recurrent respiratory infections (Soto-Cardenas et al, 2010). The classic pulmonary function test manifestation of this disease complication is a decreased maximal expiratory flow at 25% of vital capacity and a reduced diffusing capacity for carbon monoxide. Chest radiographs in these individuals are usually normal or show an ill-defined pattern of infiltrates that suggests interstitial lung disease (Ramos-Casals et al, 2009).

Cystic lung disease is a relatively common condition in SS. It has been reported in 15% of patients with chest imaging, being in occasions not evident in plain radiographs. In CT scans it has been observed in 30% of the patients. It does not progress in serial radiologic or function tests follow-up. In the absence of other radiographic findings it may represent a direct manifestation of SS (Martinez-Balzano, et al. 2016*

SS-related pulmonary disease is clearly associated with a poorer quality of life and shorter survival, with a two- to four-fold increase in the risk of death (Nannini et al, 2013; Palm et al, 2013) compared with patients without pulmonary disease. Enomoto et al (2013) identified PaCO₂, the extent of reticular abnormality and the severity of fibroblastic foci as the main baseline factors associated with death, while the histopathological patterns (UIP vs NSIP) had no influence in mortality.

4.2.4 Cardiovascular features

Raynaud's phenomenon, with a prevalence of 10–20%, is probably the most common vascular feature seen in primary SS and can appear before sicca symptomatology (García-Carrasco et al, 2002). The clinical course of Raynaud's phenomenon in primary SS is milder than in other systemic autoimmune diseases, such as SSc. Vascular complications (eg, digital loss, digital pulp pitting or fingertip infarctions) are uncommon, and pharmacological interventions are required in only 40% of cases. Capillaroscopic findings are long, thin capillaries with no avascular areas or ectasia.

Cardiac involvement is rarely seen, with pericardial effusions (usually mild and asymptomatic) being the most common feature (Vassiliou et al, 2008). Persistent pericarditis with signs of serositis, should raise the suspicion of another autoimmune disease (i.e., RA or SLE).

Several studies have reported autonomic cardiovascular disturbances, including orthostatic intolerance, secretomotor dysfunction, male sexual dysfunction, urinary dysfunction, gastroparesis, pupillomotor dysfunction, vasomotor dysfunction or sleep disorders (Ng et al, 2012).

Congenital heart block may develop in babies from anti-RO positive pregnant woman.

Other studies have reported a prevalence of pulmonary arterial hypertension in primary SS of 22% (Vassiliou et al, 2008). It should be suspected in patients with primary SS presenting with unexplained dyspnoea and normal chest radiography (Launay et al, 2007); associated SSc should always be investigated in these patients.

4.2.5 Gut

Gastrointestinal involvement may include altered oesophageal motility (dysphagia), chronic gastritis, and less frequently, malabsorption. *Helicobacter pylori* infection should be excluded in patients with gastritis, owing to the close association with gastric mucosa-associated lymphoid tissue lymphoma.

Liver function tests may be abnormal in 10–20% of patients with primary SS. After exclusion of potentially hepatotoxic drugs and steatohepatitis, the main causes are associated diseases, including chronic viral infections (mainly HCV infection) and associated organ-specific diseases (primary biliary cirrhosis and, less frequently, type 1 autoimmune hepatitis) (Ramos-Casals et al, 2006) (figure 9).

Celiac disease may be more prevalent in SS than compared to the general population.

Pancreatic involvement, usually asymptomatic, is demonstrated by altered pancreatic enzymes. Some patients may present with chronic pancreatitis, although investigation of a possible IgG4-RD should be mandatory in all patients with SS diagnosed with autoimmune pancreatitis or with autoimmune or sclerosing cholangitis (Stone et al, 2012; Mavragani et al, 2014).

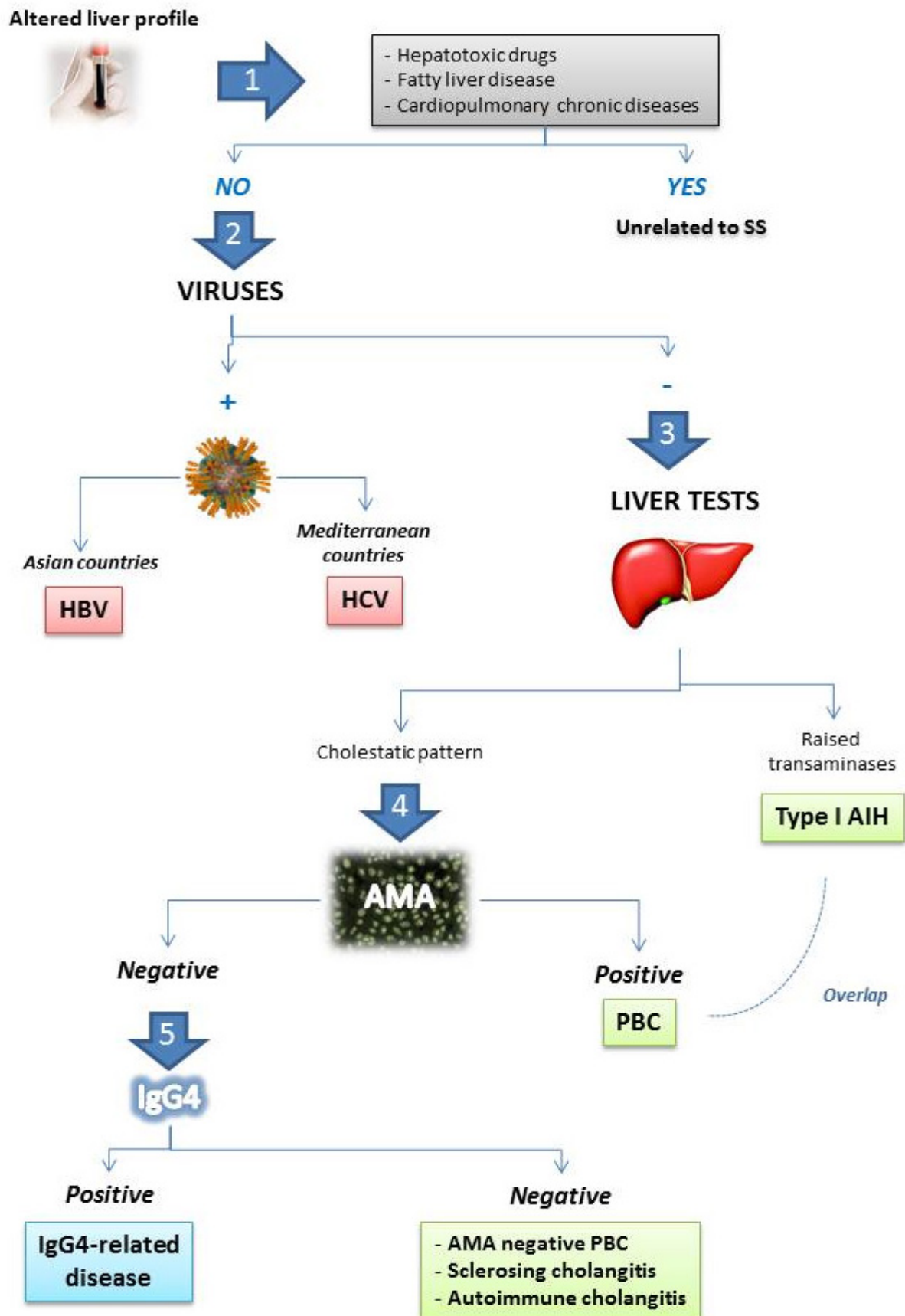
4.2.6 Nephro-urological and gynaecological involvement

Renal involvement is found in 5% of the nearly 2000 patients included in the largest reported series; the two types of renal involvement described are tubulointerstitial renal disease and glomerulonephritis.

Tubulointerstitial nephritis can be an early manifestation of SS and is caused by type I renal tubular acidosis (distal). The diagnosis is based on a persistent urine pH >5.3 even in the presence of a metabolic acidosis induced by NH₄Cl loading. Renal tubular acidosis may be diagnosed by two clinical features in two-thirds of cases, and by asymptomatic laboratory findings (mainly mild renal failure and/or proteinuria) in the remaining cases. Of symptomatic patients, the main feature (70%) is hypokalaemic weakness/paralysis (some with respiratory failure). Other clinical presentations may include nephrolithiasis and radiological nephrocalcinosis; there are some reported cases of osteomalacia (some with pathological fractures) and diabetes insipidus; renal failure was reported in 24% of patients. Renal biopsy was carried out in nearly half of the cases and disclosed tubulointerstitial nephritis in more than 90% of biopsies. Anti-SSA/SSB antibodies are frequent in tubulointerstitial nephritis and are associated with worse prognosis.

Glomerulonephritis, usually membranous and membranoproliferative, appears late in the course of the disease. The clinical presentation is often indolent. However, patients may present oedema/nephrotic syndrome, proteinuria, haematuria and renal failure. Patients with glomerulonephritis present with cryoglobulins, usually type II (mixed monoclonal, containing an IgMk monoclonal rheumatoid factor). Patients with glomerulonephritis have high rates of adverse outcomes, especially those with cryoglobulinaemia-mediated glomerular damage, while interstitial nephritis has a better prognosis. (Goules et al, 2013)

Figure 9 Differential diagnosis of liver involvement in patients with primary Sjögren's syndrome. AIH, autoimmune hepatitis; AMA, antimitochondrial antibodies; HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; SS, Sjögren's syndrome.



Finally, interstitial cystitis, sometimes with severe symptoms, has been identified as a new extra glandular SS feature (Leppilahti et al, 2003). The clinical presentation may include a chronic history of pain/discomfort in the pelvic area and/or perineal pain accompanied by urinary urgency, frequency, dysuria and nocturia. These symptoms have been reported to be more frequent in SS patients compared to the general population (20 fold increase).

Gynaecologic manifestations include vulvovaginal dryness, dyspareunia, pruritus and frequent yeast infections. Moreover, anti-ovarian antibodies (AOA) occur frequently in patients with SS. High OAO may be an indication of Oophoritis and a possible cause of premature menopause.

4.2.7 *Peripheral neuropathy*

Peripheral neuropathy has been reported in 1.8% (Pavlakakis et al, 2011) to 10% of patients with primary SS undergoing electrodiagnostic testing (Brito-Zerón et al, 2013). The clinical course of the different types of peripheral neuropathies differs:

- Sensory or sensorimotor axonal polyneuropathy is the most common type of neuropathy and has the lowest frequency of SS-related immunological markers.
- Multiplex mononeuropathy is predominantly diagnosed in patients with a profile of 'high systemic activity' and has the poorest survival rate, and
- Pure sensory neuropathy is the most disabling in the long term and has the most discouraging therapeutic management (Brito-Zerón et al, 2013; Jamilloux et al, 2014). It is recognised as a typical neurological complication of primary SS, caused by damage to the sensory neurons of the dorsal root and gasserian ganglia. A recent study characterised 40 patients with primary SS diagnosed with sensory small-fibre neuropathy (Sene et al, 2013); these patients had an older age at diagnosis and a lower frequency of hypergammaglobulinaemia and autoantibodies. The diagnosis often relies on quantitative sensory testing and sural nerve biopsy, but skin biopsy is an increasingly useful technique for demonstrating a decrease in the density of epidermal nerve fibres (Chai et al, 2005; Gøransson et al, 2006). Patients with small-fibre neuropathy have normal nerve conduction studies, because the size of nerve fibres involved is below the resolution of conventional electrodiagnostic studies (Ramos-Casals et al, 2009). Sural nerve biopsy may show vascular or perivascular inflammation of small epineurial vessels (both arterioles and venules) and, in some cases, necrotizing vasculitis. The loss of myelinated nerve fibres is common and loss of small-diameter nerve fibres occurs. The histopathology of sensory ganglioneuronopathy consists of the loss of neuronal cell bodies and T cell infiltration.

Patients with SS may also present cranial nerve involvement, mainly of the trigeminal (V), vestibulocochlear (VIII) and facial (VII) cranial pairs. Trigeminal neuralgia is a common complication of primary SS, reported in

about 15% of patients with any kind of neuropathy. It is usually unilateral. The pain is distributed in the regions that are innervated by the branches of the trigeminal nerve (Ramos-Casals et al, 2009).

4.2.8 Central nervous system involvement

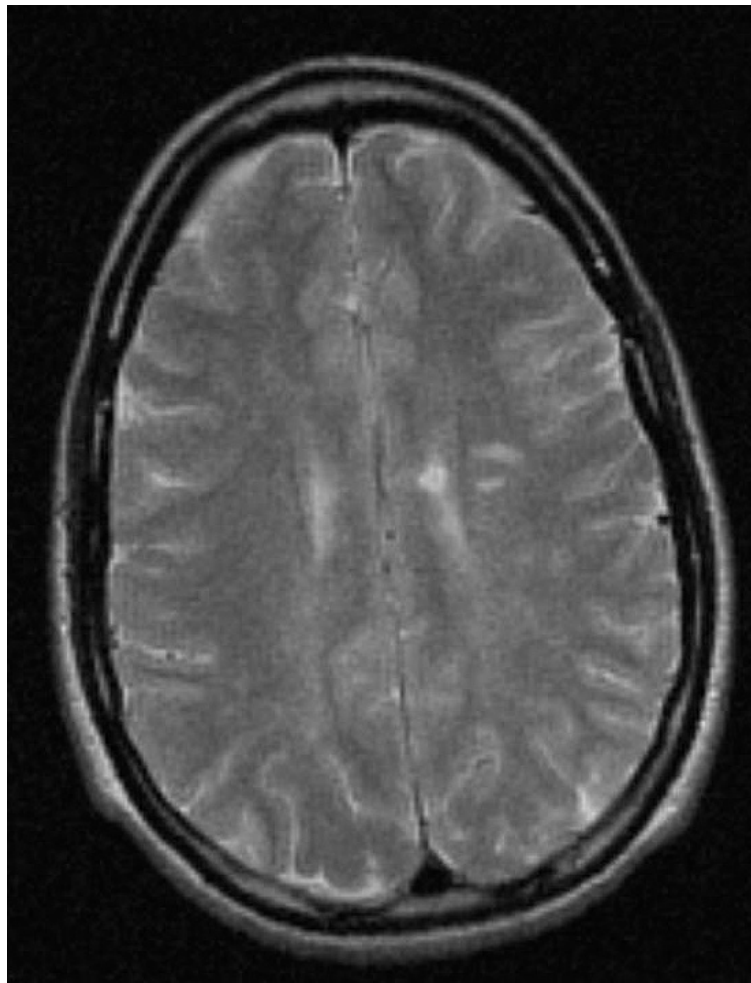
Severe organic central nervous system (CNS) involvement in patients with primary SS is extremely rare. However, some patients may present a wide spectrum of non-specific neurological manifestations that can be difficult to differentiate from other neurological diseases, including those frequently reported in non-autoimmune patients. A recent study found features such as pain, fibromyalgia, fatigue, headache and psychiatric/cognitive disorders in more than 70% of 120 patients with primary SS (Morreale et al, 2014), while Jamilloux et al (2014) found a sevenfold lower prevalence (10%) in 420 patients, including only neurological involvements confirmed by specific diagnostic tests. Tjensvoll et al (2013) confirmed the high frequency of headache in patients with primary SS (70%), likewise the prevalence in an age-sex matched control group was similar (60%).

The most frequently detected CNS feature in primary SS is asymptomatic white matter lesions in magnetic resonance studies. A recent study found that these lesions are overwhelmingly associated with concomitant cardiovascular risk factors, although isolated cases of patients with SS presenting with a multiple sclerosis (MS)-like disease (figure 10) were also reported (Akasbi et al, 2012).

Furthermore, cognitive dysfunction including memory loss and poor concentration are other manifestations. Patients frequently call this “brain fog”. Neurocognitive studies reveal a lower performance. These patients often suffer from depression. Further studies are needed to determine the relationship between depression and these cognitive impairment.

Some patients may develop aseptic meningitis or features of myelitis with or without optic neuritis, similar to ‘Devic's disease’.

Figure 10 Demyelinating central nervous system lesions in a patient with primary Sjögren's syndrome and multiple sclerosis-like disease.



The clinical approach to patients with primary SS with suspected CNS involvement requires diagnostic procedures to define the type of neurological involvement, and also the exclusion of processes not directly related to primary SS. These include the coexistence of other systemic autoimmune diseases (antiphospholipid syndrome, SLE and systemic vasculitis), the differential diagnosis from organ-specific autoimmune CNS disorders (MS, Devic's disease) and lymphoma of the CNS. Much more frequently, however, the clinician should consider non-autoimmune processes involving CNS in patients aged >50 years (cardiovascular disease, neurodegenerative processes).

4.2.9 Ear, nose and throat involvement

Although ear, nose, and throat involvement has been little studied in patients with primary SS, some studies have described sensorineural hearing loss in nearly 25% of patients with SS whose results were pooled from four studies (Ramos-Casals et al, 2005b). Associations with immunological parameters such as ANAa, antiphospholipid antibodies and anti-Ro/SSA or anti-La/SSB antibodies have been postulated but not proved. Sensorineural hearing loss in primary SS preferentially affects high-frequency hearing, but deficits often

remain subclinical (Boki et al, 2001). Retrocochlear disease and symptoms of vestibular dysfunction are not typical of SS (Ramos-Casals et al, 2009).

5 Diagnostic approach

5.1 Glandular functioning

5.1.1 Assessment of oral involvement

Several methods for assessing oral involvement have been proposed, including measurement of the salivary flow rate, ultrasonography, sialography or scintigraphy.

- Unstimulated whole sialometry ≤ 1.5 mL/15 min, or 0.1 mL/min is pathologically decreased. It is the easiest and less invasive exam to assess mouth dryness. Stimulated whole sialometry can also be performed 5 min after the unstimulated whole sialometry, using standardised paraffin chewing gums or lemon juice. Patients should be instructed to spit saliva into a graduated test tube every minute, with a quantity of <1.5 mL collected over a 15 min period; this has a sensitivity of 56% and a specificity of 81% for SS (Vitali et al, 2002*). These procedures are easy to perform at a physician's office during each visit.
- Parotid scintigraphy has greater sensitivity (80%) and specificity (86%) (Vitali et al, 1993) and classifies the grade of involvement of the major salivary glands into four grades, with severe involvement (grade IV) at diagnosis being prospectively associated with a higher risk of lymphoma and death (Ramos-Casals et al, 2010a). It is an expensive test and it is performed in referral centres.
- Ultrasonography is a non-invasive method that may provide useful information about the aetiology of parotid enlargements (Cornec et al, 2014a). Theander and Mandl (2013) recently evaluated the usefulness and prognostic value of a simplified salivary gland ultrasonography scoring system. This test has the potential to be included in the diagnostic/classification criteria of the disease (Goules and Tzioufas, 2014). It should be noted, however, that further validation, particularly against disease controls, is required (Tzioufas and Moutsopoulos, 2008). Typical findings include hypoechoic areas with convex borders in early stages, and hyperechoic bands, cysts and calcifications in more established disease. The sensibility for ultrasonography is around 55-66% and the specificity 93-98% depending on the different authors. There are ongoing studies on elastography that must be evaluated in the future.
- Magnetic resonance imaging (MRI): MRI of the parotid gland typically shows a nodular pattern, with multiple hypo and hyperintense areas of varying size. MRI correlates well with salivary gland biopsy.
- Sialography. Conventional x-ray sialography may show the so-called cherry blossom or snow flake pattern. The procedure is invasive and painful. It is a test that is not currently recommended.

5.1.2 Assessment of ocular involvement

There are several tests that evaluate the grade of ocular involvement. The most common is the Schirmer's test followed by corneal staining using colourants (Rose Bengal, fluorescein) (figure 11) for slit lamp examination to detect conjunctival epithelium destroyed by desiccation.

- Schirmer's test evaluates tear production. A filter paper is placed between the middle and lateral fornix of each eye. The patient is then asked to close the eyes during 5 minutes. The extent of tear wicking is recorded and is considered normal when greater than 5mm.
- Rose Bengal scoring involves placement of 25 mL of Rose Bengal solution in the inferior fornix of each eye and asking the patient to blink twice. Slit lamp examination detects destroyed conjunctival epithelium due to desiccation. The van Bijsterveld score expresses the results of this test.
- The Lissamine green test evaluates conjunctiva structural damage and has widely replaced the painful Rose Bengal test. The conjunctiva are stained with green colourant. If the epithelium is damaged, the conjunctivas are stained. Each area of the eye (nasal, central, temporal) is scored semi quantitatively from 0 to 3, depending on the extent of surface staining. The sum of the different scores constitutes the van Bijsterveld score (figure 12), which ranks from 0 to 9 for each eye. It is considered as a diagnostic criterion if the score is ≥ 4 in both eyes.
- Ocular staining score (OSS) implies the use of fluorescein and lissamine green dye. First, fluorescein is instilled in each eye. Then a drop of lissamine green dye is instilled in each anaesthetised eye. The number of dots of staining in the cornea and in the nasal and temporal portions of the conjunctiva are graded. The sum of the fluorescein score for the cornea and the lissamine green scores for the nasal and temporal conjunctiva yields the total OSS. This score is the one used in the new set of classification criteria. (Witcher 2010)
- Tear break-up time. It evaluates the stability of the lachrymal film. Normally, the tear film does not break for 10 seconds, at least. This test is not included in the 2002 American-European classification criteria.

Figure 11 Fluorescein corneal staining.

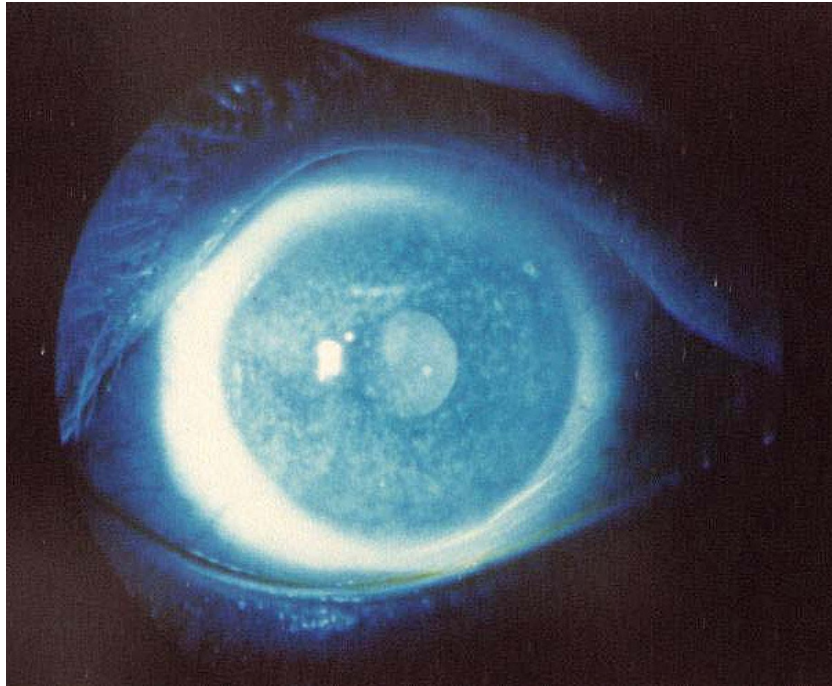
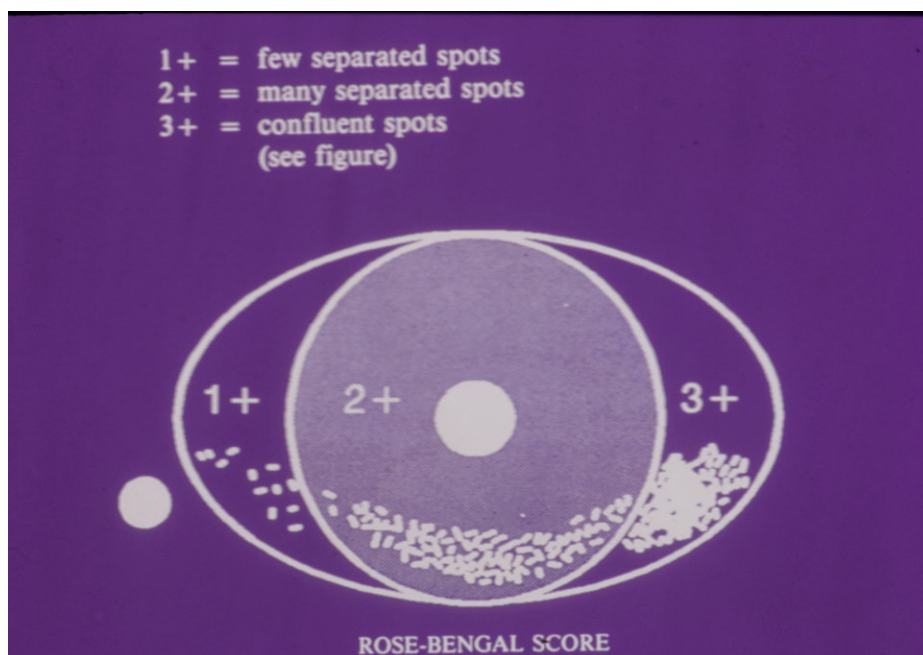


Figure 12 Queratoconjunctivitis sicca: the van Bijsterveld score.



5.2 Laboratory findings

The most common analytical features in routine laboratory tests are cytopenia, raised erythrocyte sedimentation rate (ESR) and hypergammaglobulinaemia (20–30%) (table 2).

Table 2 Laboratory evaluation in Sjögren's syndrome

Test	Typical result
Complete blood cell count	Normochromic, normocytic anaemia. Isolated cases of haemolytic anaemia Mild leukopenia ($3-4 \times 10^9/L$); lymphopenia, neutropenia Mild thrombocytopenia ($80-150 \times 10^9/L$)
Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)	Raised ESR (>50 mm/h) in 20–30% of cases, especially in patients with hypergammaglobulinaemia Normal values of CRP
Serum protein	Hypergammaglobulinaemia Monoclonal band
Liver function tests	Raised transaminases (associated with hepatitis C virus or autoimmune hepatitis) Raised alkaline phosphatase and/or bilirubin (associated with primary biliary cirrhosis)
Electrolytes and urine analysis	Proteinuria (glomerulonephritis) Hyposthenuria, low plasma bicarbonate and low blood pH (renal tubular acidosis)
Antinuclear antibody test	Positive in $>80\%$
Rheumatoid factor	Positive in 40–50% of patients, often leading to diagnostic confusion with rheumatoid arthritis
Anti-extractable nuclear antigen antibodies	Positive anti-Ro/SSA (30–70%) and anti-La/SSB (25–40%)
Complement (C3, C4 and CH50)	Complement levels are decreased in 10–20% of patients (predictive factor for future lymphoma development)
Cryoglobulins	Present in 10–20% of patients (predictive factor for future lymphoma development)
Other autoantibodies	Antimitochondrial antibodies (associated with primary biliary cirrhosis) Antithyroid antibodies (associated with thyroiditis Hashimoto's disease) Anti-dsDNA (associated with systemic lupus erythematosus) Anticentromere (associated with a limited form of systemic sclerosis)

- Cytopenias are usually asymptomatic. The most frequent are normocytic anaemia, leukopenia and thrombocytopenia; the most common abnormality is lymphopenia, closely followed by neutropenia. Cytopenias are found more commonly in patients with positive immunological markers.
- Raised ESR levels correlate closely with the percentage of circulating gamma globulins (hypergammaglobulinaemia), while serum C-reactive protein levels are usually normal. Greatly increased serum C-reactive protein levels in a patient with primary SS should raise the suspicion of an infection. Clinicians who observe high ESRs in patients with SS should therefore not leap to conclusions about occult infections, subclinical malignancies, or the presence of systemic vasculitis as potential causes of ESR elevations: it may simply be the SS itself. In such patients, the C-reactive protein is usually normal (Ramos-Casals et al, 2009).

- **Hypergammaglobulinaemia.** Polyclonal hypergammaglobulinaemia is one of the most characteristic laboratory abnormalities found in primary SS. It reflects the polyclonal B cell activation implicated in the pathogenesis of the disease and provides useful analytical data that may strengthen the diagnosis of primary SS in a patient with sicca syndrome. The prevalence of hypergammaglobulinaemia varies according to the classification criteria and the parameter used to define it, ranging from 22% to 42%. Hypergammaglobulinaemia is closely associated with the key immunological markers of SS (RF, anti-Ro/SSA and anti-La/SSB) (Brito-Zerón et al, 2012*).
- Hypogammaglobulinemia is less common than hypergammaglobulinemia and may develop as a predictor sign of lymphoma.

5.3 Immunological studies

The proven diagnosis of SS requires documentation of sicca symptoms and objective evidence of dry eyes and mouth, and also analytical evidence of autoimmunity, as sicca syndrome has many causes. Autoantibodies may appear several years before the disease diagnosis, as recently shown by Jonsson et al (2013*). Although dryness is the first symptom to appear in most patients, a large number of non-sicca features may appear before the sicca symptoms arise (box 3), including extra glandular manifestations and a specific condition in which the disease presents 'indirectly': with congenital heart block in the baby of an asymptomatic pregnant women carrying anti-Ro antibodies.

Box 3 Non-sicca manifestations suggestive of Sjögren's syndrome se puede agregar aqui cognitive dysfunction ? generalized pain ?

Clinical features

- Chronic fatigue
- Fever of unknown origin
- Leucocytoclastic vasculitis
- Parotid or submandibular gland swelling
- Raynaud's phenomenon
- Peripheral neuropathy
- Clinical features of renal tubular acidosis of unknown origin
- Cough dyspnoea dysphagia
- Mother of a baby born with congenital heart block

Analytical features

- Raised erythrocyte sedimentation rate
- Hypergammaglobulinaemia
- Leukopenia and thrombocytopenia
- Serum and/or urine monoclonal band
- Positive antinuclear antibodies or rheumatoid factor in an asymptomatic patient

The main immunological markers found in primary SS are ANAs, anti-Ro/SSA or anti-La/SSB antibodies, RF, hypocomplementaemia and cryoglobulins (table 2).

- ANA and RF. Antinuclear antibodies are the most frequently detected antibodies in primary SS (in >80% of cases). Patients with rheumatoid factor positivity show a higher frequency of extra glandular and immunological features including articular involvement, cutaneous vasculitis, ANA and anti-Ro/SSA. The results in larger studies support a key role of rheumatoid factor in the diagnosis of primary SS because this immunological marker has an independent association with most of the main clinical and immunological features of the disease. Thus, rheumatoid factor is a useful immunological test for the diagnosis of some subsets of patients with primary SS, such as those with extra glandular manifestations or with circulating cryoglobulins (Retamozo et al, 2012a).
- Anti-Ro/SSA and La/SSB antibodies are detected in 30–70% of patients and are closely associated with extra glandular features, especially with cutaneous lesions, neurological features, congenital heart block, cytopenias and vasculitis. They are also associated with the intensity of lymphocytic infiltrates in the salivary glands (Routsias and Tzioufas, 2010). Their prevalence may vary widely according to the method of detection (ELISA, double immunodiffusion, western blot), due to their varying capacity to recognise antibodies against the Ro52 and Ro60 subunits. Our group found that 12% of our patients who tested negative for the standard detection of anti-Ro/SSA antibodies were positive for anti-Ro52 antibodies (Retamozo et al, 2012a), while Mekinian et al (2013) found that immunoblot identified anti-Ro52/60 antibodies in >20% of patients with negative Ro/SSA. In addition, anti-Ro60 antibodies are more easily detected if a native antigen is used (95% vs 54% using recombinant antigens) (Gordon et al, 2004). In patients with a high clinical suspicion of primary SS and negative results for the standard determination of anti-Ro/SSA antibodies (or even those negative for antinuclear antibodies), specific detection of anti-Ro52/60 antibodies using the most appropriate techniques is recommended.
- New early Sjögren tests include Salivary Protein SP-1, carbonic Anhydrase-6 (CA6) and parotid Specific Protein (PSP). These tests require more studies before they are accepted worldwide.
- Cryoglobulins. Nearly 10% of cases, with primary SS may present with circulating cryoglobulins, overwhelmingly mixed (Ramos-Casals et al, 2012c). The clinical significance of cryoglobulinaemia in primary SS is threefold. First, cryoglobulins are associated with a higher prevalence of extra glandular disease. Second, patients with cryoglobulinaemia are at a higher risk of B cell lymphoma than are those who do not have cryoglobulins (Tzioufas et al, 1996). Third, there is a close association between cryoglobulinaemia and life-threatening vasculitis (Retamozo et al, 2012).
- Low complement levels. In patients with primary SS, hypocomplementaemia is found in 10–25% of patients. Hypocomplementaemia is closely associated with the two main adverse outcomes of primary SS (lymphoma development and death) (Skopouli et al, 2000, Ramos-Casals et al, 2005a).
- Monoclonal immunoglobulins. The presence of monoclonal immunoglobulins in the sera and urine of patients with primary SS has been well known since the 1960s (Moutsopoulos et al, 1983; Moutsopoulos et al, 1985). In >20% of patients it may appear as monoclonal gammopathy of undetermined significance

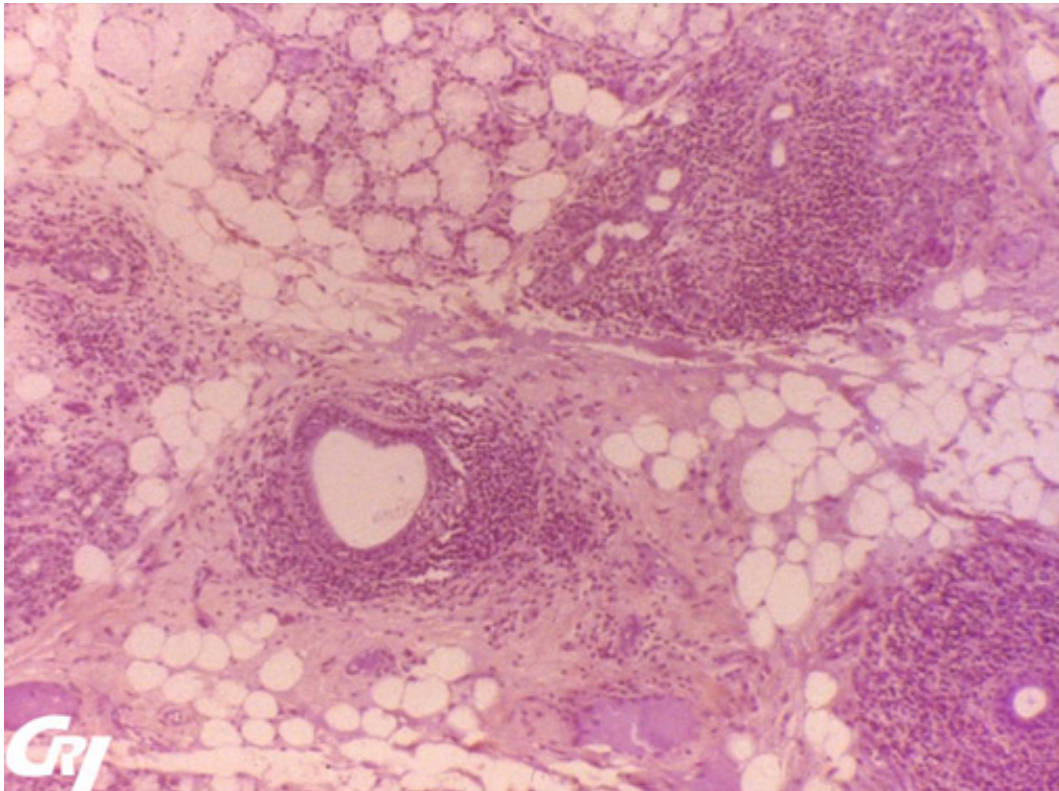
(MGUS) (Brito-Zerón et al, 2012*); these studies have led to the inclusion of MGUS as a key marker of disease activity in the recently proposed European SS Disease Activity Score (ESSDAI) (Seror et al, 2010).

5.4 Histopathology

Minor salivary gland biopsy remains a highly specific test for the diagnosis of SS (Guellec et al, 2013), although it is an invasive technique, it is safe and associated with few adverse local effects (Caporali et al, 2008). Focal lymphocytic sialadenitis (figure 13), defined as multiple, dense aggregates of ≥ 50 lymphocytes in perivascular or periductal areas in the majority of sampled glands, is the characteristic histopathological feature of SS. The key requirements for a correct histological evaluation are an adequate number of informative lobules (at least four) and the determination of an average focus score (a focus is a cluster of at least 50 lymphocytes). However, non-specific sialadenitis is quite common in-- samples of minor salivary glands in healthy control populations. Although sialadenitis is the key histopathological feature of SS, this finding in the absence of symptoms and markers suggestive of SS should be interpreted with caution. Minor salivary gland biopsy may be also useful in resolving the differential diagnosis of patients with systemic diseases that infiltrate salivary glands and who also present with sicca symptoms (e.g., sarcoidosis, amyloidosis, IgG4-RD).

A positive lip biopsy is found in 66 to 90% of patients classified with SS according to the 2002 AECG criteria, resulting in an 80% sensitivity. Thus, it is not pathognomonic for SS, being also found in patients with rheumatoid arthritis, lupus, limited systemic sclerosis and in healthy individuals.

Figure 13 Focal lymphocytic sialadenitis. (Source: CRI (Club Rhumatismes et Inflammation, <http://www.cri-net.com>)



5.5 Classification criteria

At least 10 diagnostic/classification criteria for SS have been published since the 1960s. The 2002 AECG classification criteria for SS (Vitali et al, 2002*) were created to update the 1993 European Community Criteria for Classifying SS (Vitali et al, 1993) and were adopted by the scientific community worldwide. These criteria sought to correct problems with earlier criteria sets by requiring that evidence of an autoimmune process characteristic of SS should be included. The 2002 criteria stipulate that a positive anti-Ro/SSA or La/SSB antibody assay or a positive labial salivary gland biopsy is mandatory (box 4) (Vitali et al, 2002*) with a sensitivity of 93.5% and a specificity of 94%.

Box 4 2002 American–European classification criteria for Sjögren's syndrome

- 1. Ocular symptoms: a positive response to at least one of the following questions:**
 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
 2. Do you have a recurrent sensation of sand or gravel in the eyes?
 3. Do you use tear substitutes more than three times a day?
- 2. Oral symptoms: a positive response to at least one of the following questions:**
 1. Have you had a daily feeling of dry mouth for more than 3 months?
 2. Have you had recurrently or persistently swollen salivary glands as an adult?
 3. Do you often drink liquids to help in swallowing dry food?
- 3. Ocular signs: objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:**
 1. Schirmer test, performed without anaesthesia (5 mm in 5 min)
 2. Rose Bengal score or other ocular dye score (4 according to the van Bijsterveld scoring system)
- 4. Histopathology.** In minor salivary glands (obtained through normal-appearing mucosa), focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score of 1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm² of glandular tissue
- 5. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:**
 1. Unstimulated whole salivary flow (1.5 mL in 15 min)
 2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
- 6. Antibodies to Ro/SSA or La/SSB antigens, or both**

Patients are classified as having primary SS when they fulfil four or more of the six classification criteria; either criterion 4 (salivary gland biopsy) or criterion 6 (anti-Ro/La antibodies) is mandatory.

In 2012, Shiboski et al, proposed a new set of classification criteria for SS on behalf of the American College of Rheumatology (ACR criteria). These differ from the AECG criteria in the exclusion of some features (sicca symptoms and diagnostic tests of salivary glands) and the modification of others (inclusion of a new ocular staining score and of ANA plus RF in the immunological criteria) (Vitali et al, 2013).

Recent studies have compared the two sets of criteria (ACR vs AECG). Cornec et al (2014b) found a moderate degree of agreement between the two sets, mainly due to differences in the ocular criteria, while Rasmussen et al (2014) found that 20% of the Oklahoma cohort fulfilled only one of the two sets of criteria, with 35 patients not classified as primary SS using the ACR criteria, despite having a positive biopsy or Ro/La antibodies. The ACR criteria more easily classified Ro/La-negative patients and those with early disease (Cornec et al, 2014b), while the AECG criteria were more specific (Rasmussen et al, 2014) and more easily classified patients with systemic disease. Quartuccio et al (2014a*) found a higher prevalence of glandular swelling and extra glandular involvement, and more frequent use of systemic treatments in patients fulfilling the AECG criteria. These findings suggest that a final agreement on classification criteria for primary SS is still necessary. This is a current endeavour, as a collaborative project between EULAR and ACR.

In 2016, a new set of classification criteria were presented for primary SS. These were developed and validated using approaches approved by ACR and EULAR. This new set of classification criteria are applicable to any patient with at least one symptom of ocular or oral dryness according to AECG questions, or suspicion of SS due to systemic features derived from the ESSDAI. Exclusion criteria are: history of head and neck radiation treatment, active HCV, AIDS, sarcoidosis, amyloidosis, graft versus host disease and IgG4 related disease. The new criteria differs from previous ones in that they are based on weighted sum of items derived from expert opinion and analyses of patient data. Furthermore, positive anti-SSB/La in the absence of anti-SSA/Ro is no longer considered a criteria. They include Schirmer's test and unstimulated whole saliva flow. The cut-off value for ocular staining score was raised to 5, and the van Bijsterveld score was added as an alternative to this. They removed ANA and RF as items. (Shiboski C et al. 2016*)

Box 5 2016 American College of Rheumatology–European League Against rheumatism classification criteria for primary Sjögren's syndrome

ITEM	WEIGHT/SCORE
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4mm ²	3
Anti-SSA/Ro positive	3
Ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) in at least 1 eye	1
Schirmer's test ≤ 5 mm/5 minutes in at least 1 eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/minute	1

Patients are classified as primary SS if they have a total score of ≥ 4 , derived from the sum of the weights of each positive item.

6 Differential diagnosis

The most common cause of sicca features is the chronic use of dry drugs (mainly antihypertensive, antihistamine and antidepressant agents) (box 6), especially in the elderly. After excluding this cause, three other main causes of sicca syndrome remain (box 7).

Tear and unstimulated saliva production decline with age, due to age-related histologic alterations in lacrimal and salivary glands. These patients lack of the typical histologic changes seen in SS, and anti-SSA/Ro and anti-SSB/La are in general negative.

Box 6 Drugs causing sicca syndrome

- Anticholinergic drugs (atropine, scopolamine)
- Sympathomimetic drugs (ephedrine)
- Benzodiazepines
- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants
- Phenothiazines
- Antihistamines
- Nicotine
- Opioids
- α -1 Antagonists (terazosin and prazosin)
- α -2 Agonists (clonidine)
- β Blockers (atenolol, propranolol)
- Diuretics

Box 7 Diseases that may mimic Sjögren's syndrome

Other diseases infiltrating exocrine glands

- Granulomatous diseases (sarcoidosis and tuberculosis)
- Amyloidosis
- Neoplasias (lymphoma)
- IgG4-related disease
- Type V hyperlipidaemia

Other processes

- Graft-versus-host disease
- Eosinophilia-myalgia syndrome
- Radiation injury
- Medication-related dryness
- Diabetes mellitus
- Dehydration

1. *External or environmental factors*, including allergy/atopy, local infections, dehydration or irradiation may be a cause of mucosal dryness.
2. *Chronic viral infections* such as HCV or human immune deficiency virus, which may induce lymphocytic infiltration of exocrine glands. The aetiopathological and clinical significance of viral infection in patients with SS varies depends on the geographical area. In Japan, where human T cell lymphotropic virus type I (HTLV-I) is endemic, nearly 25% of patients with primary SS have HTLV-I infection (Nakamura et al, 2000). HTLV-I may be considered the viral counterpart in Asian countries of HCV in the Mediterranean region (Ramos-Casals et al, 2009).
3. *Some systemic diseases* may mimic the clinical picture of SS through infiltration of the exocrine glands by granulomas (sarcoidosis and tuberculosis), amyloid proteins (amyloidosis) or malignant cells (haematological neoplasia). A more recently recognised cause of salivary gland infiltration is IgG4-RD (see online in-depth discussion).

7 Outcome and prognosis

Primary SS usually progresses very slowly, with no rapid deterioration in salivary function or dramatic changes in sicca symptoms. The main exceptions to this benign course are the development of systemic manifestations and the high incidence of lymphoma.

7.1 Systemic activity

Systemic involvement plays a key role in the prognosis of primary SS. Three recent multicentre studies, including more than 2500 European patients, confirmed that primary SS is, undeniably, a systemic autoimmune disease (Seror et al, 2013; Baldini et al, 2014; Ramos-Casals et al, 2014).

Box 8 describes patients with poor prognosis.

Box 8. Poor prognostic factors

Severe parotid involvement
Vasculitis/purpura
Hypocomplementemia
Cryoglobulinaemia
Hypergammaglobulinaemia
Rheumatoid Factor
Germinal centres
Dendritic cells

EULAR has recently promoted an international collaboration between primary SS experts to develop consensus disease activity indexes. Two indexes have been developed: (i) a patient-administered questionnaire to assess subjective symptoms, the EULAR Sjögren's Syndrome Patients Reported Index (ESSPRI) and (ii) a systemic activity index to assess systemic complications, the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).

Development of the ESSDAI (Seror et al, 2014*) by the EULAR task force on SS represents a step forward in the evaluation of systemic SS. The ESSDAI includes specific organ-by-organ definitions and allows homogeneous evaluation of systemic features in large series of patients.

In contrast, a large percentage of patients with primary SS have no systemic involvement, with a clinical pattern totally dominated by severe dryness, associated sometimes with fatigue and pain, which are not life-threatening but have a serious impact on the quality of life (Lendrem et al, 2013). Greater intensity of dryness, fatigue and pain seems to go in tandem with less systemic involvement and identification of immunological SS features. Physical impairment and pain do not always correlate with serologic positivity.

7.2 Lymphoma

Patients with primary SS are at higher risk of lymphoma than healthy people (10- to 44-fold) and patients with other autoimmune diseases (seven- and fourfold in patients with SLE and RA, respectively) (Zintzaras et al, 2005). The main series included 2–9% of patients diagnosed with lymphoma (Tzioufas and Voulgarelis, 2007; Ramos-Casals et al, 2012). The most recent studies have found similar figures, with a nine fold risk reported by Johnsen et al (2013) and a pooled 14-fold risk found in a recent meta-analysis by Liang et al (2013), with the prevalence of lymphoma estimated at 2%, 6% and 11% in three large series of patients with primary SS (Voulgarelis et al, 2012; Johnsen et al, 2013; Quartuccio et al, 2014b).

Lymphomas that develop in patients with primary SS are extra nodal in 80% of cases, with the most common site being the parotid glands (Voulgarelis et al, 1999). Persistently hard enlargement of the parotid gland or (much more rarely) of the lachrymal glands should alert the clinician of the possibility of a lymphoma. Lymphomas developing in SS may also occur in the gastrointestinal tract or lungs. Mucosa-associated lymphoid tissue lymphomas are the most common type, followed by marginal zone lymphomas. After years of slow progression, low-grade tumours in some patients may progress to rapidly growing, high-grade lymphomas.

Prospective studies have identified severe parotid involvement, purpura, splenomegaly, cryoglobulins, monoclonal band and hypocomplementaemia as risk factors for lymphoma (Tzioufas et al, 1996; Skopouli et al, 2000; Ioannidis et al, 2002*; Ramos-Casals et al, 2008). Also, raised levels of BAFF and $\beta 2$ microglobulin (Gottenberg et al, 2013b), leukopenia and anti-La antibodies (Quartuccio et al, 2014b), may serve as risk factors. Quartuccio et al (2014b) also reported that, in patients with parotid enlargement, only those presenting with these biomarkers had an increased risk of lymphoma.

Most interesting is the information provided by a labial salivary gland biopsy. Theander et al (2011) showed that the presence of ectopic germinal centre-like structures may predict lymphoma development in pSS, while in another study it was shown that the presence of macrophages and dendritic cells in the salivary gland biopsy specimen, as well as the cytokine interleukin 18, may also correlate with adverse predicting factors for lymphoma development (Manoussakis et al, 2007). These findings open new avenues for the definition of cellular and molecular biomarkers for adverse outcome of the disease, derived from the affected tissue.

7.3 How to follow-up and monitor?

We recommend a multidisciplinary approach follow-up guided by the rheumatologist. Patients with stable disease limited to mucosal surfaces may require only annual evaluation, while those with extra glandular manifestations should be evaluated every 6 months and those with end-organ damage every 3 months). However, the frequency of follow-up evaluations should be individualized according to each patient's needs. Routine physical examination should include evaluation of the mouth and eyes to treat sicca complains which

diminish the quality of life, exclude local complications and examination for peripheral lymphadenopathy and enlargement of parotid/submandibular glands, the liver and the spleen. Yearly laboratory tests should include full blood count, erythrocyte sedimentation rate (ESR) and renal and liver function tests. Immunological tests are not necessary in routine follow-up, with two exceptions: patients with markers (low complement levels, mixed cryoglobulinaemia, monoclonal gammopathy) associated with a poor prognosis, or when there is clinical suspicion of a concomitant systemic autoimmune disease. Advise fertile anti-Ro positive women about the risk of foetal congenital heart block and the need of frequent ultrasound examination during pregnancy.

8 Treatment

No treatment can modify the evolution of SS, but improvement in quality of life may be achieved. A systematic review highlights the limited evidence available for the drugs most frequently used in primary SS and the difficulties in offering therapeutic recommendations (Ramos-Casals et al, 2010a). The therapeutic management of SS focuses mainly on the control of sicca features, using substitutive and oral muscarinic agents, while glucocorticoids and immunosuppressive agents play a key role in the treatment of extra glandular manifestations.

Basic measures for dry mouth:

Preventive measures against dry mouth include maintenance of good hydration, avoid medication that may worsen oral dryness and avoid low-humidity environments. Patients should be recommended to avoid acidic beverages like cola, coffee, herbal tea and energy drinks. Topical saliva stimulation can benefit from sugar-free candies and chewing gums. Dental care includes regular visit to the dentist, avoid high sugar foods that may favour dental caries, use of dental floss after each meal and use fluoride toothpaste specially developed for dry mouth. We recommend the consumption of water together with meals to facilitate swallowing.

Basic measures for dry eye:

We recommend avoidance of aggravating factors like dry or windy environments, irritants and smoke. Patients can benefit from wraparound sunglasses to conserve tear film. Room humidifiers are useful and warm compresses over the eye may improve meibomian gland secretion.

8.1 Main drugs: synthesis of the evidence

8.1.1 Topical drugs

8.1.1.1 Saliva substitutes

Saliva substitutes are used in clinical practice as the first therapeutic approach in patients with a dry mouth, especially in those with mild symptoms, as they have no significant side effects and have specific benefits for nocturnal dryness.

Topical fluorides are recommended to reduce the incidence, arrest of coronal or root caries. Chlorhexidine and no fluoride remineralizing agents may be considered as an adjunct therapy but the strength of recommendation is weak.

Fungal infection are very common and should be treated with nystatin and ketoconazole.

8.1.1.2 Eye drops

- Several studies have analysed the use of topical eye drops, mainly containing sodium hyaluronate and hydroxypropylmethylcellulose as active principles. All studies found significant improvements from baseline measurements.
- Non-steroidal anti-inflammatory drugs and glucocorticoids. Limited evidence is available for the use of drops containing topical non-steroidal anti-inflammatory drugs (NSAIDs)/glucocorticoids in patients with primary SS. Side effects are the key point to consider when using these eye drops.
- Cyclosporine A. In 2002, an ophthalmic formulation containing cyclosporine A (CsA) was approved by the Food and Drug Administration (FDA) to treat dry eye disease. The dose recommended is 0.05% CsA drops twice daily. Of the adverse events that occurred, most were mild-to-moderate and transient, and only 2% of patients discontinued because of burning and stinging.
- Autologous serum tears are obtained by dilution of patients sera and are useful for more severe disease.

8.1.1.3 Punctual occlusion

Temporary or permanent punctual plugs may be useful for patients with moderate to severe ocular dryness with no response to artificial- tears, lubricants or topical cyclosporine. This should be performed by eye care professionals. The occlusion can be performed in the upper or lower canaliculus. This is a simple and well tolerated procedure but sometimes the patient rejects the plugs.

8.1.2 Systemic drugs

8.1.2.1 Secretagogues

For patients with SS with residual salivary gland function, stimulation of saliva flow with a secretagogue is the preferred treatment. Some choleric (anetholtrithione) and mucolytic (bromhexine, N-acetylcysteine) agents have been used as secretagogues in primary SS since the 1980s, although without solid scientific evidence.

Two muscarinic agonists (pilocarpine and cevimeline) are licensed for the treatment of sicca symptoms in SS. These agents stimulate the M1 and M3 receptors present on salivary glands, leading to increase secretory function. The usual dose for pilocarpine is 5mg four times a day, and for cevimeline 30mg three times a day. Patients should start with one dose daily for a week and if tolerated it should be gradually increased. The response may frequently be delayed, so a three month trial is suggested.

Omega 6 essentials fatty acids are a novel treatment under study.

8.1.2.2 Glucocorticoids

The use of glucocorticoids in clinical practice in patients with primary SS is not supported by reliable scientific evidence, since no study has specifically evaluated their use, but in some cases like arthritis and for extra glandular SS features it is a useful tool. It should be used in the minimal possible dose and for short time. The use of systemic glucocorticoids has been associated with a higher rate of adverse events, including increased appetite and weight gain and a twofold higher incidence of diabetes mellitus.

8.1.2.3 Antimalarial agents

The use of antimalarial agents in primary SS is based on their use in similar diseases, such as RA and SLE. A retrospective study of 50 patients described significant improvements in sicca features, parotid gland enlargement, oral infection, myalgia, arthralgia, fatigue and joint swelling after 12 months of hydroxychloroquine treatment (Fox et al, 1996), while other studies found significant improvements in baseline analytical and immunological parameters. Hydroxychloroquine is preferred over chloroquine, and the usual dose is 6,5mg/kg/day. As it may produce maculopathy it is recommended an ophthalmologic evaluation prior it's use and as follow-up, including colour vision testing and ocular fundus exam.

8.1.2.4 Immunosuppressive agents

The use of immunosuppressive agents in primary SS is based on the same level of evidence as that for glucocorticoids. Several studies with a low number of patients have analysed the use of methotrexate (MTX), leflunomide, azathioprine (AZA) and mycophenolic acid and found limited benefits for sicca features. However, they are useful for specific indications;

- methotrexate and leflunomide for arthritis
- azathioprine for lung and neurological involvement
- mycophenolic acid for renal involvement
- cyclosporine for neurological involvement
- IVIG for neurological involvement and congenital heart block during pregnancy.

The benefit: risk ratio should always be taken into consideration before their prescription. further studies with a larger sample size and using the ESPPRI and ESSDAI as outcome measure are needed.

8.1.3 Biological therapies

The emergence of biological therapies has increased the therapeutic armamentarium available for treating SS, but their use is limited by the lack of licensing. More than 20 studies have analysed the use of seven biological agents in primary SS (table 3): two anti-TNF agents (infliximab—a monoclonal antibody against TNF, and etanercept—a recombinant soluble TNF receptor), three B cell targeted therapies (rituximab—a monoclonal antibody against CD20, epratuzumab—a monoclonal antibody against CD22, and belimumab—a monoclonal antibody against BAFF), a T cell targeted therapy (abatacept) and IFN α .

Randomised controlled trials (RCTs) have demonstrated the lack of efficacy of anti-TNF agents and promising results for B cell-depleting agents (Ramos-Casals et al, 2012). Four recent studies evaluated the use of rituximab in patients with primary SS. Gottenberg et al (2013a*) studied the use of rituximab in 78 patients with SS with systemic involvement and found an overall efficacy of 60%, while Carubbi et al (2013) found a faster and more-pronounced ESSDAI reduction in patients treated with rituximab than in those treated conventionally. In contrast, the successful use of rituximab in the most-prominent triad of symptoms (dryness, fatigue and pain) is not clear. St Clair et al (2013) found only modest improvements in a small open-label trial of 12 patients treated with rituximab, while recent data from a French RCT of 120 patients found no significant changes in the primary outcome (Devauchelle-Pensec et al, 2014). Almost the same results for sicca manifestations were seen even when rituximab was given for 24 months (Carubbi et al, 2013).

Several studies have supported a role for BLYS in the pathogenesis of primary SS (Ramos-Casals, 2013), suggesting that blocking of BLYS might be a potential therapeutic approach. Mariette et al (2013*) were the first to use belimumab (10 mg/kg at weeks 0, 2 and 4 weeks, and then every 4 weeks to week 24) in 30 patients with primary SS. The primary endpoint was defined as an improvement in two or more items (dryness, fatigue, pain, systemic activity and B cell biomarkers) and was achieved in 18 (60%) patients, together with a significant reduction in the ESSDAI score.

Conclusions cannot yet be reached about the recent use of CLA4Ig (abatacept) in primary SS, because of the small number of patients (Adler et al, 2013; Meiners et al, 2014).

Table 3 Studies that have analysed the use of biological agents in primary Sjögren's syndrome (SS) (2004–2014)

Author (year)	Biological agent	Study design	Number of patients with primary SS	Main therapeutic indication
Mariette <i>et al</i> (2004)	Infliximab	RCT	103	Active disease
Zandbelt <i>et al</i> (2004)	Etanercept	Open-label	15	Not defined
Sankar <i>et al</i> (2004)	Etanercept	RCT	14	Not defined
Pijpe <i>et al</i> (2005)	Rituximab	Open-label	15	Early disease + lymphoma
Gottenberg <i>et al</i> (2005)	Rituximab	Retrospective	6	Systemic
Seror <i>et al</i> (2007)	Rituximab	Retrospective	16	Systemic involvement
Devauchelle-Pensec <i>et al</i> (2007)	Rituximab	Open-label	16	Active disease
Meijer <i>et al</i> (2010)	Rituximab	RCT	30	Salivary flow rate
Dass <i>et al</i> (2008)	Rituximab	RCT	17	Fatigue
Vasil'ev <i>et al</i> (2009)	Rituximab	Retrospective	10	Systemic involvement
Ramos-Casals <i>et al</i> (2010c)	Rituximab	Retrospective	15	Systemic
Pollard <i>et al</i> (2011)	Rituximab	Retrospective	19	MALT lymphoma
Zhou <i>et al</i> (2012)	Rituximab	Retrospective	4	Thrombocytopenia
Mekinian <i>et al</i> (2012a)	Rituximab	Retrospective	11	CNS involvement
Voulgarelis <i>et al</i> (2012)	Rituximab	Retrospective	26	MALT lymphoma, NMZL, DLBCL
Mekinian <i>et al</i> (2012b)	Rituximab	Retrospective	17	Peripheral neuropathy
Gottenberg <i>et al</i> (2013a*)	Rituximab	Retrospective	78	Systemic disease
Carubbi <i>et al</i> (2013)	Rituximab	Case-control	41	Early/active disease
St Clair <i>et al</i> (2013)	Rituximab	Open-label	12	Active disease
Mariette <i>et al</i> (2013*)	Belimumab	Open-label	30	Active/systemic disease
Devauchelle-Pensec <i>et al</i> (2014)	Rituximab	RCT	120	Active disease

CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; MALT, mucosa-associated lymphoid tissue; NMZL, nodal marginal-zone B cell lymphoma; RCT, randomised controlled trial.

8.2 Therapeutic scenarios

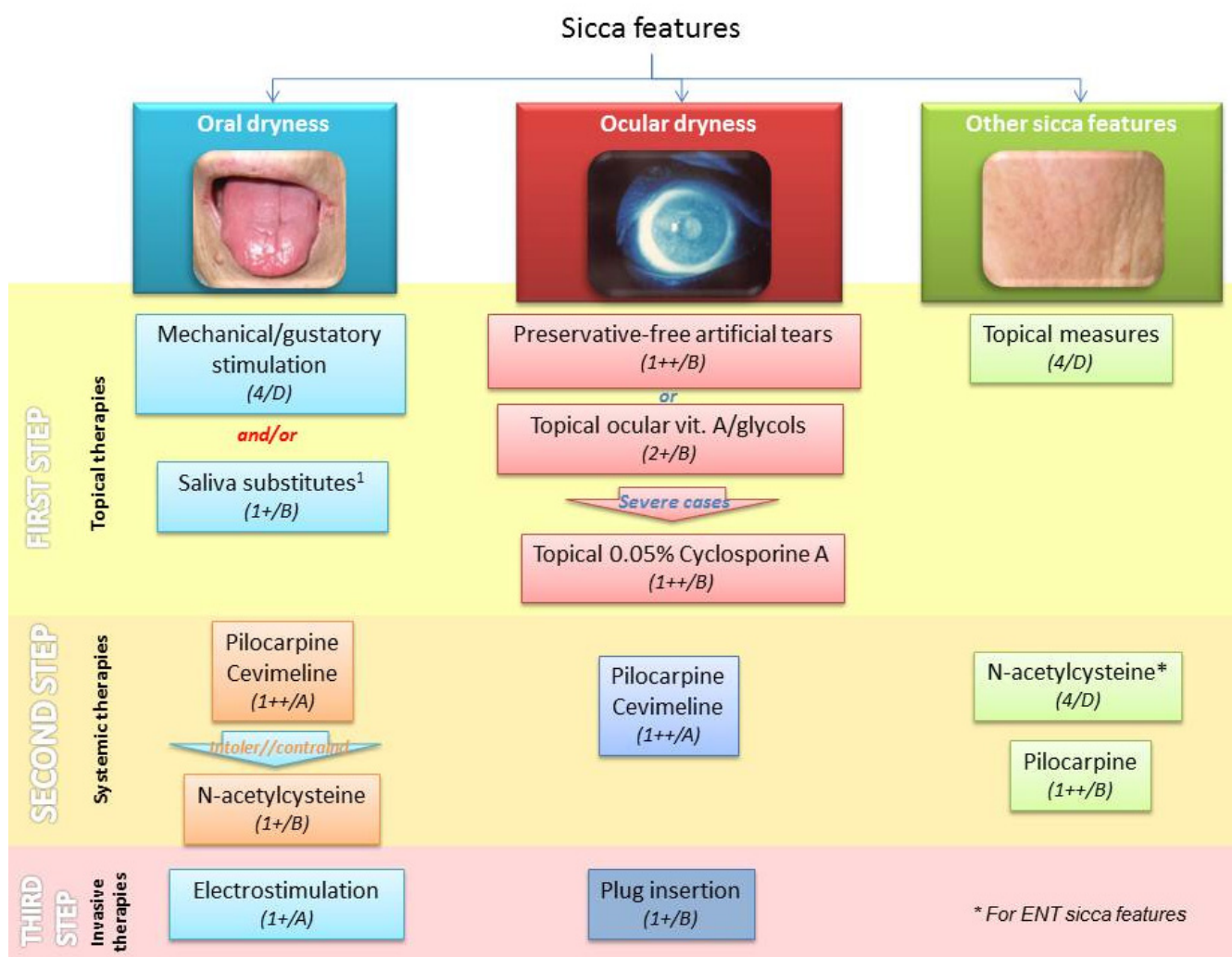
8.2.1 Management of sicca features

The primary therapeutic approach for sicca manifestations should be symptomatic, using artificial tears and saliva substitutes (figure 14)—a recommendation based on reported studies that support their daily use without any kind of side effects and with improvements in the quality of life. However, the available data on treatment for oral dryness does not show conclusively that one specific saliva substitute is better than another in SS (Furness *et al*, 2011). More than one substitute should always be tried, especially when there is poor

tolerance to the first agent. However, patients with acceptable salivary flow outputs may have a poor tolerance due to the sticky feeling caused by saliva substitutes; in these patients, mechanical/gustatory stimulation may be useful. The use of anticholinergic drugs, alcohol (including mouthwashes and fluoride rinses that contain alcohol) and smoking should be discouraged, while non-pharmacological approaches (water intake, mechanical/gustatory stimulation with sugar-free gums and candies, fluoride toothpaste) may be useful.

Other measure useful for xerodermia include the use of neutral soaps, sun protection and body lotions, while topical oestrogens and lubricants may be useful to treat dyspareunia.

Figure 14 Therapeutic management of sicca features.



Patients with severe sicca features affecting their quality of life may require a more intensive therapeutic approach.

- For patients with moderate/severe oral dryness and residual salivary gland function, oral muscarinic agonists (pilocarpine or cevimeline) are the preferred treatment, as long as contraindications are taken into account (figure 14). The best efficacy/side effects ratio dose is 5 mg/6 h for pilocarpine and 30 mg/8 h for cevimeline. No studies have compared the efficacy of the two drugs. Tolerance must be considered, with a frequency of reported adverse events as high as 40%, which include palpitations, sweating, increased urinary frequency, flushing (these 2 more common for pilocarpine) and diarrhoea (more common for cevimeline). In patients with intolerance to muscarinic agonists, N-acetylcysteine may be an alternative.
- Patients with severe or refractory keratoconjunctivitis sicca may require the addition of topical anti-inflammatory agents. Ocular NSAIDs or glucocorticoids should only be prescribed by ophthalmologists for the minimum time necessary, as adverse events seem to be more frequently reported after continued use longer than 2 weeks. In contrast, controlled trials support the use of topical 0.05% CsA twice daily, which has an acceptable safety profile, although no further benefits were seen beyond 6 months of treatment.
- Meibomian gland inflammation can be treated with topical tetracycline.

8.2.2 Management of general symptoms

Patients with primary SS often present with non-specific general symptoms, including non-inflammatory muscle and joint involvement, fatigue and weakness, which may have a much greater impact on the quality of life than sicca features. In these patients, the first step should be a differential diagnosis with associated conditions such as hypothyroidism, neoplasia, depression and, especially, fibromyalgia, which is reported in 22–33% of patients with primary SS and may influence both the patient and physician global health status assessment. The positive effect of aerobic exercise on depression, physical capacity and fatigue was shown in a controlled trial (Strombeck et al, 2007). In patients presenting without severe non-exocrine manifestations this approach should be chosen as the first-line (or at least parallel) therapy for pain, depression and fatigue in view of its low cost, general health-promoting effects and lack of potential side effects compared with drugs. Taking into account the chronic but rarely disabling nature of the disease, coping strategies should be promoted—for example, by contact with a local self-help group/patient association.

After discarding these processes, hydroxychloroquine should be the keystone drug, with clinical benefits being reported beyond fatigue and musculoskeletal pain; uncontrolled studies found additional improvements in subjective and objective sicca features, reductions in parotid enlargement and oral infections and improvements in analytical and immunological parameters.

Biological agents tested in primary SS have been associated with significant improvements in fatigue (including one small RCT using rituximab). Studies with rituximab showed good results for systemic involvement, but should be considered, at most, modest for the triad of dryness, pain and fatigue. It is worth noting that the available data are based in subjective measures using mostly visual analogue scales. We consider that the off-

label use of these new drugs to treat only general symptoms (even when severe) is not warranted. Further studies with objective outcome measures are needed to improve treatment recommendations.

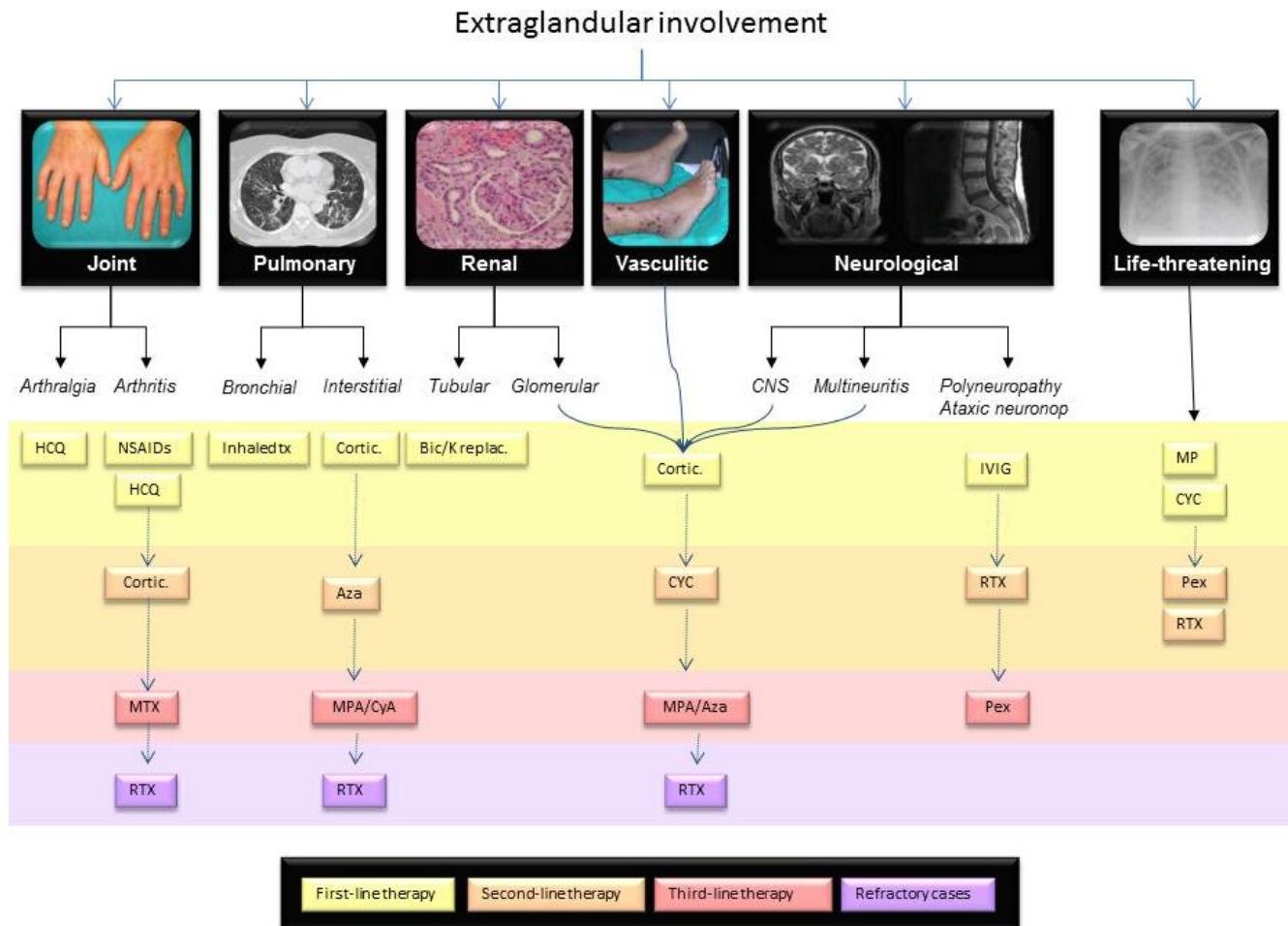
8.2.3 Management of systemic involvement

As a rule, the management of extra glandular features should be organ-specific, with glucocorticoids and immunosuppressive agents limited to potentially severe situations. NSAIDs usually provide relief from the minor musculoskeletal symptoms of SS, and from painful parotid swelling. Hydroxychloroquine may be used in patients with fatigue, arthralgias and myalgias. For patients with moderate extra glandular involvement (mainly arthritis, extensive cutaneous purpura and non-severe peripheral neuropathy), 0.5 mg/kg/day of prednisone may suffice. For patients with internal organ involvement (pulmonary alveolitis, glomerulonephritis or severe neurological features), a combination of prednisone and immunosuppressive agents (cyclophosphamide (CYC), AZA or mycophenolate mofetil) is suggested.

Some retrospective studies and case series have specifically analysed the use of glucocorticoids and immunosuppressive agents in organ-specific involvement (Kassan and Moutsopoulos, 2004; Fox, 2005; Ramos-Casals et al, 2010b*). The most frequently used immunosuppressive agents are AZA in interstitial lung disease, MTX in joint involvement and CYC for glomerulonephritis, vasculitis, multiple neuritis and CNS involvement (figure 15). In contrast, some extra glandular features, such as interstitial nephritis or ataxic neuronopathy, seem to have a poor response to glucocorticoids and immunosuppressive agents.

Evidence suggests that rituximab may be considered in patients with systemic involvement refractory to standard treatment (lack of response or intolerance to glucocorticoids and immunosuppressive agents) (Engel et al, 2011*). The amount and quality of evidence on the off-label use of rituximab in SS-related extra glandular features is greater than that reported for the use of the standard options (glucocorticoids and immunosuppressive agents), although a reasonable assessment of the risk of serious adverse events versus the benefits of treatment should be always made on an individual basis.

Figure 15 Treatment of extra glandular features. AZA, azathioprine; Cortic, glucocorticoids; CYC, cyclophosphamide; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulins; MP, methylprednisolone; MPA, mycophenolic acid; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; Pex, plasma exchanges; RTX, rituximab; tx, treatment.



8.2.4 Management of life-threatening situations

Severe, life-threatening involvement has rarely been reported in primary SS, and accounts for nearly 10% of deaths (Brito-Zerón et al, 2008). Vasculitis (overwhelmingly cryoglobulinaemic) is the main cause of life-threatening presentation of primary SS, affecting vital organs such as the kidneys, the lungs and the gastrointestinal tract. Other severe involvements included CNS features, progressive ataxic neuropathy, pulmonary arterial hypertension and severe cytopenia (Ramos-Casals et al, 2011). Scarce evidence, taken together with expert review, suggests that methylprednisolone and CYC pulses should be used in patients with severe systemic vasculitis or CNS involvement, with plasma exchange being added in the most severe situations (Pollard et al, 2011; Ramos-Casals et al, 2011). Combined treatment with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) is highly recommended for SS-associated B cell aggressive non-Hodgkin's lymphomas, under the guidance of an experienced haematologist (Voulgarelis et al, 2004, Voulgarelis et al, 2006).

9 Lymphoma in autoimmune diseases other than primary SS

We discussed the increased risk of lymphoma in primary SS, the autoimmune disease in which the risk of lymphoma is the highest. An increased risk of B cell lymphoma, especially diffuse large B-cell lymphoma and marginal zone lymphoma, is also found in other autoimmune diseases. Chronic immune stimulation, genetic and environmental factors and some immunosuppressive drugs might be involved in lymphomagenesis in these patients (Dias and Isenberg, 2011). In addition, recent studies have also reported an increased risk of Hodgkin's lymphoma (HL) associated with a personal history of several autoimmune diseases, including RA, SLE or sarcoidosis, among others (Fallah et al, 2014).

9.1 Re-evaluation of the risk of non-Hodgkin's and Hodgkin's lymphoma

Studies have re-evaluated the risk of non-Hodgkin's and Hodgkin's lymphoma in autoimmune diseases. The first study compared the prevalence of registered autoimmune disease in 3055 patients with a recent diagnosis of lymphoma compared with 3187 age- and sex-matched controls. The risk of lymphoma was increased in four autoimmune diseases, as mentioned in table 4 (Smedby et al, 2006).

Table 4 Relative risk of NHL in autoimmune diseases

Autoimmune diseases	Relative risk of NHL (*)
RA	1.5 (1.1 to 1.9)
SLE	4.5 (1.0 to 21)
pSS	6.1 (1.4 to 27)
Coeliac disease	2.1 (1.0 to 4.8)

**Relative risks are provided as odds ratios (ORs) with 95% confidence intervals and are adjusted for age (in 5-year intervals) and sex.*

NHL, non-Hodgkin's lymphoma; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

This study is interesting but it is a case–control study, which depends on the unbiased selection of controls. The incidence of lymphoma in patients with autoimmune diseases might be slightly underestimated since the prevalence of some autoimmune diseases in the control population seems high—notably, the prevalence of RA, which affects 2.8% of the control population versus 1.5% of the general population after adjustment for age and sex. This prevalence might be overestimated (for example, prevalence of RA in France is 0.3%).

The second study examined the prevalence of records of autoimmune disease in 7476 patients with a recent diagnosis of HL compared with 18 573 age- and sex-matched controls. The results showed that HL, which is 10 times more infrequent than non-Hodgkin's lymphoma (NHL), was also increased in autoimmune diseases (table 5).

Table 5 Relative risk of HL in autoimmune diseases

Autoimmune diseases	Relative risk of HL*
RA	2.7 (1.9 to 4.0)
SLE	5.8 (2.2 to 15.1)
pSS	10.3 (0.9 to 120)
Sarcoidosis	14.1 (5.4 to 36)

*Relative risks are provided as odds ratios (ORs) with 95% confidence intervals and are adjusted for age (in 5-year intervals) and sex.

HL, Hodgkin's lymphoma; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

The third study, a meta-analysis, included six studies of lupus (8700 patients), nine studies of RA (95 104 patients) and five studies of primary SS (1300 patients). Table 6 summarises the main results of the meta-analysis (Zintzaras et al, 2005).

Table 6 Risk of lymphoma in autoimmune diseases

Autoimmune diseases	Risk of lymphoma*
RA	3.9 (2.5 to 5.9)
SLE	7.4 (3.3 to 17)
pSS	18.8 (9.5 to 37.3)

*Standardised incidence rate estimates of development of NHL with the corresponding 95% confidence intervals.

NHL, non-Hodgkin's lymphoma; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

The fourth study analysed the risk of HL in 878 161 Swedish patients diagnosed with 33 different autoimmune diseases between 1964 and 2010; during a mean follow-up of 10 years, 371 incident cases of HL were diagnosed. The overall standardised incidence ratio (SIR) for HL after the diagnosis of autoimmune disease was significantly increased to 2.0 (95% CI 1.8 to 2.2). Specific SIRs for the main autoimmune diseases are summarised in table 7 (Fallah et al, 2014).

Table 7 Risk of Hodgkin's lymphoma (HL) in autoimmune diseases

Autoimmune diseases	Risk of HL*
Autoimmune haemolytic anaemia	19.9 (7.2 to 43.6)
Sarcoidosis	10.3 (7.8 to 13.4)
Systemic lupus erythematosus	8.4 (5.2 to 12.9)
Immune thrombocytopenic purpura	7.0 (3.2 to 13.3)
Polyarteritis nodosa	6.6 (1.2 to 19.5)
Polymyositis/dermatomyositis	6.3 (2.0 to 14.9)
Behçet's disease	5.6 (2.7 to 10.3)
Sjögren's syndrome	5.0 (2.1 to 9.8)
Rheumatoid arthritis	3.2 (2.6 to 3.9)
Polymyalgia rheumatica	2.2 (1.4 to 3.5)
Psoriasis	1.9 (1.3 to 2.6)

*Relative risks are provided as odds ratios (ORs) with 95% confidence intervals.

9.2 Confirmation of the increased risk of lymphoma in patients with SLE

Recent studies have evaluated 16 409 patients with SLE from the Systemic Lupus International Collaborating Clinics (SLICC) cohort (Bernatski et al, 2012) across 30 centres; these patients were followed up for 121 283 (average 7.4) person-years. In total, 644 cancers occurred. Some cancers—notably, haematological malignancies, were substantially increased (SIR = 3.02, 95% CI 2.48 to 3.63), particularly NHL (SIR = 4.39, 95% CI 3.46 to 5.49) and leukaemia.

A specific study evaluated the main characteristics of 75 patients with SLE with lymphoma (72 NHL, three HL) and 4961 cancer-free controls. Most lymphomas were of B cell origin. As is seen in the general population, the lymphoma risk in SLE was higher in male than female patients and increased with age. Lymphomas occurred a mean of 12.4 years (median 10.9) after SLE diagnosis. There was a trend for a greater exposure to CYC and to higher cumulative steroids in patients with lymphoma than in the cancer-free controls. Disease activity itself was not clearly associated with lymphoma risk (Bernatsky et al, 2014).

Another study evaluated 33 non-lymphoma haematological cancers, including 13 classified as of lymphoid lineage (multiple myeloma in five, plasmacytoma in three, B cell chronic lymphocytic leukaemia in three, precursor cell lymphoblastic leukaemia and unspecified lymphoid leukaemia in one case each, respectively), and 20 cases as of myeloid lineage (myelodysplastic syndrome in seven, acute myeloid leukaemia in seven, chronic myeloid leukaemia in two and four unspecified leukaemias). In this large SLE cohort, the most common non-lymphoma haematological malignancies were myeloid types, and the majority (80%) of multiple myeloma cases occurred in blacks. This is in contrast to the general population, where lymphoid types are 1.7 times more common than myeloid non-lymphoma haematological malignancies (Lu et al, 2013).

9.3 Disease activity is the main risk factor of lymphoma in RA but not in SLE

Large Swedish studies have compared, using the national registry of RA, 378 patients with RA and lymphoma with 378 age- and sex-matched controls (patients with RA without lymphoma) (Baecklund et al, 2014). There was a slight mismatch between the two groups for the disease duration, which was longer in patients with lymphoma than in controls (20 vs 17 years). All histological slides were reassessed and investigated for the presence of EBV. EBV was detected in 12% of all lymphomas, and in 47% of HL. The authors established a global disease activity score and a cumulative disease activity score during the 20 years preceding lymphoma. This cumulative score was then divided into 10 deciles of activity, each decile including the same number of patients.

The risk of lymphoma is not much increased until the end of the seventh decile. This risk increases by 9.4 (95% CI 3.1 to 28) in patients in the ninth and by 61.6 in patients of the 10th decile, which includes the 10% of patients in whom disease activity was the highest.

This study also allowed an evaluation of the role of treatments. All patients were included before 1995, and none had received TNF blockers. Overall, use of disease-modifying antirheumatic drugs was not associated with an increased risk of lymphoma. However, AZA administration was associated with lymphoma development (OR = 2.3, 95% CI 1.2 to 4.6).

In contrast, a case-control study by Bernatski et al (2014), including 75 patients with lymphoma and 4961 cancer-free controls, found that unadjusted and adjusted analyses failed to show a clear association between SLE disease activity and lymphoma risk.

9.4 Methotrexate is not associated with an increased risk of NHL

Some EBV-associated lymphomas have been reported in patients with RA, one-third being regressive after the discontinuation of MTX, but the long-term evolution of the disease in these patients is rarely reported. These often-aggressive lymphomas share similarities with lymphomas occurring in immunosuppressed patients (after allogeneic bone marrow transplantation, organ transplantation, in late stages of AIDS).

Interestingly, MTX was not associated with an increased risk of lymphoma in Swedish studies (Baecklund et al, 2014). This result is concordant with the previous results of six long-term follow-up studies of patients with RA. For instance, a French prospective study collected 25 lymphomas during a 3-year follow-up, including 18 NHL and 7 HL. The HL was severe (four deaths) and often associated with EBV (five out of seven patients). The incidence of NHL in the patients with RA was not higher than that in the general French population, after adjustment for age and sex. However, the incidence of HL was increased (Mariette et al, 2002).

9.5 Controversial association between anti-TNF agents and lymphoma

Several studies have provided insight into this complex problem.

9.5.1 Data from the 'National Data Bank of Rheumatic Diseases'

Wolfe coordinated the follow-up of around 20 000 patients with RA (Wolfe et al, 2004). Twenty-nine lymphomas have been reported in 18 572 patients with RA since 1998. The SIR of lymphomas in RA was estimated to be 1.9. The SIR of patients treated with MTX (1.7) was not significantly different from that of the general population, and the SIR was 2.9 in patients with anti-TNF (table 8).

Similar SIRs were obtained in controlled trials with adalimumab: 15 lymphomas in 9460 patients, which corresponds to 9894 patients/year, with a SIR of 3.19 (95% CI 1.78 to 5.26), non-significantly different from the SIR of infliximab or etanercept.

Table 8 Incidence of lymphomas in RA according to the data from the National Data Bank of Rheumatic Diseases

	Standardised incidence rate (SIR)	
	SIR	95% CI
General population	1.0	
All patients with RA	1.9	1.3 to 2.7
No biological agents or MTX	1.0	0.4 to 2.5
MTX	1.7	0.9 to 3.2
Infliximab	2.6	1.4 to 5.0
Etanercept	3.8	1.9 to 7.5
All biological agents	2.9	1.7 to 4.9

9.5.2 Data from the national Swedish registry

This registry which, as previously mentioned, included about 70% of all patients with RA in Sweden, compared three cohorts: one prevalent including inpatients between 1990 and 2003 (n = 53 067), one incident including patients diagnosed with RA between 1995 and 2003 (n = 3703) and one cohort of patients treated with anti-TNF (etanercept, infliximab and adalimumab) (Askling et al, 2005).

These three cohorts were compared with the general population after referring to the Swedish registry of cancer to evaluate the risk of haematological malignancy. The SIRs (95% CI) of lymphomas in the prevalent, incident and exposed to anti-TNF cohorts were 1.9 (1.7 to 2.1), 2.0 (1.0 to 3.5), and 2.9 (1.3 to 5.5), respectively (table 9). No increased risk due to anti-TNF exposure was found after adjustment for sex, age and disease duration. Thus, to interpret the marginal increase of the risk of lymphoma in patients treated with anti-TNF, one should take into account the fact that such patients have an important inflammatory activity.

Table 9 Data on lymphoma from the national Swedish registry

	Prevalent RA n = 53067		Incident RA n = 3703		RA exposed to anti-TNF n = 4160	
	N	SIR* (95% CI)	N	SIR* (95% CI)	N	SIR* (95% CI)
Lymphomas (including CLL)	319	1.9 (1.7 to 2.1)	11	2.0 (1.0 to 3.5)	9	2.9 (1.3 to 5.5)

*Adjusted results. CLL, chronic lymphocytic leukaemia; RA, rheumatoid arthritis; SIR, standardised incidence rate.

9.5.3 Data from a French registry

According to the results from recent French studies (Mariette et al, 2010; Mariette et al, 2011), the incidence of lymphoma was found to be increased among patients with RA treated with (infliximab/adalimumab) compared with soluble-receptor anti-TNF (etanercept), with corresponding SIR (95% CI) of 4.1 (2.3 to 7.1) or 3.6 (2.3 to 5.6) vs 0.9 (0.4 to 1.8).

9.5.4 Review of T cell NHL reported to the FDA in patients receiving TNF α inhibitors

A recent study (Deepak et al, 2013) has evaluated a total of 3 130 267 reports downloaded from the FDA Adverse Event Reporting System (AERS) (2003–2010). Ninety-one cases of T cell NHL related to TNF α inhibitors were identified in the FDA AERS and nine additional cases were identified on Medline search. A total of 38 patients had RA, 36 had Crohn's disease, 11 had psoriasis, nine had ulcerative colitis and six had ankylosing spondylitis. Sixty-eight of the cases (68%) involved exposure to both a TNF α inhibitor and an immunomodulator (AZA, 6-mercaptopurine, MTX, leflunomide, or CsA). Hepatosplenic T cell lymphoma was the most commonly reported subtype. The authors concluded that the risk of T cell NHL is increased by the use of a TNF α inhibitor in combination with thiopurines, but not by use of TNF α inhibitors alone.

9.5.5 Lymphoma and anti-TNF agents: summary

Recent data suggest a possible increase of the incidence of lymphoma in patients treated with anti-TNF (Wong et al, 2012). However, the interpretation of this increase is complex since disease activity is a major risk factor for lymphoma, and the more active the RA, the more likely are patients to receive anti-TNF agents. Thus, a recent meta-analysis of the risk of lymphoma from RA registries concluded that the risk of lymphoma with anti-TNF agents was the same as the risk of lymphoma with other classic disease-modifying antirheumatic drugs (Mariette et al, 2011).

Thus, it is impossible to know whether this increased risk of lymphoma is related to anti-TNF agents or to increased disease activity of the patients treated with biological agents. If the latter hypothesis is correct, the risk related to increased disease activity should be rapidly corrected by clinical improvement allowed by anti-TNF. The question remains...

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SUMMARY POINTS

- Sjögren's syndrome (SS) is a multi systemic autoimmune disease that mainly affects the exocrine glands, with a clinical spectrum that extends to systemic involvement (extra glandular manifestations).
- The disease can appear in many guises depending on specific epidemiological, clinical or immunological features, although it overwhelmingly affects middle-aged women.
- It may be a serious disease with excess mortality, mainly related to systemic involvement and haematological cancer., but also it can be a disease with very little objective signs but with burden of the patient because a poor quality of life
- The proven diagnosis of SS requires documentation of sicca symptoms, objective evidence of dry eyes and mouth analytical evidence of autoimmunity, as sicca syndrome has many causes and a lip biopsy specially in serological negative patients.
- The therapeutic management of SS should have a multisystemic approach taking in account a clear and comprehensive teaching of the patient about his illness and understanding the poor quality of life patients normally experience.
- It mainly centres on the control of sicca features, using substitutive and oral muscarinic agents, while glucocorticoids, immunosuppressive and biological agents play a key role in the treatment of extra glandular features.
- Primary SS is the autoimmune disease in which the risk of lymphoma is the highest. An increased risk of B cell lymphoma has also been reported in other rheumatic and autoimmune diseases.
- Chronic immune stimulation, genetic and environmental factors and some immunosuppressive/biological drugs might be involved in lymphomagenesis in autoimmune diseases other than SS.

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Sjögren's syndrome and lymphoproliferations in autoimmune diseases

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IN-DEPTH DISCUSSION I

**Primary and associated Sjögren's syndrome:
Role of autoantibodies**

Patients with primary Sjögren syndrome (SS) sometimes demonstrate autoantibodies considered characteristic of other systemic autoimmune diseases (SAD). In such cases, the clinical significance of this immunological overlap (if any) has not been established. Some studies have attributed the presence of certain autoantibodies merely to the B-cell hyperactivity that is characteristic of primary SS. In contrast, other studies have implied that the presence of such autoantibodies signals a predictive role and a greater likelihood for the emergence of an additional associated SAD. Indeed, a significant clinical and immunological overlap between SS and other autoimmune diseases may exist (Table 1).

Table 1. Clinical and immunological overlap between primary SS and other systemic autoimmune diseases

Systemic autoimmune diseases	OVERLAP FEATURES	
	Clinical	Immunological
Systemic lupus erythematosus	Arthritis Leukopenia Thrombocytopenia SCLE	ANA Anti-DNA Hypocomplementaemia
Rheumatoid arthritis	Arthritis	RF
Systemic sclerosis	Raynaud phenomenon Pulmonary fibrosis	ACA
Mixed connective tissue disease	Puffy hands Raynaud phenomenon Myositis Synovitis	Anti-RNP
Sarcoidosis	Parotid enlargement Erythema nodosum	-
Systemic vasculitides	MVV Livedo reticularis Purpura Neuropathy	Cryoglobulins ANCA
Antiphospholipid syndrome	Thrombocytopenia Livedo reticularis	aPL

SCLE: sub-acute cutaneous lupus erythematosus; ACA anticentromere antibodies; MVV: medium-vessel vasculitis; aPL: antiphospholipid antibodies.

I. ANTIMITOCHONDRIAL ANTIBODIES

There is a small subset of patients with primary SS and positive anti-mitochondrial antibodies (AMA) (8%), an immunological marker closely related to primary biliary cirrhosis (PBC). However, 50% of SS patients who have AMA demonstrate clinical or laboratory test evidence of liver disease (Ramos-Casals et al, 2008). Liver biopsy reveals usually a stage I PBC (Hatzis et al 2008). This suggests the existence of an incipient or incomplete PBC in some patients with primary SS, progressing very rarely to end-organ damage.

II. ANTI-dsDNA ANTIBODIES

Few studies have analysed the clinical significance of anti-dsDNA antibodies in patients with primary SS. In a study of 26 patients with primary SS patients who had anti-dsDNA autoantibodies (Ramos-Casals et al, 2006), features of systemic lupus erythematosus (SLE) included ANA positivity in all cases, leukopenia in 14 (54%) and articular involvement in 9 (35%). Other SLE features, such as skin, renal and central nervous system involvement were uncommon. After a median follow-up of nearly 6 years, 8 (31%) of the 26 SS patients with anti-dsDNA antibodies at baseline fulfilled 4 or more of the classification criteria for SLE and 10 (38%) fulfilled 3 criteria.

In another study, Manoussakis et al (2004) described the clinical characteristics of 26 patients with coexistence of SS and SLE. Autoantibodies were not useful in distinguishing between SLE and SS-SLE patients and the clinical presentations of the two patient groups were similar. Therefore, there is a substantial overlap in the clinical and serologic features of primary SS and SLE, and the consequent difficulties in using classification criteria to distinguish between them has been emphasized (Isenberg et al, 2004).

III. ANTI-Sm ANTIBODIES

Anti-Sm antibodies are rarely found in patients with primary SS (Ramos-Casals et al, 2006). A close follow-up of primary SS patients with positive anti-Sm antibodies is suggested, in order to detect clinical and/or analytical data suggesting the development of an additional SAD, and thus, an evolution from a single autoimmune disease (primary SS) to an overlap syndrome (generally, SS associated with SLE).

IV. ANTI-RNP ANTIBODIES

Some patients with primary SS have positive anti-RNP antibodies. Several studies have analysed anti-RNP antibodies in small series including patients with primary and associated SS and found a prevalence ranging between 4% and 28% (Ramos-Casals et al, 2006). Overlap syndromes between SS and mixed connective tissue disease occurs in some patients.

V. ANTIPHOSPHOLIPID ANTIBODIES

Antiphospholipid antibodies (aPL) are the most frequently detected atypical autoantibodies in primary SS (Table 2) (Ramos-Casals et al, 2006). In spite of the frequency in which aPL are detected, the fully-expressed antiphospholipid syndrome (APS) occurs in only a minority of primary SS patients. In a meta-analysis by Ramos-Casals et al, 2006, only 12 (9%) of 134 SS-aPL patients fulfilled the 1999 APS classification criteria. The coexistence of primary SS and APS should be considered an infrequent (but not exceptional) event that occurs in approximately 10% of primary SS patients who have aPL. Routine aPL determination in patients with

primary SS is not recommended except in those with specific clinical (thrombosis or repeated miscarriages) or analytical (thrombocytopenia, haemolytic anaemia) features consistent with APS (Ramos-Casals et al, 2007).

Table 2. Prevalence of atypical immunological markers in patients with primary SS (Ramos-Casals et al, 2006)

Atypical antibodies	Patients with primary SS (positive/tested)	Prevalence
aPL	120/589	20.4%
ANCA	43/357	12%
ACA	11/137	8%
Anti-CCP	11/166	6.6%
Anti-dsDNA	34/718	4.7%
Anti-RNP	34/782	4.3%
Anti-Scl70	2/92	2.2%
Anti-Sm	8/457	1.7%

VI. ANTI-Scl70 ANTIBODIES

No studies have analysed the prevalence and clinical significance of these autoantibodies in patients with primary SS, with only two isolated cases being reported in patients with coexisting SS and SLE (Al Attia et al, 2003) and 2 cases with primary SS and anti-Scl70 (anti-topoisomerase I) antibodies. None of these 4 patients presented clinical features suggestive of systemic sclerosis (SSc). However, Fauchais AL et al (2010) described 3 SS patients with Scl70 antibodies, 2 of whom developed SSc. Therefore, clinicians should be aware of the possibility of the development of scleroderma features in patients who have these autoantibodies.

VII. ANTICENTROMERE ANTIBODIES

In contrast to anti-Scl70 antibodies, anticentromere antibodies (ACA) seem to have a higher prevalence and greater clinical significance in patients with primary SS, with nearly 100 cases being reported (Ramos-Casals et al, 2006) (Salliot et al, 2007) and a prevalence ranging from 4-8% in large series of primary SS patients (Bournia et al, 2010) (Baldini et al, 2013) (Ramos-Casals et al, 2006).

Although, SS patients with ACA antibodies seem to have little tendency to evolve to a full-blown systemic sclerosis (Bournia et al, 2010) (Baldini et al, 2013), routine testing for ACA in patients with primary SS is recommended for those who have Raynaud's phenomenon, and especially in patients with high titers of ANA but negative anti-Ro/La antibodies. Close physical examination for incipient cutaneous changes that suggest limited systemic sclerosis, particularly a nailfold capillaroscopic analysis, is essential. In addition, SS-ACA

patients should be monitored closely for the development of gastrointestinal or pulmonary manifestations that may commonly complicate systemic sclerosis.

A recent study (Baer et al. 2016) from the SICCA cohort including over 1300 patients described a subset of pSS patients with positive ACA. ACA was associated with older age, female sex, and lower frequency of anti-SSA/SSB, rheumatoid factor and hyperglobulinemia. ACA-SS patients were more likely to have a worse exocrine glandular dysfunction and a higher focus score in salivary gland biopsy; however, ACA was not associated with glandular fibrosis.

VIII. ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)

A total of 59 patients with primary SS and positive ANCA have been reported (Ramos-Casals et al, 2006). The potential clinical significance of these autoantibodies in patients with primary SS is defined by three points: the prevalence of the different immunofluorescence patterns and enzyme immunoassay specificities; the association of these autoantibodies with specific extra glandular features of SS; and the overlap with systemic vasculitis.

The clinical significance of ANCA in patients with primary SS can be summarized by an overwhelming prevalence of the p-ANCA pattern, although antibodies directed against myeloperoxidase are found in less than 20% of cases. Thus, there appears to be little utility in the routine determination of ANCA in patients with primary SS. ANCA testing should be reserved for those in whom a high index of suspicion for a true “pauci-immune” form of systemic vasculitis exists.

IX. ANTI-CITRULLINATED ANTIBODIES

Arthritis in primary SS has been predominantly reported in the proximal interphalangeal (35%) and metacarpophalangeal joints (35%), and wrists (30%). Radiologically, SS-related arthritis is overwhelmingly classified as non-erosive, with bone erosions being found in only 4% of patients. The main autoimmune disease that should be discarded in the presence of anti-CCP is rheumatoid arthritis (RA). The high frequency of rheumatoid factor (RF) in primary SS means this marker is not suitable for the differentiation of RA and SS, but anti-CCP antibodies may be more useful. Seventeen studies have tested anti-CCP in patients with primary SS and found positivity in only 7% of cases (Table 3).

Table 3. Prevalence of anti-CCP antibodies positivity in patients with primary SS

Author	Year	Primary SS patients (n)	Anti-CCP+ (%)	Characteristics of joint involvement in CCP+ patients (n)
Dubucquoi et al	2004	47	2 (4%)	Not detailed
Gottenberg et al	2005	134	10 (7%)	Arthritis (2)
Kamali et al	2005	35	1 (3%)	Not detailed
Sauerland et al	2005	30	1 (3%)	Not detailed
Tobon et al	2005	53	5 (10%)	Arthritis (2), arthralgias (2), no X-ray erosions
Van noord et al	2005	108	3 (3%)	Arthritis (1)
Haga et al	2007	102	5 (5%)	Arthritis (1)
Atzeni et al	2008	155	14 (9%)	Arthritis (12)
Bodil et al	2008	78	4 (5%)	Arthritis (3)
Barcelos et al	2009	31	2 (6%)	Arthritis (0)
Iwamoto et al	2009	73	3 (4%)	Joint involvement (3), no X-ray erosions
Riente et al	2009	48	0 (0%)	-
Fauchais et al	2010	419	3 (1%)	Joint involvement (3)
Iagnococco et al	2010	32	1 (3%)	Not detailed
Haga et al	2011	62	5 (8%)	Arthritis (1)
Kim et al	2012	95	21 (22%)	Arthralgia (20), arthritis (16)
Ryu et al	2012	405	38 (9%)	Arthralgia (32), arthritis (28)
TOTAL		1907	118 (7%)	

X. MUSCARINIC TYPE 3 RECEPTOR AUTOANTIBODIES

Anti-muscarinic type 3 receptor autoantibodies (anti-M3R) are potential inhibitors of saliva secretion in SS. Extensive efforts have shown that anti-M3R are positively associated with focus score and negatively associated with saliva flow rate. Although there is not yet a test commercially available to detect them, studies supporting their inclusion as a non-invasive serologic marker for the diagnosis of SS exist. (Zuo et al. 2016)

XI. NOVEL ANTIBODIES

Recent studies have identified new autoantibodies; these are anti-salivary gland protein-1 (SPS 1), anti-carbonic anhydrase 6 (CA6) and anti-parotid secretory protein (PSP). A recent study has identified these antibodies in 60% of patients suffering from dry eye. Only 30% of the patients with one of these autoantibodies had longstanding SS. Therefore, testing for these novel autoantibodies may allow an earlier recognition of SS. (Everett S, et al 2017)

CONCLUSION

In conclusion, a great heterogeneity in the immunological presentation of primary SS is often observed, including the presence of multiple autoantibodies against both nuclear and non-nuclear antigens. ANA play a central role in the immunological expression of primary SS because of their frequency, their association with clinical SS features and their close association with autoantibodies directed against ENA. Anti-Ro/SSA and anti-La/SSB antibodies are closely related to the extra glandular expression of primary SS and identify the most clinically and immunologically “active” subset of primary SS patients. The presence of some antibodies directed against non-nuclear antigens, e.g., anti-mitochondrial antibodies, suggests an association between primary SS and other organ-specific autoimmune diseases, especially primary biliary cirrhosis. For other antibodies directed against non-nuclear antigens, e.g., parietal cell antibodies and smooth muscle antibodies, the associations are less clear or even believed to be of little or no clinical significance.

Testing for atypical autoantibodies mainly anti-dsDNA, aPL, anti-centromere, ANCA, anti-CCP may be helpful in diagnosing a possible overlap between primary SS and other SAD. Although patients with atypical autoantibodies are often classified initially as having primary SS (most of them also fulfilling the 2002 classification criteria for SS), 20% may fulfil classification criteria for an additional SAD during follow-up. The risk of developing an additional SAD differs according to the atypical autoantibody present at the diagnosis of “primary” SS. Patients having anti-dsDNA or anti-centromere antibodies are at higher risk of developing an additional disease and require closer follow-up in order to detect clinical and/or analytical data suggestive of coexisting SLE or systemic sclerosis.

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Sjögren's syndrome and lymphoproliferations in autoimmune diseases

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IN-DEPTH DISCUSSION II

IgG4-related disease

IgG4-related disease (IgG4-RD) is a systemic immune-mediated disease described in Japan in the first years of the 21st century and is characterized by tissue infiltration of IgG4-bearing plasma cells (Stone et al, 2012). It is not a new disease, because many previously-recognised conditions of an unknown aetiology and pathogenesis, formerly regarded as entirely disparate disorders, are now known to comprise parts of the IgG4-RD spectrum. Such conditions include Mikulicz disease, Küttner's tumour, Riedel thyroiditis, and Ormond disease, among others (Kamisawa et al, 2015).

The cardinal feature of IgG4-RD is single or multiple organ swelling. IgG4-RD usually presents sub acutely and most patients are not severely or acutely ill. The disease may be diagnosed incidentally through radiological findings or unexpectedly in pathological specimens, especially in single organ presentations. Multi-organ disease is easier to identify at diagnosis but may evolve metachronously over months to years. Involvement of major organs is common and may lead to organ failure, particularly in the pancreas, liver and biliary tree, kidneys, thyroid gland, lungs, and aorta. Signs and symptoms at presentation are diverse and may be divided into general and organ-specific. Most reports have focused on describing the organs involved and not on the signs and symptoms that led ultimately to the diagnosis (Brito-Zerón et al, 2015).

It is important to note that the presenting features vary substantially according to the specialty to which the patient presents first (Table 1). Gastroenterologists are more likely to encounter patients with jaundice, pruritus and mild abdominal discomfort resulting from autoimmune pancreatitis or IgG4-related sclerosing cholangitis. Rheumatologists, in contrast, are more likely to encounter patients with major salivary gland enlargement because this disease feature often raises the spectre of Sjögren's syndrome. Ophthalmologists are more likely to be referred patients with lachrymal gland swelling or other orbital lesions; nephrologists to evaluate patients with renal dysfunction caused by tubulointerstitial nephritis; and so forth.

Major salivary glands are one of the organs more frequently involved in the IgG4-related disease, reported in 40% of cases (40%). IgG4-related glandular involvement has been specifically studied in several studies including patients with Mikulicz disease (defined as the bilateral swelling of at least two major salivary or lachrymal glands) and Kuttner disease (also known as chronic sclerosing sialadenitis, affecting submandibular glands). Glandular swelling, often subacute, is the key sign on examination: submandibular glands are affected in more than 90% of patients, parotid glands in 30% and sublingual glands in less than 10 cases (Moriyama et al, 2012). Bilateral involvement is more frequent in systemic than in localized IgG4-RD. A recent study has reported that all affected glands showed well-defined borders, with two types of sonographic appearance (localized tumour-forming and diffuse focal involvement) (Asai et al, 2013). In patients with IgG4-related glandular disease, sicca symptoms have been reported in two thirds of patients.

Four main laboratory abnormalities (eosinophilia, hypergammaglobulinaemia, elevated serum IgE levels, and hypocomplementaemia) may lead to suspicion of IgG4-RD. Raised serum IgG4 levels were the key feature in

identifying the first cases of IgG4-RD, although recent studies have reported some significant limitations of serum IgG4 measurement (Carruthers et al, 2014). Histopathological studies showing specific histological features (storiform fibrosis, eosinophilic infiltration and obliterative phlebitis) and IgG4 tissue immunostaining are the most reliable diagnostic tools, although they are not pathognomonic and may show significant variations according to the organ biopsied, the time of disease evolution or the therapies administered. Recent studies have suggested a potential role of flow cytometry studies in the diagnosis and longitudinal management of IgG4-RD.

IgG4-RD should be suspected in patients presenting with unexplained enlargement or swelling of one or more organs (Stone et al, 2012). General symptoms such as asthenia or weight loss (especially reported by patients with intra-abdominal involvement) are common but usually subacute and therefore difficult to recognise. Fever occurs in only a small minority of patients, even those with impressive degrees of weight loss. The diagnosis of IgG4-RD relies on the coexistence of various clinical, laboratory and histopathological findings, although none are pathognomonic alone (Deshpande et al, 2012). Nevertheless, demonstration of the classic histopathologic proof of the diagnosis is crucial in most cases and strongly preferred before the initiation of treatment.

The diagnostic approach is heterogeneous, and the first proposed sets of criteria centred on a specific organ (the best examples are the specific criteria for IgG4-related pancreatitis, sclerosing cholangitis, kidney disease and glandular disease). In 2012, Umehara et al, proposed a set of criteria for the diagnosis of systemic IgG4-RD designed to be used independently of the predominant organ involvement. The sensitivity and specificity of these criteria remain untested.

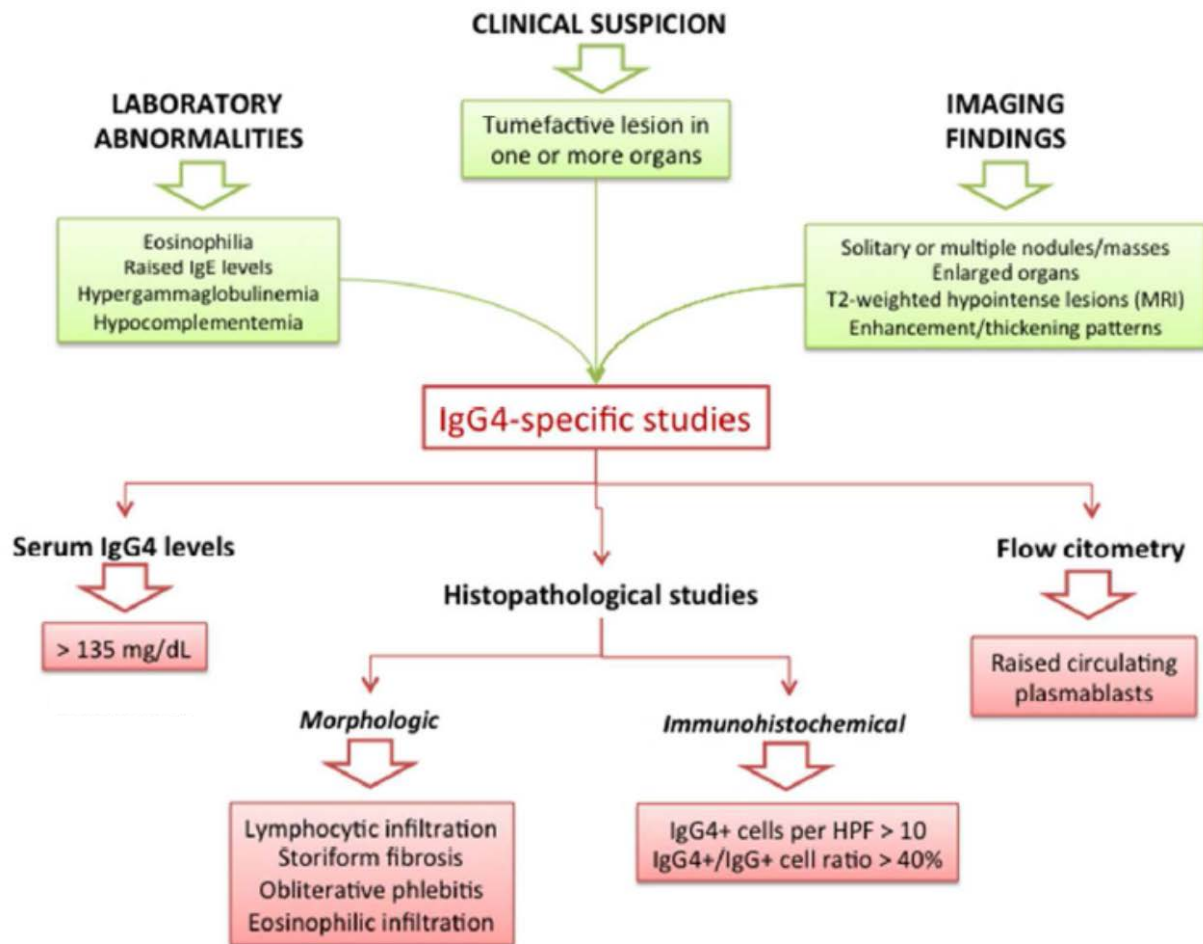
Diagnostic and therapeutic decision-making continues to be based on clinical experience and expert opinion (Mahajan et al, 2014) (Figure 1). Steroids are currently the cornerstone of treatment. In relapsing or refractory cases, Rituximab may be of help.

Greater understanding of the aetiopathogenesis of IgG4-RD, active multidisciplinary collaboration promoting international multicentre registries and clinical guidelines, and the development of more-specific therapies, may help improve the prognosis for patients with this emerging immune-mediated systemic disease.

Table 1. List of involvements of organs and clinical presentations reported in IgG4-RD

1. Pancreas
2. Biliary tree
3. Gallbladder
4. Major salivary glands
5. Ocular involvement
6. Pulmonary involvement
7. Pleural involvement
8. Mediastinal involvement
9. Thymus
10. Renal involvement
11. Retroperitoneal involvement
12. Urinary tract and bladder
13. Mesenterium
14. Aorta
15. Arterial involvement
16. Meninges
17. Cranial nerves
18. Vertebral nerve roots
19. Brain
20. Pineal gland
21. Thyroid involvement
22. Prostate
23. Breast
24. Testes
25. Allergic processes
26. ENT involvement
27. Skin involvement
28. Lymph nodes
29. Oesophagus
30. Stomach
31. Small intestine
32. Large intestine
33. Liver
34. Spleen
35. Articular involvement
36. Pericardium
37. Peripheral nerves

Figure 1. Diagnostic algorithm in IgG4-RD: sequential diagnostic approach integrating clinical suspicion and IgG4-specific diagnostic tests. HPF = high power field



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Vasculitis: Classification, Secondary Forms and Mimics

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LEARNING OBJECTIVES

- ➔ Describe the principles of classification of vasculitis
- ➔ Use the main tools available for the purposes of vasculitis classification
- ➔ Describe and explain the main primary vasculitides and their classification characteristics
- ➔ Describe and explain the main secondary vasculitides and their underlying aetiologies
- ➔ Evaluate the clinical features of those systemic conditions that may mimic systemic vasculitis and be able to distinguish conditions such as cholesterol embolism, infective endocarditis, atrial myxoma and fibromuscular dysplasia from vasculitis

1 Introduction

This chapter describes the current schemes for classifying and defining the systemic vasculitides. The strengths and weaknesses of these schemes are described together with an approach that enables them to be used consistently and logically.

The vasculitides are a heterogeneous group of relatively rare conditions that can occur independently—for example, granulomatosis with polyangiitis (Wegener's), or as a secondary feature of an established disease, such as rheumatoid arthritis. The word vasculitis means inflammation of blood vessels; the blood vessel is the primary site of inflammation. The pathological consequence of such inflammation is destruction of the vessel wall, seen histologically as fibrinoid necrosis, hence the term 'necrotising vasculitis'. Vasculitis may be localised to a single organ or vascular bed and be clinically insignificant but, more commonly, is generalised. Muscular arteries may develop focal or segmental lesions and these may be life threatening. The former (affecting part of the vessel wall) may lead to aneurysm formation and possible vessel rupture; segmental lesions (affecting the whole circumference) are more common and lead to stenosis or occlusion with distal infarction. Small-vessel vasculitis, by contrast, most commonly affects the skin, but may also cause dysfunction of internal organs.

The aetiology of vasculitis is unknown but is clearly multifactorial; among the influences on disease expression are ethnicity, genes (HLA and others), gender and environment (ultraviolet light, infections, toxins, drugs, allergy, smoking, etc).

1.1 Historical classifications

Kussmaul and Maier (1866) are generally accepted as providing the first description of 'periarteritis nodosa' when they described a patient with a systemic illness characterised by numerous nodules along the course of small muscular arteries. Earlier descriptions suggest that formal recording of the disease is at least 200 years old (Matteson, 1999). Zeek (1952) reviewed the literature relating to vasculitis and periarteritis nodosa and used the generic term 'necrotising angiitis' to indicate the specific damage to the blood vessel wall rather than the presence of inflammatory cells alone; she classified these into five distinct entities: (i) hypersensitivity angiitis, (ii) allergic granulomatous angiitis, (iii) rheumatic arteritis, (iv) periarteritis nodosa and (v) temporal arteritis. Most modern classifications are based on Zeek's work, which essentially combined histological changes and clinical features. Notable omissions from Zeek's classification were granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and Takayasu arteritis. Microscopic polyangiitis had been described by Davson et al (1948), but was not generally recognised until the 1990s. Granulomatosis with polyangiitis (Wegener's) and Takayasu arteritis were not fully described in the English literature until after 1953.

The most widely accepted classification system based on Zeek's work reflects dominant vessel size and association with antineutrophil cytoplasmic antibodies (ANCA) (table 1). This classification system also reflects broadly the therapeutic approaches that are applied to the different groups (table 2). The medium-vessel and small-vessel groups respond well to immunosuppression with cyclophosphamide and glucocorticoids, whereas the large-vessel group requires moderate-to-high-dose steroids and the small-vessel group sometimes requires only low-dose glucocorticoids.

Table 1 Classification of the vasculitic syndromes according to vessel size and ANCA. (Reproduced with permission from Scott and Watts, *Br J Rheumatol* 1994;33:897–9)

Dominant vessel	Primary	Secondary
Large arteries	Giant cell arteritis, Takayasu's arteritis	Aortitis associated with RA, infection (e.g., syphilis, TB)
Medium arteries	Classic PAN Kawasaki disease	Hepatitis B-associated PAN
Small vessels and medium arteries	Granulomatosis with polyangiitis (Wegener's)*, Churg–Strauss syndrome*, Microscopic polyangiitis*	Vasculitis secondary to RA, systemic lupus erythematosus, Sjögren's syndrome, drugs, infection (e.g., HIV)
Small vessels	Henoch–Schönlein purpura Cryoglobulinaemia Cutaneous leukocytoclastic angiitis	Drugs Hepatitis C associated Infection

*Diseases most commonly associated with ANCA and a significant risk of renal involvement, and most responsive to immunosuppression with cyclophosphamide.

ANCA, antineutrophil cytoplasmic antibodies; HIV, human immunodeficiency virus; PAN, polyarteritis nodosa; RA, rheumatoid arthritis; TB, tuberculosis.

Table 2 Relation between vessel size and response to induction treatment. (Reproduced with permission from Scott and Watts, *Br J Rheumatol* 1994;33:897–9)

Dominant vessels involved	Glucocorticoids alone	Cyclophosphamide + glucocorticoids	Others
Large arteries	++	–	+
Medium arteries	+	++	++*
Small vessels and medium arteries	+	+++	+
Small vessels	+	±	++

*Includes plasmapheresis, antiviral therapy for hepatitis B-associated vasculitis and intravenous immunoglobulins for Kawasaki disease.

1.2 1990 American College of Rheumatology classification criteria

There are no validated diagnostic criteria for systemic vasculitis. However, the American College of Rheumatology (ACR) presented classification criteria in 1990. They proposed criteria for the classification of seven types of systemic vasculitis: Takayasu arteritis (table 3), giant-cell arteritis (table 4), granulomatosis with polyangiitis (Wegener's) (table 5), polyarteritis nodosa (table 6), eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (table 7), hypersensitivity vasculitis (table 8) and IgA vasculitis (Henoch–Schönlein) (table 9).

Table 3 American College of Rheumatology classification criteria for Takayasu arteritis

Criterion	Definition
1. Age <40 years old	Development of symptoms or signs related to Takayasu arteritis at age <40 years
2. Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities
3. Decreased brachial arterial pulse	Decreased pulsation of one or both brachial arteries
4. Blood pressure difference >10 mm Hg	Difference of >10 mm Hg in systolic blood pressure between arms
5. Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
6. Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its proximal branches, or large arteries in the proximal upper or lower extremities, not due to atherosclerosis, fibromuscular dysplasia or similar causes; changes usually focal or segmental

For purposes of classification, a patient shall be said to have Takayasu arteritis if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and specificity of 97.8% (Arend et al, 1990).*

Table 4 American College of Rheumatology classification criteria for giant-cell arteritis

Criterion	Definition
1. Age at onset >50 years	Development of symptoms or findings beginning aged ≥50 years
2. New headache	New onset, or new type, of localised pains in the head
3. Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to atherosclerosis of cervical arteries
4. Increased ESR	ESR >50 mm in first hour by Westergren method
5. Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterised by a predominance of mononuclear infiltration or granulomatous inflammation

For purposes of classification, a patient shall be said to have giant-cell arteritis if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5% and specificity of 91.2% (Hunder et al, 1990).*

ESR, erythrocyte sedimentation rate.

Table 5 American College of Rheumatology classification criteria for granulomatosis with polyangiitis (Wegener's)

Criterion	Definition
1. Nasal or oral inflammation	Development of painful or painless oral ulcers or purulent or bloody nasal discharge
2. Abnormal chest radiograph	Chest radiograph showing the presence of nodules, fixed infiltrates or cavities
3. Urinary sediment	Microhaematuria (>5 red cells per high power field) or red cell casts in urinary sediment
4. Granulomatous inflammation on biopsy	Histological changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

For purposes of classification, a person shall be said to have granulomatosis with polyangiitis (Wegener's) if at least two of these four criteria are present. The presence of any two or more criteria yields a sensitivity of 88.2% and specificity of 92.0% (Leavitt et al, 1990).*

Table 6 American College of Rheumatology classification criteria for polyarteritis nodosa

Criterion	Definition
1. Weight loss	Loss of ≥ 4 kg of body weight since the illness began, not because of dieting or other factors
2. Livedo reticularis	Mottled reticular pattern over the skin of portions of the extremities or torso
3. Testicular pain or tenderness	Pain or tenderness of the testicles, not the result of infection, trauma or other causes
4. Myalgias, weakness or leg tenderness	Diffuse myalgias (excluding shoulder or hip girdle) or weakness of muscles or tenderness of leg muscles
5. Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies or polyneuropathy
6. Diastolic BP >90 mm Hg	Development of hypertension with diastolic BP >90 mm Hg
7. Raised blood urea or creatinine	Raised blood urea nitrogen >40 mg/dL or creatinine 1.5 mg/dL, not because of dehydration or obstruction
8. Hepatitis B virus	Presence of hepatitis B surface antigen or antibody in serum
9. Arteriographic abnormality	Arteriogram showing aneurysms or occlusion of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia or other non-inflammatory causes
10. Biopsy of small or medium-sized artery containing polymorphonuclear neutrophils	Histological changes showing the presence of granulocytes or granulocytes and mononuclear leucocytes in the artery wall

For purposes of classification, a patient shall be said to have polyarteritis nodosa if at least three of these 10 criteria are present. The presence of any three or more criteria yields a sensitivity of 82.2% and specificity of 86.6% (Lightfoot et al, 1990). BP, blood pressure.*

Table 7 American College of Rheumatology classification criteria for Churg–Strauss syndrome

Criterion	Definition
1. Asthma	History of wheezing or diffuse high-pitched rales on expiration
2. Eosinophilia	Eosinophilia >10% on white cell differential count
3. Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies or polyneuropathy (i.e., glove/stocking distribution) attributable to systemic vasculitis
4. Pulmonary infiltrates, non-fixed	Migratory or transient pulmonary infiltrates on radiographs (not including fixed infiltrates), attributable to a systemic vasculitis
5. Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
6. Extravascular eosinophils	Biopsy including artery, arteriole or venule showing accumulations of eosinophils in extravascular areas

For purposes of classification, a person shall be said to have Churg–Strauss syndrome if at least four of these six criteria are present. The presence of any four or more criteria yields a sensitivity of 85.0% and specificity of 99.7% (Masi et al, 1990).*

Table 8 American College of Rheumatology classification criteria for hypersensitivity vasculitis

Criterion	Definition
1. Age at disease onset >16 years	Development of symptoms age >16 years
2. Medication at disease onset	Medication was taken at the onset of symptoms, which might have been a precipitating factor
3. Palpable purpura	Slightly raised purpuric rash over one or more areas of the skin, does not blanch with pressure and is not related to thrombocytopenia
4. Maculopapular rash	Flat and raised lesions of various sizes over one or more areas of the skin
5. Biopsy including arteriole and venule	Histological changes showing granulocytes in a perivascular or extravascular location

For purposes of classification, a patient shall be said to have hypersensitivity vasculitis if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 71.0% and specificity of 83.9% (Calabrese et al, 1990).*

Table 9 American College of Rheumatology classification criteria for Henoch–Schönlein purpura

Criterion	Definition
1. Palpable purpura	Slightly raised purpuric rash over one or more areas of the skin not related to thrombocytopenia
2. Bowel angina	Diffuse abdominal pain worse after meals, or bowel ischaemia, usually bloody diarrhoea
3. Age at onset <20 years	Development of first symptoms at age ≤20 years
4. Wall granulocytes on biopsy	Histological changes showing granulocytes in the walls of arteries or venules

For purposes of classification, a patient shall be said to have Henoch–Schönlein purpura if at least two of these four criteria are present. The presence of any two or more criteria yields a sensitivity of 87.1% and specificity of 87.7% (Mills et al, 1990).*

The clinical and laboratory features of 807 patients were analysed, criteria being sought that would distinguish one individual disease from another. The findings in one group were compared with those in the remaining groups. The sensitivity rates varied considerably from 71.0% to 95.3% and from 78.7% to 99.7% for specificity (Fries et al, 1990*; Rao et al, 1998). Eosinophilic granulomatosis with polyangiitis (Churg–Strauss), giant-cell arteritis and Takayasu arteritis had the most sensitive criteria. Hypersensitivity vasculitis was the least well-defined condition, and these patients are now usually classified as having cutaneous leukocytoclastic angiitis or drug-associated vasculitis. The criteria were subsequently tested against a cohort of patients with systemic vasculitis and performed poorly (Rao et al, 1998). The ACR scheme has two major weaknesses: first, it does not include microscopic polyangiitis (this condition was not well recognised in the 1980s when the scheme was being developed) and second, it does not include ANCA (which were not widely used as a diagnostic tool in the 1980s).

1.3 Chapel Hill Consensus Conference

In 1994, the Chapel Hill Consensus Conference (CHCC) produced definitions for vasculitis. They included for the first time microscopic polyangiitis, but were not intended as classification or diagnostic criteria. Like the ACR criteria, ANCA were not included. They also recognised that histological data would not be available for all patients, especially when the clinical condition of the patient might preclude obtaining appropriate biopsies or the sample might not be representative and thus might miss salient histological features. This is particularly a problem for focal lesions such as granulomas. The concept of surrogate markers of vasculitis was therefore introduced. In addition, the potential importance of ANCA in diagnosis was recognised, but not included in the definitions. The result has been that although the ACR criteria and CHCC definitions are widely used, there is no agreement as to how they should be applied.

The CHCC definitions have recently been modified following an international consensus meeting held in 2011 to reflect changes in our understanding of the aetiopathogenesis of vasculitis (Jennette et al, 1994*). A new tree hierarchy was developed which recognised that some conditions cannot be simply classified by vessel size (table 10) (Jennette et al, 2013*). ANCA-associated vasculitis was recognised as a specific type of small-vessel vasculitis together with immune-complex-mediated vasculitis. The hierarchy was expanded to include vasculitis affecting vessels of variable size, single-organ vasculitis and vasculitis associated with either systemic disease or specific aetiologies. A new nomenclature was adopted, with a move away from eponyms towards names reflecting pathology or aetiopathogenesis following the introduction of the term GPA for Wegener's granulomatosis. The name 'eosinophilic granulomatosis with polyangiitis' was adopted for Churg–Strauss syndrome and 'IgA vasculitis' for IgA vasculitis (Henoch–Schönlein). Definitions were developed for new categories of conditions, including single-organ vasculitis, vasculitis associated with specific aetiologies including systemic disease (rheumatoid arthritis, systemic lupus erythematosus) and aetiologies such as

infection (cryoglobulinaemia, hepatitis B and C), or drugs (e.g., propylthiouracil) (table 10) (Jennette et al, 2013*).

Table 10 Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis*. (Reproduced with permission from Jennette et al, *Arthritis Rheum*, 2013;65:1–11*)

Large vessel vasculitis.	Description
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 years and often is associated with polymyalgia rheumatica
Takayasu's arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50 years
Medium-sized vessel vasculitis.	
Polyarteritis nodosa [†] (classic polyarteritis nodosa)	Necrotising inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules
Kawasaki disease	Arteritis involving large, medium-sized, small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often affected. Aorta and veins may be involved. Usually occurs in children
Small vessel vasculitis.	
Granulomatosis with polyangiitis (Wegener's) [‡]	Granulomatous inflammation involving the respiratory tract, and necrotising vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles and arteries). Necrotising glomerulonephritis is common
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) [‡]	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotising vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia
Microscopic polyangiitis [†] (microscopic polyarteritis) [‡]	Necrotising vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules or arterioles). Necrotising arteritis involving small and medium-sized arteries may be present. Necrotising glomerulonephritis is very common. Pulmonary capillaritis often occurs
Henoch–Schönlein purpura	Vasculitis, with IgA-dominant immune deposits, affecting small vessels (i.e., capillaries, venules or arterioles). Typically involves skin, gut and glomeruli, and is associated with arthralgia or arthritis
Essential cryoglobulinaemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e., capillaries, venules or arterioles), and associated with cryoglobulins in serum. Skin and glomeruli are often involved
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis glomerulonephritis

**Large vessel refers to the aorta and the largest branches directed towards the major body regions (e.g., to the extremities and the head and neck); medium-sized vessel refers to the main visceral arteries (e.g., renal, hepatic, coronary and mesenteric arteries); small vessel refers to venules, capillaries, arterioles and the intraparenchymal distal arterial radicals that connect with arterioles. Some small and large vessel vasculitides may involve medium-sized arteries, but large and medium-sized vessel vasculitides do not involve smaller arteries. † Preferred term. ‡ Strongly associated with antineutrophil cytoplasmic antibodies.*

1.4 Problems of the ACR criteria and CHCC definitions for vasculitis

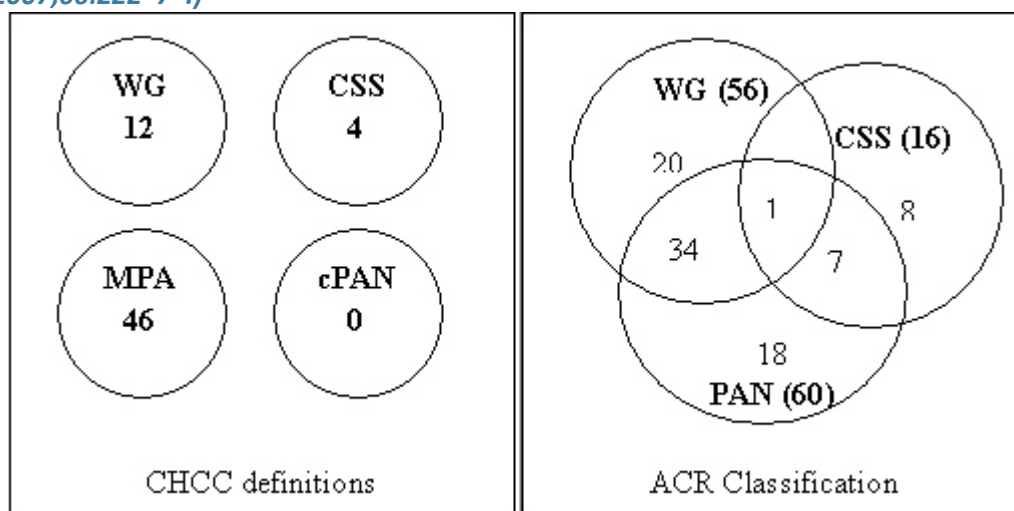
There have been two major attempts at adapting the CHCC definitions for use in classification. Hagen et al used the 1994 CHCC definitions in a study assessing the standardisation of ANCA assays (Hagen et al, 1998). The same methods have been used subsequently in the European trials of immunosuppressive therapy in ANCA-associated vasculitis. Their method accepted that histology was not available for all patients and used surrogate markers for vasculitis. For granulomatosis with polyangiitis (Wegener's) they described four groups: (i) histologically proved vasculitis with granulomata and/or giant cells (with or without nephritis); (ii) clinical evidence of airway involvement and histological evidence of crescentic and/or necrotising glomerulonephritis with few or no immune deposits; (iii) clinical evidence of airways disease, no renal involvement but biopsy evidence of vasculitis in any other organ; and (iv) clinical evidence of airways involvement without histology. Renal limited vasculitis (idiopathic rapidly progressive glomerulonephritis) was considered to be histologically proved crescentic and/or necrotising glomerulonephritis with few or no immune deposits, or histologically proved small-vessel vasculitis. Microscopic polyangiitis was defined in the same way but with evidence of additional extra renal manifestations compatible with vasculitis but no airway manifestations of granulomatosis with polyangiitis (Wegener's). Classic polyarteritis nodosa required proof of arterial vasculitis (angiography or biopsy) and was excluded by the presence of small-vessel vasculitis or crescentic glomerulonephritis. Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) required histological evidence of vasculitis, crescentic glomerulonephritis, granulomata in combination with asthma, and eosinophilia. There was no attempt to validate this scheme and use of ANCA was specifically excluded.

Sorensen et al evaluated the use of the 1994 CHCC definitions with surrogate markers as diagnostic classification criteria in 118 patients with primary and secondary vasculitis (Sorensen et al, 2000). They found the definitions unhelpful for diagnosis but proposed new criteria for the diagnosis of granulomatosis with polyangiitis (Wegener's) and eosinophilic granulomatosis with polyangiitis (Churg–Strauss) based upon histology, surrogate markers of vasculitis and the presence of proteinase 3 (PR3)-ANCA in granulomatosis with polyangiitis (Wegener's).

A study applied the criteria suggested by Sorensen et al to a cohort of patients with primary systemic vasculitides enrolled via a prospective vasculitis register. The criteria suggested for microscopic polyangiitis were not helpful; 50 of 55 patients who fulfilled the ACR classification for granulomatosis with polyangiitis (Wegener's) could also be classified as having microscopic polyangiitis by the Sorensen criteria (Lane et al, 2002). On review of these patients, it was clear that they had been excluded by the Sorensen criteria owing to the presence of eosinophilia. It was therefore suggested that a level of eosinophilia $<1.5 \times 10^9/L$ could be accepted in granulomatosis with polyangiitis (Wegener's).

Another study applied the ACR criteria (for granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg–Strauss) and polyarteritis nodosa) and 1994 CHCC definitions to a cohort of 99 patients from a well-defined population. There was significant overlap between diagnoses (i.e., 34 patients could be classified as having both granulomatosis with polyangiitis (Wegener's) and polyarteritis nodosa, seven eosinophilic granulomatosis with polyangiitis (Churg–Strauss) and polyarteritis nodosa, and one eosinophilic granulomatosis with polyangiitis (Churg–Strauss), granulomatosis with polyangiitis (Wegener's) and polyarteritis nodosa) and 11 patients were unclassifiable (figure 1A). Applying the 1994 CHCC definitions without surrogate markers/ANCA resulted in no overlapping diagnoses, but 37 patients could not be classified (figure 1B) (Lane et al, 2005). Some patients with eosinophilic granulomatosis with polyangiitis (Churg–Strauss) were unclassifiable using both the CHCC definitions and ACR criteria, but were classifiable with the use of additional clinically based but invalidated Lanham criteria (Lanham et al, 1984).

Figure 1 *Overlap diagnosis of vasculitis. Results of the application of the (A) American College of Rheumatology (ACR) (1990) criteria for granulomatosis with polyangiitis (Wegener's) (GPA), Churg–Strauss syndrome (CSS), microscopic polyangiitis (MPA) and cutaneous polyarteritis nodosa (cPAN) and (B) Chapel Hill Consensus Conference (CHCC) definitions for a cohort of 99 patients. (Reproduced from Watts et al, Ann Rheum Dis 2007;66:222–7*.)*



1.5 Other sets of classification criteria

1.5.1 European Medicines Agency classification algorithm

An attempt has been made to reconcile these differences and produce a consensus method for the application of both the ACR scheme and the 1994 CHCC definitions for granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg–Strauss), polyarteritis nodosa and microscopic polyangiitis (Watts et al, 2007*). An algorithm has been developed by consensus (figure 2), which classifies patients into a single category. The algorithm incorporates both ANCA surrogate markers. The algorithm has been validated using paper cases and has been shown to successfully classify patients into a single category.

Later, the algorithm was tested in large cohort of 550 Chinese patients with primary systemic vasculitis, 493 of whom were ANCA positive (Liu et al, 2008). In accordance with the findings reported in the original study (Watts et al, 2007*), the algorithm successfully achieved the aim of classifying the patients into a single category with only 20 (3.6%) patients unclassified. When the algorithm was used, no patients were classified as having polyarteritis nodosa compared with four using the 1994 CHCC definition. Patients with a classification of microscopic polyangiitis by CHCC (n = 363) could be divided into granulomatosis with polyangiitis (Wegener's) (n = 37), microscopic polyangiitis (n = 324) and eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (n = 2). The number of unclassified patients was reduced from 56 to 20. It is important to recognise that the algorithm was developed and validated for epidemiological studies rather than for clinical trials. Its use in the latter setting requires validation.

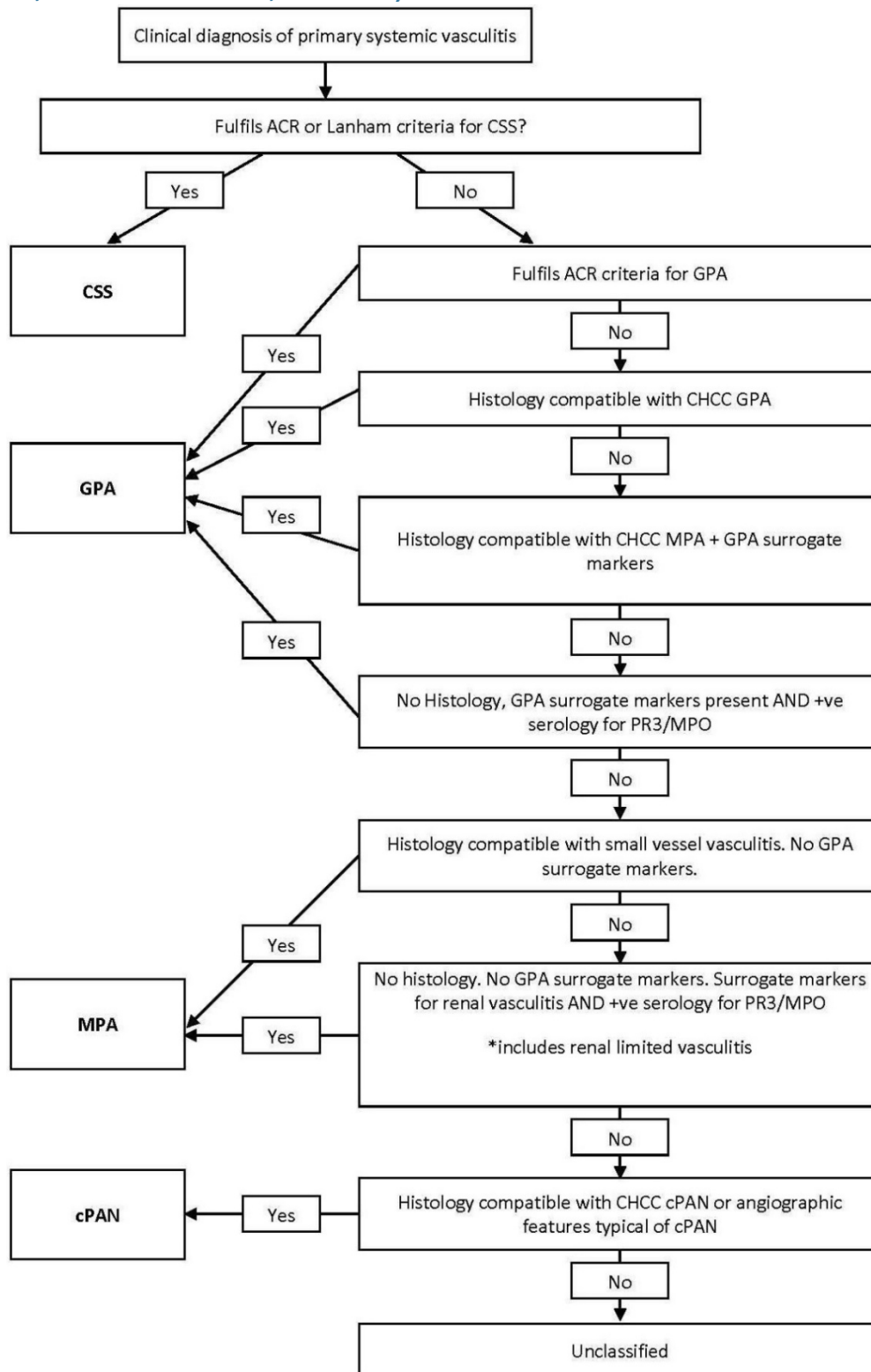
1.5.2 EULAR/PReS working group criteria for childhood vasculitis

A EULAR/Paediatric Rheumatology European Society (PReS) working group has developed classification criteria for childhood vasculitis (Ozen et al, 2010; Ruperto et al, 2010). Childhood vasculitis was classified according to vessel size, with small-vessel diseases subdivided into granulomatous and non-granulomatous. Classification criteria were developed for IgA vasculitis (Henoch–Schönlein), childhood polyarteritis nodosa, granulomatosis with polyangiitis (Wegener's) and Takayasu arteritis. These criteria have been validated (Ozen et al, 2010).

The existing ACR criteria for IgA vasculitis (Henoch–Schönlein) were modified to remove the age criterion, and the presence of IgA deposits on histopathology was highlighted. The presence of palpable purpura was made mandatory, and at least one of abdominal pain, positive histopathology, arthritis/arthralgia and renal involvement had to be present.

The existing ACR criteria for polyarteritis nodosa were felt by consensus to be unsuitable for the classification of childhood polyarteritis nodosa—in particular, because streptococcal infections are often felt to be causative in children. Hepatitis B virus (HBV) infection is not a criterion (as this is rarely a feature in children with improved vaccination protocols). The criteria require the presence of either histopathological evidence of vasculitis or positive angiographic evidence plus one of skin involvement, myalgia, hypertension, neuropathy and renal involvement.

Figure 2 European Medicines Agency algorithm for classification of vasculitis. ACR, American College of Rheumatology; CHCC, Chapel Hill Consensus Conference; CSS, Churg–Strauss syndrome; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PAN, polyarteritis nodosa; PR3, proteinase 3; PSV, primary systemic vasculitis; WG, Wegener's granulomatosis, now known as granulomatosis with polyangiitis. (Reproduced from Watts et al, *Ann Rheum Dis* 2007;66:222–7*.)



The ACR criteria for granulomatosis with polyangiitis (Wegener's) were modified to include two new criteria: (i) the presence of subglottic, tracheal or endobronchial stenosis; and (ii) the presence of high-titre ANCA (PR3 or myeloperoxidase (MPO)) or positive ANCA (cytoplasmic or perinuclear) by indirect immunofluorescence. Microscopic polyangiitis was not classified by the ACR; the EULAR/PreS group adopted the CHCC definition, but added an association with MPO-ANCA to the definition.

EULAR/PreS modified the ACR criteria for Takayasu arteritis by making the presence of angiographic abnormalities mandatory. This can be assessed using conventional contrast angiography, CT or magnetic resonance angiography. Hypertension (age appropriate) was added, as this may be the sole presenting feature of Takayasu arteritis in childhood; the age criterion was removed.

1.5.3 French Vasculitis Study Group criteria for the diagnosis of polyarteritis nodosa

One of the main problems with the ACR criteria is that they do not include microscopic polyangiitis and consequently, the ability to distinguish between polyarteritis nodosa and microscopic polyangiitis is poor.

Henegar et al conducted a study of 949 patients with systemic vasculitis in the French Vasculitis Study Group database with the aim of developing better criteria for polyarteritis nodosa (Henegar et al, 2008). The study included 262 patients with polyarteritis nodosa (108 HBV-associated polyarteritis nodosa), 256 with granulomatosis with polyangiitis (Wegener's), 207 with microscopic polyangiitis, 150 with Churg–Strauss syndrome, 18 with cryoglobulinaemic vasculitis and 56 with other types of vasculitis. Of the original 10 ACR criteria, they retained only three: presence of HBV antigen, arteriographic abnormalities and polyneuropathy. They introduced five negative criteria, including negative indirect immunofluorescence detection of ANCA (table 11). These criteria had 70.6% sensitivity against all vasculitis controls with 92.3% specificity. When compared against microscopic polyangiitis, there was 89.7% sensitivity and 83.1% specificity. These criteria remain to be validated as diagnostic criteria.

Table 11 The French Vasculitis Study Group minimal set of low-redundant polyarteritis nodosa predictive criteria. (Reproduced with permission from Henegar et al, *Arthritis Rheum* 2008;58:1528–38)

Criterion	PAN association	Definition
1. HBV infection	Positive	Markers reflecting active HBV replication, such as the presence of HBeAg in serum and/or the detection of HBV DNA at >105 copies/mL
2. ANCA positivity	Negative	Presence of ANCA in serum, as determined by indirect immunofluorescence
3. Asthma	Negative	Previous history of asthma
4. ENT signs	Negative	Signs of maxillary sinusitis or otitis media
5. Cryoglobulin positivity	Negative	Detection of cryoglobulins in serum
6. Glomerulopathy	Negative	Signs of glomerulopathy, such as proteinuria and/or haematuria with or without renal insufficiency, not due to urinary tract infection, urolithiasis, or haematological or other non-glomerular causes
7. Arteriographic abnormalities	Positive	Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia and other non-inflammatory causes
8. Mono-/polyneuropathy	Positive	Development of polyneuropathy, multiple mononeuropathies or polyneuropathy

ANCA, antineutrophil cytoplasmic antibodies; ENT, ear, nose and throat; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; PAN, polyarteritis nodosa.

1.5.4 Lanham criteria for eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

The invalidated ‘Lanham’ criteria for eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (box 1) are sometimes used for classification purposes in combination with the ACR classification criteria and the CHCC definition (Churg–Strauss).

Box 1 Lanham criteria for Churg–Strauss syndrome

1. Asthma
 2. Peripheral blood eosinophilia $>1.5 \times 10^9/L$
 3. Systemic vasculitis involving two or more extrapulmonary organs.
- All three items are required; biopsy evidence of granuloma is not required.

*Reproduced with permission from Lanham et al, *Medicine (Baltimore)* 1984;63:65–81.*

1.5.5 International Study Group criteria for Behçet’s disease

Behçet’s disease is a rare chronic inflammatory multisystem disorder characterised by recurrent oral and genital ulcers and skin, articular, eye, vascular or central nervous system disease. Various classification systems have been developed for Behçet’s disease. The International Study Group criteria (table 12), which were published as diagnostic criteria, are the most frequently employed classification system for Behçet’s disease. A large international effort undertaken to revise these criteria, named ‘International criteria for Behçet’s

disease', was recently published. These criteria added neurological and vascular involvement as classifying criteria and included a new item weighting system (table 13).

Table 12 International Study Group diagnostic criteria for Behçet's disease. (Reproduced with permission from International Study Group for Behçet's disease, Lancet 1990;335:1078–80)

Criterion	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous or herpetiform ulceration seen by physician or patient, which recurred at least three times in one 12-month period
Plus two of:	
1. Recurrent genital ulceration	Aphthous ulceration or scarring seen by the physician or patient
2. Eye lesions	Anterior uveitis, posterior uveitis or cells in vitreous on slit-lamp examination; or: retinal vasculitis seen by ophthalmologist
3. Skin lesions	Erythema nodosum seen by physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules seen by physician in post adolescent patients not receiving glucocorticoid treatment
4. Positive pathergy test	Read by physician at 24–48 h

For the diagnosis to be made, a patient must have recurrent oral ulceration plus at least two of the other findings in the absence of other clinical explanations (sensitivity: 91%, specificity: 96%).

Table 13 International criteria for Behçet's disease. (Reproduced from International Team for the Revision of the International Criteria for Behçet's Disease, J Eur Acad Dermatol Venereol. 2014;28:338-47)

Sign/symptom	Point
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test*	1*

**Pathergy test is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted one extra point may be assigned for a positive result.*

A patient scoring ≥ 4 points is classified as having Behçet's disease (sensitivity: 93.9%, specificity: 92.1%)

1.5.6 American Heart Association diagnostic criteria for Kawasaki disease

Kawasaki disease is an acute febrile mucocutaneous and lymph node illness affecting children aged <5 years, mainly of Asian descent. The most widely used criteria for Kawasaki disease are those established by the American Heart Association (box 2). These criteria were labelled as being diagnostic criteria.

Box 2 American Heart Association diagnostic criteria for Kawasaki disease

Fever of at least 5 days' duration

Presence of four of the following principal features:

1. Changes in extremities
2. Polymorphous exanthema
3. Bilateral conjunctival injection
4. Changes in the lips and oral cavity
5. Cervical lymphadenopathy

Patients with fever and fewer than four principal clinical features can be diagnosed as having Kawasaki disease when coronary artery disease is detected by two-dimensional echocardiography or coronary angiography.

Exclusion of other diseases with similar findings, including measles, scarlet fever, drug reactions, Stevens–Johnson syndrome, other febrile viral exanthemas, Rocky Mountain spotted fever, Staphylococcal scalded skin syndrome, toxic shock syndrome, juvenile rheumatoid arthritis, leptospirosis, mercury poisoning.

Source: Dajani et al, *Circulation* 1993;87:1776–80.

1.6 Perspectives

There is still, however, a need for new validated classification and diagnostic criteria for granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and polyarteritis nodosa. New criteria for IgA vasculitis (Henoch–Schönlein) and cutaneous leukocytoclastic angiitis are also required because of the low specificity of the existing ACR criteria. The criteria for giant-cell arteritis and Takayasu arteritis have high specificity and sensitivity and are generally accepted. A research agenda has been developed and a major international effort, the Diagnostic and Classification criteria in Vasculitis Study (DCVAS), is underway to develop new classification and diagnostic criteria (Basu et al, 2010; Luqmani et al, 2011; Watts et al, 2011). 2017 provisional classification criteria for granulomatosis with polyangiitis (Wegener's) have been presented at the 2016 annual meeting of the American College of Rheumatology.

2 Secondary vasculitis and vasculitis mimics

A heterogeneous group of diseases may mimic systemic vasculitis and if treated as such, lead to unnecessary morbidity. The key conditions discussed include infection-related vasculitis, especially vasculitis related to hepatitis B and C. Other conditions include cholesterol embolism, infective endocarditis, atrial myxoma and fibromuscular dysplasia.

Vasculitis occurring in association with rheumatoid arthritis is described in chapter 9 and the in-depth online discussion.

Vasculitis may be idiopathic (e.g., granulomatosis with polyangiitis (Wegener's)), occur in the setting of established rheumatic disease or malignancy, or be triggered by other exogenous stimuli such as drugs and infection. There are also a number of conditions that can mimic vasculitis.

2.1 Infection and vasculitis

The notion that infection could trigger vasculitis was first suggested over 100 years ago. A wide variety of organisms have been implicated (table 14). Possible mechanisms for infection-related vasculitis include: (i) direct microbial toxicity either by endothelial invasion (e.g., *Rickettsia*, *Bartonella* or cytomegalovirus) or the effect of microbial toxins on endothelium; and (ii) an immune-mediated process by either humoral (immune complex, e.g., hepatitis C and cryoglobulinaemia) or cellular responses (Somer and Finegold, 1995). Infection may also be a consequence of intensive immunosuppression for primary vasculitis.

Table 14 Infection and vasculitis

Vessel involved		Infection
Large arteries	Bacterial	<i>Staphylococcus</i> , <i>Salmonella</i> , mycobacteria, <i>Streptococcus</i>
	Spirochaetal	<i>Treponema pallidum</i>
	Fungal	Coccidiomycosis
Medium arteries	Bacterial	Group A streptococcus, mycobacteria
	Viral	HBV, HCV, HIV, parvovirus B19
Small vessels and medium arteries	Bacterial	<i>Streptococcus</i>
	Viral	HBV, HCV, HIV, CMV
Small vessel (leukocytoclastic)	Bacterial	<i>Staphylococcus</i> , <i>Salmonella</i> , mycobacteria, <i>Streptococcus</i> , <i>Yersinia</i> , <i>Neisseria</i> , <i>Rickettsiae</i>
	Viral	HIV, CMV, herpes zoster, parvovirus B19, HBV, HCV

CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

2.1.1 Viral infections

Viral infection may be followed by several different outcomes: (i) viral clearance; (ii) latency with periodic reactivation—for example, herpes zoster; or (iii) persistent viral replication with stable or progressive course—for example, hepatitis B and C.

HBV infection has been firmly associated with polyarteritis nodosa for 40 years (Trepo and Thivolet, 1970). In areas endemic for HBV infection, up to 95% of polyarteritis nodosa cases are associated with HBV infection, with an incidence of 77 per million population (McMahon et al, 1989).

In France, falling HBV infection rates have been correlated with a decrease in HBV-associated polyarteritis nodosa. In the 1970s, 38% of cases of polyarteritis nodosa were HBV-related compared with 17% in 2000 (Guillevin et al, 2005*). This reduction is attributable to the introduction of HBV vaccination and screening of blood donations. The commonest cause is now injecting drug use. In the Alaskan population with HBV-associated polyarteritis nodosa, D is the most common HBV genotype (Hurlburt et al, 2007). The clinical characteristics of HBV-associated polyarteritis nodosa are similar to those seen in non-HBV-associated classic polyarteritis nodosa apart from more frequent gastrointestinal involvement, extraglomerular renovascular disease with malignant hypertension and orchitis in HBV-associated polyarteritis nodosa. The most common

features are mononeuritis multiplex (83.5%), gastrointestinal (57%), renal tract (38%), skin (31%) and hypertension (31%). HBV-associated polyarteritis nodosa usually develops within 12 months of infection; hepatitis is mild before the development of polyarteritis nodosa. Angiography shows the typical microaneurysms and/or stenosis in the coeliac axis and renal vasculature. ANCA are not associated with HBV-associated polyarteritis nodosa.

HBV-associated polyarteritis nodosa should be identified, as treatment with antiviral drugs is effective. Excellent initial results were achieved using a combination of antiviral agents (vidarabine or interferon α -2a) (table 15). The preferred protocol is lamivudine (100 mg/day) combined with plasma exchange to remove immune complexes (de Menthon and Marr, 2011). This is accompanied by a short course of glucocorticoids. The outcome for patients treated with this approach is excellent and only 6% relapse. Seroconversion from hepatitis B e antigen to hepatitis B e antibody is usually achieved and is associated with a decreased risk of relapse. Gastrointestinal involvement is associated with reduced survival. The 10-year survival is around 60% (Guillevin et al, 2005*; Pagnoux et al, 2006*).

Table 15 Major viruses associated with vasculitis and their treatment

Virus	Type of vasculitis	Standard treatment
HBV	PAN	Short GC, PE, lamivudine
HCV	Cryoglobulinaemic vasculitis	Short GC, antiviral therapy (DAAs or IFN α and ribavirin) \pm PE
HIV	PAN large/medium/small vessel vasculitis cerebral vasculitis	Short GC with ARV \pm PE
Parvovirus B19	PAN	GC
	HSP-like	GC and/or IVIg
Varicella zoster	Retinitis meningoencephalomyelitis	Acyclovir \pm GC
CMV	Retinitis	Valganciclovir, ganciclovir or foscarnet
	Colitis PAN	

ARV, antiretroviral drugs; CMV, cytomegalovirus; DAAs, direct-acting antiviral agents; GC, glucocorticoid; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSP, Henoch–Schönlein purpura; IFN α , interferon α ; IVIg, intravenous immunoglobulin; PAN, polyarteritis nodosa; PE, plasma exchange.

Hepatitis C virus (HCV) was first identified in 1989. There is a strong association between HCV infection and essential mixed cryoglobulinaemia, with 80–90% of such patients positive for anti-HCV antibodies (Agnello et al, 1992). Type II cryoglobulins with a monoclonal IgM- κ is most typically associated with cryoglobulinaemic vasculitis. Circulating HCV RNA has been identified in the peripheral blood of patients with cryoglobulinaemia. HCV has been identified within cutaneous vasculitic lesions and has been selectively concentrated together with its specific antibody in cryoprecipitates.

The most common clinical feature of HCV-associated cryoglobulinaemic vasculitis is purpura, and less often urticaria, livedo, exanthema, acral necrosis, leg ulcers, arthralgias, arthritis, muscle weakness and

polyneuropathy (typically subacute, distal, symmetrical or asymmetrical, motor and/or sensory polyneuropathy, or acute mononeuritis multiplex). The majority of patients have hypocomplementaemia (90%) and circulating rheumatoid factor (70%) (Landau et al, 2008); they are ANCA negative.

Hypocomplementaemia is a useful feature to distinguish HCV-associated disease from ANCA-associated systemic vasculitis. HCV infection has also been associated with a polyarteritis nodosa-type vasculitis with involvement of medium-sized arteries and a necrotising vasculitis (Saadoun et al, 2007). Renal disease is common and is distinguishable from ANCA-associated vasculitis. The characteristic lesion is membranoproliferative glomerulonephritis with intracapillary thrombi, which contain cryoglobulin precipitates.

Severe or life-threatening disease should be treated with steroids and cyclophosphamide with or without plasma exchange (table 15), while awaiting the slower response to antiviral agents. Less severe disease (arthralgias, purpura, sensory neuropathy) is treated with antiviral agents combined with short course of glucocorticoids (Pagnoux et al, 2006*). Pegylated IFN α and ribavirin are effective. Ribavirin alone cannot suppress viral replication. Antiviral therapy options have been recently expanded with the introduction of direct-acting antiviral agents (DAAs). These new drugs are providing the opportunity for a dramatic change in the anti-HCV therapeutic approach, eradicating HCV with shorter therapy duration, minimal side-effects and efficacy approaching 100%. Limited, but essentially concordant data suggest that IFN-free antiviral therapies with DAAs are safe, generally well tolerated and effective in patients with HCV-associated cryoglobulinaemic vasculitis (Zignego et al, 2017). Anti-CD20 therapy may have a useful role in selected cases (Saadoun et al, 2008a; Saadoun et al, 2008b).

The introduction of the highly effective DAAs may improve the prognosis of HCV-related vasculitis, that is not as good as for HBV-associated polyarteritis nodosa, with deaths due to infection or renal disease (Landau et al, 2010).

Human immunodeficiency virus (HIV) infection has been associated with a wide variety of autoimmune and inflammatory vascular conditions. Vasculitis may either be directly related to HIV infection or be a consequence of secondary opportunistic infection, particularly with cytomegalovirus or tuberculosis (Chetty, 2001). Vasculitis is a rare manifestation of HIV infection (Guillevin, 2008) and can occur at any stage of the infection. A number of patterns of vasculitis have been described, including polyarteritis nodosa-like, hypersensitivity vasculitis and large-vessel disease (Guillevin, 2008). No clear treatment strategy has been developed. Glucocorticoids remain the mainstay of treatment for HIV vasculitis. Conventional immunosuppressant drugs should be avoided where possible as they may allow the development of opportunistic infection, especially if the CD4 T cell count is $<200 \times 10^6/L$ (Guillevin, 2008). Thus most regimens advocate suppression of HIV replication with combination antiviral therapy, possibly with adjunctive plasma exchange (Pagnoux et al, 2006*).

Parvovirus B19 infection, especially during the viraemic phase, has been associated with a small-vessel vasculitis that may mimic IgA vasculitis (Henoch–Schönlein). Parvovirus infection can be detected by serological tests. Most patients recover spontaneously, but for severe episodes glucocorticoids may be required.

Varicella zoster infection may result in an acute vasculitis affecting the central nervous system (CNS), retinal and/or thyroidal small vessels and, rarely, the skin and kidney. Encephalitis or myelitis may be seen in immunocompromised patients. Cerebral angiography may show an arteritis. Virus may be detected in cerebrospinal fluid or meningeal biopsy by polymerase chain reaction. Treatment is with acyclovir.

Cytomegalovirus (CMV)-associated vasculitis usually occurs in severely immunocompromised patients with HIV or after a bone marrow transplant. CMV seems to directly infect endothelial cells. Commonly affected organs include the gut, CNS and skin. Typical CMV inclusions can be seen in endothelial cells, suggesting a direct effect on small vessels. CMV vasculitis is life threatening and requires intravenous ganciclovir or foscarnet.

2.1.2 Bacterial infections

Direct endothelial invasion by pyogenic organisms (e.g., *Staphylococcus* and *Streptococcus*) is a well-recognised cause of vasculitis. The spectrum of bacteria associated with vasculitis has changed over the past three decades with more unusual infections being reported—for example, *Mycobacterium fortuitum*, *Enterobacteriaceae* and *Salmonella*. Blood cultures are often positive and the responsible organism can be identified in more than 50% of cases (Pagnoux et al, 2006*). Skin biopsy of affected skin may yield micro-organisms. There is a predisposing condition in around 60% of cases, of which the most common is diabetes mellitus. Infection often occurs at the site of previous damage by atherosclerosis or surgery.

The vascular response to direct infection depends on the organism and site of infection. In large arteries, infection leads to an erosive arteritis with mycotic aneurysm formation. Aortitis is an uncommon manifestation of *Streptococcus pneumoniae* infection. *Salmonella* aortitis is well recognised and usually presents with fever together with abdominal and back pain. The site most frequently affected is the abdominal aorta followed by the thoracic aorta. Predisposing conditions include injecting drug use, hypertension, diabetes mellitus and myelodysplastic syndrome (Soravia-Dunand et al, 1999). Treatment is with intravenous antibiotics combined with surgery.

Direct bacterial infection of small arteries and arterioles causes a necrotising vasculitis or thrombosis. *Neisseria gonorrhoea*, *Neisseria meningitidis* and *Streptobacillus moniliformis*, for example, may directly infect vascular endothelium causing maculopapular or purpuric skin lesions. Biopsies of early lesions show a small-vessel vasculitis with mononuclear cells, neutrophils, leukocytoclastic and necrosis. The organisms can be cultured from an aspirate of the lesions.

2.1.3 *Mycobacterial infections*

Vessels of any size can be affected by tuberculous infection, with veins more often involved than arteries (Somer and Finegold, 1995). The typical clinical lesion is erythema nodosum. Tuberculous vasculitis of large and small vessels manifests as a granulomatous pan arteritis or thrombophlebitis. Acid-fast bacilli may be found in, or adjacent to, the vessel wall.

Distribution of the vascular lesions of *Mycobacterium leprae* infection is focal and involves arteries and veins with equal frequency. The most common site is small vessels—for example, erythema nodosum leprosum, or the vasa vasorum of large vessels. The clinical consequences of vasculitis are rarely significant.

2.1.4 *Spirochaetal infection*

Treponema pallidum is a well-recognised cause of aortitis, with aneurysm formation and the development of aortic incompetence. These lesions are now rare since the introduction of penicillin, but have begun to reappear because of the spread of HIV infection. The primary histological changes are in the vasa vasorum with endarteritis and perivascular infiltration with lymphocytes and plasma cells. Infection occurs early in the disease and organisms lie dormant in the aortic wall. Spirochetes can, however, only rarely be detected in tissue. Symptomatic aortic disease occurs as a feature of tertiary syphilis, about 10–30 years after the initial infection. Diagnosis is based on the radiographic appearance and serological tests.

2.1.5 *Rickettsial infection*

Vascular lesions are a prominent feature of some rickettsial infections, particularly Rocky Mountain spotted fever, epidemic typhus and scrub typhus. In humans, the organism (an obligate intracellular bacterium) is usually found in vascular endothelium and in some cases, vascular smooth muscle. The pathology of the vascular lesion in *Rickettsia rickettsii* (Rocky Mountain spotted fever) follows a characteristic pattern. In the early stages, endothelial cell swelling is seen in association with intracellular rickettsiae. Later vasculitis with increased vascular permeability, haemorrhage and, occasionally, thrombosis occurs with immunoglobulin and complement deposition. Vasculitis most typically presents with an extensive maculopapular rash in Rocky Mountain spotted fever that can, if not treated, result in involvement of the kidney, lung and brain. The diagnosis is based on clinical features with subsequent serological confirmation.

2.1.6 *Fungal infections*

Fungal infections may cause vasculitis by direct spread into the vessel wall with formation of a mycotic aneurysm. This usually occurs in patients who are already severely immunocompromised from other diseases. Fungi such as *Coccidioides immitis* may also cause a local CNS vasculitis, presenting acutely with stroke-like lesions; these patients have a high mortality and require aggressive antifungal treatment.

2.2 Vasculitis and malignancy

2.2.1 Malignancies associated with concurrent or subsequent development of vasculitis

Acute vasculitis may be the presenting feature of an undiagnosed malignancy. Most types of malignancy have been associated with vasculitis (table 16). However, a review of 2800 patients with vasculitis and 69 000 patients with cancer identified only 69 patients with both vasculitis and malignancy (Hutson and Hoffman, 2000). There were 12 patients in whom the cancer and vasculitis occurred within 12 months. Six patients had solid organ tumours, four lymphoma, one leukaemia and one multiple myeloma. The most common type of vasculitis was cutaneous leukocytoclastic angiitis ($n = 7$), followed by giant-cell arteritis ($n = 2$), polyarteritis nodosa ($n = 2$) and granulomatosis with polyangiitis (Wegener's) ($n = 1$).

Table 16 Vasculitis and malignancy

Malignancies associated with subsequent development of vasculitis	Vasculitis types associated with malignancy	Malignancy developing in patients with a diagnosis of primary systemic vasculitis
Myelodysplasia	Granulomatosis with polyangiitis (Wegener's)	Renal cell carcinoma
Lymphoma	Polyarteritis nodosa	Colon adenocarcinoma
Hairy cell leukaemia	Microscopic polyangiitis	Skin
Myeloma	Henoch–Schönlein purpura	Leukaemia
	Cutaneous leukocytoclastic vasculitis	Lymphoma
		Bladder carcinoma*

*Associated with cyclophosphamide treatment.

Several epidemiological studies have examined the occurrence of malignancy in patients with granulomatosis with polyangiitis (Wegener's). A malignancy was found in 23/477 patients with granulomatosis with polyangiitis (Wegener's) compared with 18/479 patients with rheumatoid arthritis (Tatsis et al, 1999). Seven patients with renal cell carcinoma were found in the granulomatosis with polyangiitis (Wegener's) group and only one in the rheumatoid arthritis group. Among those, simultaneous occurrence of cancer was found in 14 of the 23 patients with granulomatosis with polyangiitis (Wegener's) (in 5/7 patients with renal carcinoma) and only one of the 18 patients with rheumatoid arthritis. The prevalence of other cancers was not different from that of the control population.

In the UK, a retrospective study compared 200 patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis with 129 patients with IgA vasculitis (Henoch–Schönlein), 333 patients with systemic lupus erythematosus and a normal control population (Pankhurst et al, 2004). The patients with granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and IgA vasculitis (Henoch–Schönlein) all had a focal segmental necrotising glomerulonephritis or vasculitis with associated IgA. The rate of malignancy in all patients was increased compared with that of the normal control population (relative risk

(RR) 7.5; 95% CI 5.0 to 11.4); this increased risk was present for both groups with ANCA-associated vasculitis (RR = 6.0; 3.7 to 9.7) and IgA vasculitis (Henoch–Schönlein) (RR = 5.3; 2.4 to 11.5). The most common malignancy was colon cancer (IgA vasculitis (Henoch–Schönlein): two patients, microscopic polyangiitis: three patients). This confirmed the association of ANCA-associated vasculitis with solid malignancies but could not confirm the association with renal cancer.

Conversely, one Danish study did not demonstrate an increased rate of cancer before the onset of granulomatosis with polyangiitis (Wegener's) (Faurschou et al, 2009).

IgA vasculitis (Henoch–Schönlein) has been associated with malignancy, but the risk is not greater than for other types of vasculitis or autoimmune disease (Pertuiset et al, 2000). The association appears to be with solid tumours rather than haematological malignancies. Pertuiset et al compared patients with IgA vasculitis (Henoch–Schönlein) with and without malignancy; those with malignancy were more likely to be older, male, have more joint involvement and fewer preceding infections (Pertuiset et al, 2000). It is worth noting that IgA vasculitis (Henoch–Schönlein) is characteristically a disease of younger people and therefore if it presents in the elderly, a coexisting malignancy should be considered.

A case–control study showed that patients with giant-cell arteritis have fewer cancers before diagnosis than controls and no increased risk after diagnosis (Kermani et al, 2010a; Kermani et al, 2010b).

Vasculitis associated with lymphoproliferative disorders is usually localised to the skin. In a series of 172 adults with cutaneous vasculitis, only four (2.3%) were associated with malignancy. All four malignancies were haematological (Blanco et al, 1998). Hamidou et al analysed the frequency of ANCA and vasculitis in a prospective cohort study of 60 patients with myelodysplastic syndromes and 140 patients with lymphoid malignancies (Hamidou et al, 2000). Among the 60 patients with myelodysplasia, six had ANCA-negative systemic vasculitis, one ANCA-positive systemic vasculitis, one giant-cell arteritis and one relapsing polychondritis. Of the 140 patients with lymphoid malignancies, two had ANCA-negative systemic vasculitis, two had leukocytoclastic vasculitis in association with tuberculous infection, and one giant-cell arteritis. There was no association with hepatitis B or C infection.

Hairy cell leukaemia is a rare lymphoproliferative disease characterised by the presence of mononuclear cells with hair-like cytoplasmic projections in peripheral blood, bone marrow, spleen and liver. Hairy cell leukaemia has been strongly associated with systemic necrotising vasculitis, especially polyarteritis nodosa and cutaneous leukocytoclastic angiitis (Hasler et al, 1995*). Direct infiltration of vessel walls by hairy cells has been seen in some cases. In most cases, the leukaemia is diagnosed first and the interval between the two diagnoses may be several years. The vasculitis is not usually the cause of death, which is the result of complications of leukaemia and its treatment. Bayer-Garner and Smoller reviewed 2357 cases of multiple myeloma and

identified eight patients with leukocytoclastic vasculitis. There was a preponderance of IgG myeloma, which paralleled the immunoglobulin secretion (Bayer-Garner and Smoller, 2003).

In conclusion, vasculitis may be the presenting feature of malignancy, but this is uncommon. The strongest link is between cutaneous vasculitis and haematological malignancy.

2.2.2 Malignancy developing in patients with a diagnosis of primary systemic vasculitis

A much more common situation is the development of malignancy in patients receiving immunosuppressive therapy for an established diagnosis of vasculitis (table 16). Importantly, these occurrences do not fall into the category of secondary, malignancy-associated vasculitides but rather reflect the carcinogenicity of immunosuppressive therapy. Other pathogenic mechanisms, such as chronic immune stimulation or loss of control of emerging cancer clones owing to iatrogenic immunodeficiency, may also play a role in the development of cancers in treated patients with vasculitis.

The treatment of vasculitis with cyclophosphamide has long been associated with the development of bladder cancer, with up to a 31-fold increase in patients with granulomatosis with polyangiitis (Wegener's) receiving long-term cyclophosphamide therapy (Talar-Williams et al, 1996; Knight et al, 2004*). The risk is associated with total dose exposure and whether uro-epithelial protective agents such as mesna were used (Monach et al, 2010). Lymphoma, squamous cell skin cancer and leukaemias may also be consequences of immunosuppressive therapy. Westman et al, in a study from Sweden of patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis and renal involvement, reported a fivefold increase in the risk of bladder cancer, which again was associated with cyclophosphamide therapy (Westman et al, 1998). Recent data from the French Vasculitis Study Group registry suggest that intermittently administered intravenous cyclophosphamide treatment has a much lower risk of urinary tract cancer than daily oral cyclophosphamide (Le Guenno et al, 2011).

In another study from Sweden, Knight et al described a population-based cohort of 1065 patients with granulomatosis with polyangiitis (Wegener's) from an inpatient registry and, through linkage to the Swedish Cancer Register, identified those in the cohort developing cancer (Knight et al, 2002). The cohort had a twofold increase in cancer overall, with a standardised incidence ratio (SIR) = 4.8 for bladder cancer, SIR = 7.3 for squamous cell carcinoma of the skin, SIR = 5.7 for leukaemia and SIR = 4.2 for lymphoma. There was no increased risk for other solid malignancies. A Danish study observed significantly increased rates of acute myeloid leukaemia, bladder cancer and non-melanoma skin cancers. Leukaemias and bladder cancers developed 6.9–18.5 years after cyclophosphamide therapy was started. The highest risk for leukaemia and bladder cancer was in patients who had received >36 g of cyclophosphamide (Faurschou et al, 2008).

Further insight into the incidence of malignancies among patients treated for granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis was provided based on long-term follow-up data of newly diagnosed cases enrolled in European clinical trials since 1995. This study suggested a 1.6-fold higher incidence of cancer at any sites among the patients with vasculitis compared with the general population data. Non-melanoma skin cancer was the only cancer type with a significantly increased incidence. These findings suggested that cancer risk might have decreased as a consequence of the modern trend towards using shorter courses of cyclophosphamide (Heijl et al, 2011*).

In the Wegener's Granulomatosis Etanercept Trial study of etanercept versus placebo plus conventional immunosuppression for granulomatosis with polyangiitis (Wegener's), an increased frequency of solid malignancies was found in the etanercept-treated group; whether this was a result of the combination of etanercept with previous cyclophosphamide exposure was hypothesised but uncertain (Stone et al, 2006). The malignancies seen in this study included colonic cancer, cholangiocarcinoma, breast carcinoma and renal cell carcinoma. Pertinently, an analysis of post-trial follow-up data confirmed the increased cancer incidence among these patients with granulomatosis with polyangiitis (Wegener's) as compared with the general population. However, this increased risk was not different between the etanercept and placebo groups (Silva et al, 2011).

2.2.3 Vasculitis mimicking malignancy

Vasculitis may also mimic malignancy. A large mass of inflammatory tissue associated with constitutional symptoms may be misdiagnosed as a malignancy. Differentiation between lymphoma and granulomatosis with polyangiitis (Wegener's) of the upper airways can be particularly difficult.

2.3 Drug-induced vasculitis

Drug-induced vasculitis is probably one of the commoner causes of vasculitis. A very wide range of drugs together with vaccines and desensitisation procedures have been reported as causing a vasculitic reaction; however, many of these are isolated case reports and it is not possible to conclusively prove a causal relationship. Recently more definite associations have been described—in particular, with propylthiouracil, hydralazine and leukotriene antagonists. A number of recreational drugs have also been reported to cause vasculitis, including heroin, cocaine and methamphetamine, and have been particularly associated with cerebral vasculitis. More recently, levamisole-contaminated cocaine has been reported as causing a multisystem vasculitis mimicking GPA. The majority of patients develop an isolated small-vessel vasculitis; medium-vessel involvement occurs uncommonly and large-vessel involvement is rare. The pathogenesis is generally thought to be the result of specific pathogenic mechanisms, immune complex formation, hypocomplementaemia and cell-mediated mechanisms with T cell activation.

The clinical and pathological presentation of drug-induced vasculitis is indistinguishable from that of other types of small-vessel vasculitis. The most common skin lesion is purpura, which may be palpable. The rash is symmetrical and often affects the extremities. The lesions are the same age and disappear within several weeks of drug withdrawal. They may scar or cause haemosiderosis. The most common histological appearance is a leukocytoclastic vasculitis. Other laboratory findings are non-specific with leucocytosis, hypocomplementaemia and raised acute phase response. An eosinophilia is suggestive of a drug aetiology but is also a typical feature of Churg–Strauss syndrome. ANCA may be present and they sometimes reflect systemic involvement.

Vasculitis associated with ANCA has been attributed to a number of drugs, including hydralazine and propylthiouracil, and is especially associated with anti-MPO specificity (Choi et al, 2000*; Gao et al, 2008). Choi et al reviewed 250 patients with MPO-positive systemic vasculitis and detected hydralazine, propylthiouracil, allopurinol, penicillamine or sulfasalazine use in 18 cases within 9 months before the onset of disease (Choi et al, 2000*).

Leukotriene receptor antagonists including zafirlukast, montelukast and pranlukast have been linked to the onset of eosinophilic granulomatosis with polyangiitis (Churg–Strauss). Wechsler et al described 12 patients with steroid-dependent asthma who developed eosinophilic granulomatosis with polyangiitis (Churg–Strauss) after withdrawal of steroids permitted by zafirlukast or montelukast (Wechsler et al, 2000). All the patients fulfilled criteria for eosinophilic granulomatosis with polyangiitis (Churg–Strauss). There has subsequently been some debate as to whether the introduction of leukotriene inhibitors in patients with asthma precipitates eosinophilic granulomatosis with polyangiitis (Churg–Strauss) de novo, or whether these drugs given for difficult-to-control or progressive asthma permit a reduction in steroids and therefore unmask previously undiagnosed eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (Nathani et al, 2008), or whether use of these drugs simply reflects the commonly severe asthma preceding this vasculitis requiring the prescription of multiple anti-asthma agents. The incidence rate for eosinophilic granulomatosis with polyangiitis (Churg–Strauss) was found to be similar for both zafirlukast and montelukast users (60/million patient-years), and also similar to that found in an asthmatic population not treated with leukotriene inhibitors (Loughlin et al, 2002). In contrast, findings from two case–control studies confirmed an association between antileukotrienes use and the development of eosinophilic granulomatosis with polyangiitis (Churg–Strauss), but comparable relationships were also identified for other drugs used to treat asthma—for example, inhaled long-acting β agonists or oral glucocorticoids (Harrold et al, 2007; Hauser et al, 2008*). These findings support the suggestion that antileukotrienes are merely a marker of the severity and gradual worsening of the asthma preceding eosinophilic granulomatosis with polyangiitis (Churg–Strauss) onset, rather than a real culprit in the disease. The same explanation may hold true for the very similar story which emerged after the introduction of monoclonal anti-IgE antibody (omalizumab) for the treatment of asthma, with case reports of eosinophilic

granulomatosis with polyangiitis (Churg–Strauss) developing after treatment with omalizumab for asthma (Wechsler et al, 2009).

The treatment of drug-induced hypersensitivity is unclear. Most cases respond simply to withdrawal of the inducing drug. Reported cases tend to reflect the severe end of the spectrum and reported treatments include glucocorticoids, plasmapheresis and cyclophosphamide.

2.4 Vaccination

Vaccine-induced vasculitis has been rarely described after some antiviral vaccines. Vasculitis occurring after recombinant HBV vaccination has been reported in 13 cases. Initial clinical features developed within 6–7 weeks of vaccination. Affected organs were most typically the skin, joints, retina and muscle; renal involvement was not seen. However, a large review concluded that there was no strong supportive evidence to support such a causal link (Begier et al, 2004). Vaccine-induced vasculitis, in particular eosinophilic granulomatosis with polyangiitis (Churg–Strauss), has been noted after tetanus, influenza, hepatitis B, rubella and smallpox vaccination (Guillevin et al, 1999). A detailed review of the occurrence of autoimmune reaction to commonly administered vaccines concluded that there was no association (Schattner, 2005).

2.5 Vasculitis secondary to inflammatory rheumatic disease

2.5.1 Rheumatoid vasculitis

Rheumatoid vasculitis is dealt with in chapter 9 on rheumatoid arthritis.

2.5.2 Spondyloarthropathies

Aortitis may complicate the seronegative spondyloarthropathies—in particular, ankylosing spondylitis and Reiter’s syndrome. The aortic ring and ascending aorta are the typical sites of involvement but distal aortitis has been described. Rarely, aortic incompetence occurs early in the disease, but does so with increasing frequency with disease duration, perhaps in up to 10% of cases at 30 years.

Echocardiography shows thickening of the aortic leaflets, subaortic echo-dense bumps and aortic root densities. Histologically, there is thickening of the aortic valve cusps and aorta, together with lymphocytic infiltration in the aortic wall and fibrosis of the aortic root (Townend et al, 1991).

Treatment of the inflammatory process with immunosuppressive agents has been suggested, but there are no relevant controlled data—in particular, on the need or not for aortic valve replacement.

2.5.3 Other connective tissue diseases

Vascular involvement in systemic lupus erythematosus, Sjögren's syndrome and the antiphospholipid antibody syndrome is described in chapters 20, 25 and 22, respectively.

2.6 Vasculitis mimics

Systemic vasculitis presents with numerous widespread manifestations and diagnosis is based on a combination of clinical, laboratory and histopathological features. The clinical features alone are not always diagnostic and a variety of other diseases can masquerade as systemic vasculitis (table 17). These mimics usually present with multiorgan illness or evidence of vascular damage, or a combination of both. Biopsy of involved organs is, therefore, important to identify non-inflammatory vascular changes such as embolism or thrombosis. Angiographic features including aneurysms, although typical of polyarteritis nodosa, can occur in other conditions such as myxoma and bacterial endocarditis.

Table 17 Vasculitis masquerades

Mimicking:	Clinical signs
1. Systemic multisystem disease	
Infection	Subacute bacterial endocarditis
	Neisseria
	Rickettsiae
Malignancy	Metastatic carcinoma
	Paraneoplastic
Other	Sweet's syndrome
	Scurvy
2. Occlusive vasculopathy	
Embolic	Cholesterol crystals
	Atrial myxoma
	Infection
Thrombotic	Antiphospholipid syndrome
	Procoagulant states
	Calciphylaxis
Others	Ergot
	Radiation
	Degos
	Severe Raynaud's syndrome
	Acute digital loss
3. Angiographic	
Aneurysmal	Fibromuscular dysplasia
	Neurofibromatosis
Occlusion	Coarctation

2.6.1 Cholesterol crystal embolism

Cholesterol crystal embolism has been recognised for more than a century but remains underdiagnosed. Risk factors for cholesterol embolism are male sex, age >60 years, white race, hypertension, tobacco use, diabetes

mellitus, anticoagulation therapy with either heparin or warfarin, and thrombolysis (Scolari et al, 2000; Meyrier, 2006). Cholesterol embolism may occur spontaneously or after trauma to the aortic wall during vascular surgery or angiographic procedures. The clinical consequences of cholesterol crystal embolism are variable. Embolisation may be completely asymptomatic and the diagnosis made only at renal biopsy, or may cause an ischaemic digit or a multisystem disease that mimics systemic vasculitis. The distribution of end-organ damage depends on the location of the original atherosclerotic plaques.

Clinically significant renal involvement occurs in around 50% of patients; the onset of renal disease after the triggering event may be immediate but can be more insidious with a delay of weeks or months. There may be acute renal impairment following massive embolisation; alternatively, there may be a gradual deterioration in renal function caused by showers of cholesterol emboli (Scolari et al, 2000; Meyrier, 2006).

Cutaneous manifestations are typically ischaemic digits, particularly the toes from abdominal atheroma emboli, and livedo reticularis affecting the legs (figure 3). The ischaemia usually presents as sudden onset of a small, cool, cyanotic and painful area of the foot (usually the toe). The lesions are tender to touch and may progress to ulceration, digital infarction and gangrene. The peripheral pulses are usually well preserved despite the digital cyanosis. Other common features include abdominal pain, CNS involvement, fever and weight loss.

Figure 3 *Cutaneous infarct caused by cholesterol embolisation mimicking vasculitis.*

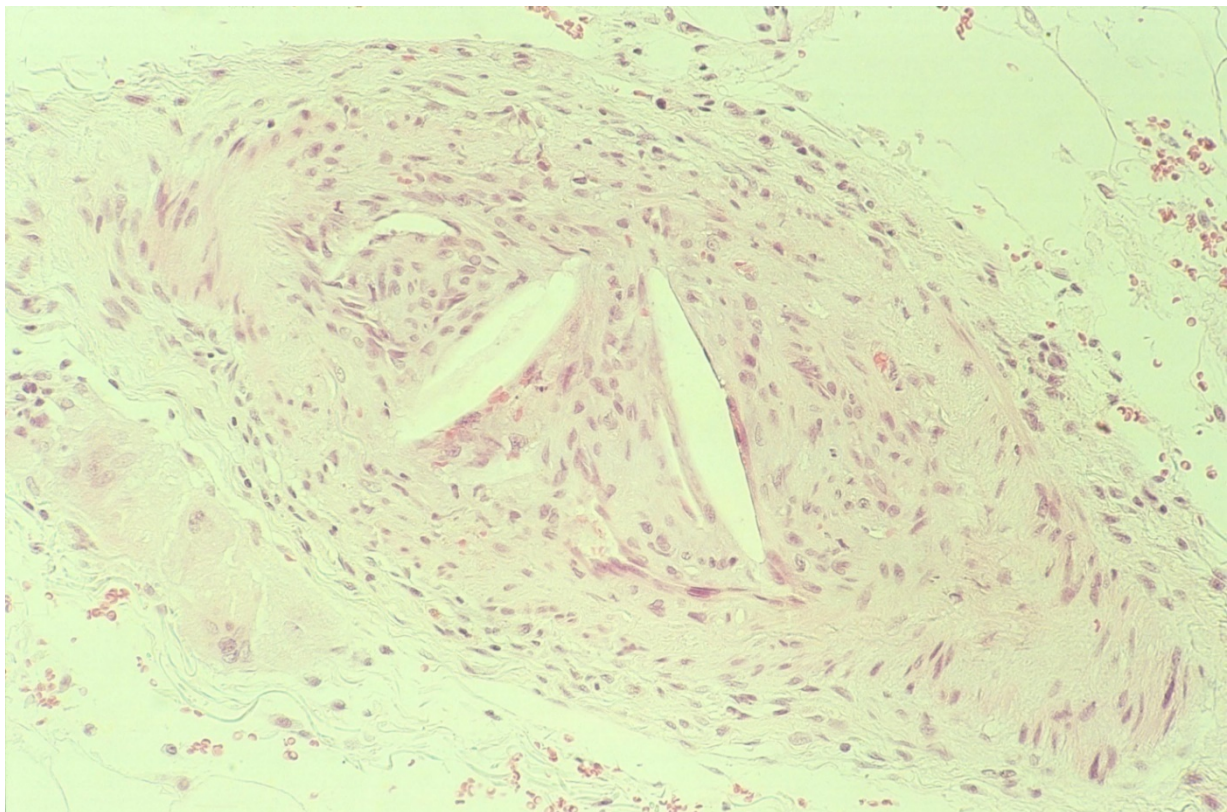


Laboratory investigations are often non-specific, including uraemia, thrombocytopenia, eosinophilia, raised erythrocyte sedimentation rate, hypocomplementaemia and disseminated intravascular coagulation. ANCA

are not usually detected in the serum (Scolari et al, 2000). Diagnosis is based on the clinical features with a typical history, supported by histological demonstration of the typical cholesterol clefts or cholesterol emboli in vessels (figure 4).

Treatment is aimed at halting the progression of tissue ischaemia and prevention of further embolisation. Anticoagulation should be avoided as this may exacerbate embolisation. Antiplatelet therapy is unsuccessful. Further endovascular procedures should be avoided (Hitti et al, 2008).

Figure 4 Histology findings from the same patient as in figure 3 showing typical clefts left by cholesterol deposits in small blood vessels.



2.6.2 Calciphylaxis

Calciphylaxis is rare but potentially fatal. It occurs in patients with chronic renal failure with secondary hyperparathyroidism. Disturbance of calcium and phosphate metabolism results in painful necrosis of the skin, subcutaneous tissue and acral gangrene. The appearance of the lesions is distinctive, but the pathogenesis remains uncertain. Correction of hyperphosphataemia or, occasionally, hypercalcaemia is vital, and parathyroidectomy, but also intravenous sodium thiosulfate, may be of benefit (Mathur et al, 2001; Malbos et al, 2013).

2.6.3 Cardiac myxoma

Cardiac myxomas are rare benign tumours most commonly found in the left atrium (90% of cases). Systemic manifestations seen in 90% of cases include fever, weight loss, Raynaud's phenomenon, clubbing, raised acute phase proteins and hypergammaglobulinaemia. Systemic embolisation occurs in 40%; emboli may be large enough to occlude the aortic bifurcation, while smaller emboli may remain viable and invade the vessel wall, resulting in aneurysm formation that mimics vasculitis. The diagnosis is made by echocardiography, which should be performed in all cases of suspected systemic vasculitis. Treatment is by surgical resection of the primary tumour and any emboli (Traill, 2003).

2.6.4 Infectious endocarditis

Infectious endocarditis is associated with both vasculitic and embolic phenomena. True vasculitic lesions are caused either by an immune complex vasculitis, the infectious agent or mycotic aneurysm formation by septic emboli where there is direct invasion of the vessel wall. Petechiae, strokes, splenic infarcts and glomerulonephritis are the most common extracardiac features. There is an immunological response with elevation of acute phase proteins, hypergammaglobulinaemia and autoantibody formation. The diagnosis is made by blood culture and echocardiography (Littler and Eykyn, 2003).

2.6.5 Fibromuscular dysplasia

Fibromuscular dysplasia is a vascular disease that affects small to medium-sized arteries. It is a non-inflammatory, non-atherosclerotic condition that occurs in younger people and women. Involvement of the renal arteries occurs in 60–75%, cervicocranial arteries in 25–30%, visceral arteries in 9% and peripheral arteries in 5% of cases (Slovut and Olin, 2004). Classification is dependent on the dominant arterial wall layer involved: intimal, medial or adventitial. The cause is unknown; smoking and hypertension are associated with an increased risk. Clinical manifestations reflect the arterial tree involved, with renovascular hypertension, renal infarction, dissection, transient ischaemic attacks and stroke. The diagnosis is made on the typical angiographic appearances with the classic 'string of beads' sign. Fibromuscular dysplasia—in particular, diffuse intimal disease, can occasionally be difficult to distinguish from vasculitis. There should not, however, be evidence of an acute phase response. Symptomatic stenotic lesions are treated by percutaneous transluminal angioplasty or bypass grafting, together with antiplatelet drugs. Hypertension should be treated according to national guidelines.

2.6.6 Chronic ergotism

Epidemic ergotism occurs after ingestion of grain contaminated with ergot (*Claviceps purpurea*) and was known in mediaeval times as St Antony's fire (Christopoulos et al, 2001). Painful gangrene of the peripheries occurs with loss of extremities. Critical mesenteric ischaemia can occur. Chronic ergotism can occur after long-

term use of ergotamine tartrate to treat migraine. Peripheral, carotid, coronary and visceral ischaemia may develop. The angiographic appearances may simulate vasculitis with irregular, long or short segmental stenosis. The diagnosis is dependent on a history of ergot consumption. The lesions may not be fully reversible on withdrawal of ergot.

2.6.7 Köhlmeier–Degos disease

Köhlmeier–Degos disease (malignant atrophic papulosis) is a rare and lethal condition which involves the skin, gut and nervous system. The typical skin lesions are circular and porcelain white with a depressed centre 4–8 mm in diameter with a slightly raised erythematous margin. The arterial lesion is luminal stenosis or occlusion caused by intimal proliferation and consequent thrombosis. Presentation is with acute abdominal pain (in association with the skin lesion), leading to bowel infarction. The multisystem nature of Köhlmeier–Degos disease mimics a vasculitis. The diagnosis is made on biopsy (Scheinfeld, 2007).

2.6.8 Cryofibrinogenaemia

Cryofibrinogenaemia comes about when a cryoprecipitate occurs in plasma which has been anticoagulated with oxalate, citrate or edetic acid (Saadoun et al, 2009). The cryoprecipitate is a complex which includes a number of plasma proteins, including fibrin, fibrinogen and fibrin split products. The cryofibrinogen is consumed in the clotting process and therefore, unlike a cryoglobulin, does not precipitate in cooled serum. Cryofibrinogenaemia may be asymptomatic but can present with purpura, skin necrosis, ulcers, gangrene, arthralgias, glomerulonephritis or a leukocytoclastic vasculitis and thus mimic a systemic vasculitis. Cryofibrinogenaemia may be primary or secondary to malignancy, infection or a connective tissue disease (figures 5 and 6). It is dealt with by avoidance of cold and treatment of the underlying condition, combined with immunosuppression, plasmapheresis and/or fibrinolytic drugs.

Figure 5 Digital gangrene in a patient with cryofibrinogenaemia secondary to malignancy.



Figure 6 Rash in patient with cryofibrinogenaemia secondary to malignancy.



2.6.9 Sweet's syndrome

Sweet's syndrome is a rare condition, otherwise known as acute febrile neutrophilic dermatosis (Cohen, 2007). It was originally described following respiratory infection (figure 7) but is more commonly seen in patients with malignancy. It may be precipitated by drugs—in particular, granulocyte-colony stimulating factor. The condition is characterised by fever, neutrophilia and tender erythematous cutaneous lesions (plaques, nodules and papules). The lesions may resemble a systemic vasculitis, especially in a febrile ill patient. Skin biopsy shows an intense infiltrate of mature neutrophils, typically in the upper dermis. Treatment is with glucocorticoids, which usually results in a rapid improvement.

Figure 7 Sweet's syndrome following a chest infection.



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SUMMARY POINTS

- Vasculitides are inflammatory vessel diseases which include around 15–20 distinct entities.
- Vasculitides are categorised as primary (i.e., idiopathic) or secondary vasculitides.
- Vasculitides are further separated into three groups according to the size of the predominantly involved vessels (i.e., large, medium or small-vessel vasculitis).
- The most common causes of secondary vasculitides are malignancies, infections or drug exposure.
- Some vasculitis entities (e.g., polyarteritis nodosa) may present both as primary and as secondary vasculitis (e.g., HBV-related polyarteritis nodosa).
- Most cases of vasculitis are primary vasculitides, with vasculitis cases with a known underlying cause being less common in clinical practice.
- The 2011 Chapel Hill Consensus Conference nomenclature devised definitions for primary vasculitides.
- The 1990 American College of Rheumatology classification criteria cover seven vasculitis entities.
- For some vasculitis entities, classification remains problematic because their disease features overlap with one or several other vasculitis entities and/or because of the lack of highly accurate classification systems.
- It is important to consider vasculitis mimics in the differential diagnosis as they require different therapeutic approaches.

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module

EULAR on-line course on Rheumatic Diseases

Vasculitis: Classification, Secondary Forms and Mimics

Francesco Muratore, Neil Basu, Nicolò Pipitone

A previous version was co-authored by Alfred Mahr, Neil Basu, Rosemary Hollick

IN-DEPTH DISCUSSION I

Drug-associated vasculitis

LEARNING OUTCOMES

Drug-associated vasculitis (DAV) represents one the commonest forms of inflammatory vascular disease. Due to the distinct approach to their management, differentiation from other vasculitic syndromes is crucial.

Following this module, the student should be able to:

- i) Recognise the commonest drugs currently associated with the development of vasculitis
- ii) Describe the evaluation and management of DAV
- iii) Distinguish DAV from primary forms of systemic vasculitis

The putative causal relationship between pharmaceutical agents and vasculitic manifestations has been recognised for decades and the resultant syndromes are often referred to by varying terms including hypersensitivity, allergic and leukocytoclastic vasculitis. Such nomenclatures are neither specific nor accurate for vasculitis related to drug exposure and only serve to confuse. The most recent Chapel Hill Consensus Conference nomenclature provided a robust alternative, proposing ‘drug-associated vasculitis’ which can be further refined to reflect the likely causative agent and subsequent disease form (e.g. hydralazine-associated microscopic polyangiitis)[1].

A review of any pharmaceutical formulary makes it clear that most classes of drug can be implicated in vasculitic adverse events. This is not to say that vasculitis is a very common consequence of overall drug prescription per se. The majority of observations relate to occasional case reports regarding routinely prescribed drugs (e.g. statins [2]). Even among the more frequently cited drug culprits (e.g. anti-rheumatic biologicals) their occurrence can be described as uncommon at best - for example a prospective study of anti-TNF therapy identified only 5 cases of DAV among 278 patients with rheumatoid arthritis [3]. Conversely, DAV comprises a significant proportion of all vasculitis cases (a relatively uncommon presentation in itself), with drug reactions deemed attributable in 11% of all subjects submitted to ACR’s original 1990 classification study[4] and >20% of cutaneous vasculitis presentations[4-5].

Indeed the pathology is limited to the skin in the vast majority of cases where purpura and maculopapular rashes represent the commonest phenotypic features. In general, such manifestations tend to develop a few days to weeks after drug exposure and preferentially involve the lower limbs. Diagnosis is supported by cutaneous biopsy which can reveal a small vessel neutrophilic or lymphocytic vasculitis and any evidence for tissue eosinophilia reinforces the suspicion of a drug aetiology further. Tissue is equally important in excluding alternative diagnoses such as cholesterol emboli and specimens should be sent for immunofluorescence, e.g. to determine the possibility of IgA vasculitis (Henoch-Schönlein), and culture, e.g. to exclude tuberculosis.

Clearly the ultimate diagnosis of DAV is predicated upon evidence of a temporal relationship with the suspect drug. As mentioned, agents across the pharmaceutical spectrum are culpable and include alternative remedies and those used for recreational purposes. A thorough drug exposure history is vital with particular attention directed towards recent antibiotics, immunomodulators (including biologics), growth factors and anti-hypertensive prescriptions. Ultimately, withdrawal of the offending drug should result in the resolution (over weeks) of most cutaneous limited forms and in doing so provides confirmatory evidence of causality. In these situations the patient should be advised to avoid future exposure.

Not all patients present with cutaneous disease and even those **who** do may experience additional systemic manifestations. Thus a cornerstone of evaluation is to quantify disease extent. The development of systemic disease may take months or even years following initial drug exposure and patients can present with the catastrophic visceral involvement as commonly observed in primary systemic vasculitides. Importantly, simple drug withdrawal is not always sufficient to avoid organ damage in systemic forms and standard immunosuppressant regimes, such as cyclophosphamide and corticosteroids, may be required in severe cases. That said, the overall requirement of immunosuppressants for systemic DAV is substantially reduced compared to primary phenotypic counterparts and so it is crucial to be able to distinguish these.

The process of distinction is perhaps most challenging in those drugs inducing phenotypes similar to those observed among ANCA associated vasculitis (GPA, MPA, EGPA) since these patients quite often harbour serological evidence of ANCA as well. However, these tend to be simultaneously directed towards multiple antigens and typically at a much higher titre than observed in primary forms of the disease [6].

Among prescription drugs, hydralazine and propylthiouracil are most commonly related to the development of AAV-like syndromes.

The vasodilatory properties of hydralazine have been employed for many decades in the treatment of hypertension and cardiac failure. Its association with a pulmonary-renal syndrome characteristic of microscopic polyangiitis has been frequently reported and best recorded by a study of 30 consecutive cases of vasculitis presenting with very high titres of anti-MPO antibodies. On retrospective review, one third of these patients had been exposed to hydralazine [7]. In addition to MPO antibodies, ANCA directed towards human neutrophil elastase and lactoferrin are commonly identified as are homogenous anti-nuclear and anti-histone antibodies. This co-occurrence of vasculitis and SLE associated autoantibodies is often clinically translated with patients presenting with overlapping phenotypic features of DAV and drug associated SLE [8]. Although the precise mechanism of hydralazine induced immune dysfunction is unknown, it is intriguing to note the drug's recognised capacity for epigenetic modification (specifically as a non-nucleoside DNA methylation inhibitor). Thus it is possible that the drug may interfere with the expression of neutrophil constituents such as MPO and PR3 - currently thought to be pivotal in the pathogenesis of primary ANCA associated vasculitis [9].

The development of a pauci-immune crescentic glomerulonephritis following exposure to the anti-thyroid medication propylthiouracil (PTU) has been frequently noted. Other systems can be involved, especially the bone marrow (agranulocytosis) and high MPO-ANCA titres are invariably observed. Recent studies from China found that patients with PTU related vasculitis predicted female sex and younger age when compared to patients with primary ANCA associated vasculitis. In addition, the degree of renal involvement was less severe and overall prognosis much more favourable [10-11]. Again the precise mechanisms are unknown, although it may be that the drug or its intermediates stimulate ANCA production [9]. It is certainly interesting to note that ANCA is evident in over a quarter of patients receiving long term PTU therapy and that titres often resolve following drug cessation [12].

In addition, leukotriene receptor antagonists have been strongly implicated with AAV and specifically the onset of EGPA [13]; although there is some data which contradicts a putative causal role. These drugs, which include zafirlukast and montelukast, are steroid sparing agents in recalcitrant chronic asthma and so may simply unmask previously undiagnosed disease. Further, case control studies have not only identified relationships between EGPA and anti-leukotrienes but also other common treatments employed to manage difficult asthma. These findings imply that antileucotrienes (and other advanced asthma therapies) may be a surrogate marker of the severity and the gradual worsening of the asthma which typically precedes EGPA onset.

Non-prescribed illicit drugs are also common culprits and not so readily reported by patients. It is therefore important to consider broad urine toxicology screens in the diagnostic work up of a new presentation of vasculitis. The association with cocaine has been best documented, initially as a mimic of ENT limited GPA where its intranasal use has led to ischemic necrosis of the nasal septum and the finding of human neutrophil elastase ANCA [14] and more recently in conjunction with the adulterant levamisole (a cheap anthelmintic agent which resembles cocaine powder and so employed to improve the financial gains of the traders) where a more systemic GPA-like illness, typically involving erosive disease of both the upper airways and the ears, is observed in the context of double-positive MPO and PR3 –ANCA [15].

Finally, although DAV predominantly involve small vessels, a recently reported case series described 9 patients with a medium vessel vasculitis in keeping with polyarteritis nodosa. All had previously received long term therapy with the tetracycline antibiotic minocycline. The phenotypes ranged from cutaneous limited to classical systemic presentations and unusually shared serological evidence of pANCA (mostly directed towards antigens other than MPO).

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IN-DEPTH DISCUSSION II

Takayasu's Arteritis

LEARNING OUTCOMES

Takayasu's arteritis (TA) is a rare type of vasculitis that most practising rheumatologists will only meet occasionally during a career.

At the end of this module the student will be able to accurately classify TA, understand the distribution of vascular lesions in TA, conduct appropriate investigations to diagnose and assess the extent of disease involvement, and adequately manage the treatment of patients with immunosuppressive drugs.

Following this module. The student should be able to:

1. Recognise Takayasu's arteritis as a large vessel arteritis and describe it
2. Be aware that it is rare with an incidence of around 1-2/million/year and is most common in Japan
3. Describe the investigation of TA using conventional, computed tomography and magnetic resonance angiography and/or 18 FDG PET scanning
4. Describe the treatment of TA with corticosteroids and the role of other immunosuppressant drugs and surgery

1. BACKGROUND

Takayasu's arteritis is a chronic large vessel vasculitis (granulomatous pan arteritis) which affects predominantly the aorta and its main branches and less frequently the pulmonary arteries. The inflammation of blood vessels generally causes stenosis or occlusion although aneurysms may also develop.

2. HISTORY

The term Takayasu's arteritis was first used by Shinmi in 1939. The first case of TA was described in 1908 by Dr. Mikito Takayasu [1]. He described interesting fundal findings in a 21-year-old girl characterised by circular anastomosis of central retinal arteries.

Onishi and Kagoshima at the same meeting reported similar eye findings in patients whose radial pulses were absent. Although TA has become the most widely used term for this disease, it is also known by different synonyms including, pulseless disease, occlusive thromboangiopathy, middle aortic arch syndrome and Martorell's syndrome.

3. EPIDEMIOLOGY AND PATHOGENESIS

Japanese series have demonstrated a female predominance of 9:1 and TA typically affects young women aged 10 – 30 years (in 70–90% of published series). An international comparative analysis reveals a decline of this female preponderance as one moves westwards from Japan; in Israel the sex ratio is almost equal [2]. The annual incidence in most populations is 1-3/million and it is generally considered to be more common in Asia.

The earliest estimate of the incidence came from the USA (Olmsted County, Minnesota) where three cases were identified during 1971-83 with an estimated annual incidence of 2.6/million [3]. The incidence in Sweden during 1969-75 was estimated to be 0.8/million [4]. In the ethnic Kuwaiti population of Kuwait the incidence between 1989 and 1994 was 2.2/million and 3.3/million in those aged < 40 years. [5]. In Japan, there are estimated to be 150 new cases per annum from a population of 125 million [6], equivalent to an annual incidence of 1-2/million. The prospective Schleswig-Holstein registry recorded an annual incidence during 1998-2002 of 0.5/million [7]. In Lithuania the incidence has been recorded as 1.3/million [8]. Recent data from a UK primary care population suggests that the incidence is 0.45/million in those aged < 40years [9]. These data suggest that the incidence is reasonably uniform across the globe and that there are no major ethnic or time trends. The prevalence of TA in Europe is around 5-7/million [4, 5, 9].

The aetiopathogenesis of TA is unknown. However, reports have suggested a possible association with *Mycobacterium tuberculosis* and other organisms, including spirochetes, bacteria and viruses. Immunological abnormalities including anti-aortic endothelial cell antibodies [10] have been described leading to the hypothesis that it may be a form of autoimmune disease (reviewed in [11]).

It has also been described occasionally associated with other autoimmune disease including juvenile idiopathic arthritis, Still's disease, systemic lupus erythematosus, chronic inflammatory bowel disease and seronegative spondylarthritis. Cellular immune mechanisms may also be involved: one study showed increased numbers of CD8+ (suppressor/cytotoxic) T cells deposited in the inflamed walls of the affected arteries and associated with increased numbers of lymphocytes in the circulation [12].

Subsequent studies have confirmed this association: also increased percentage of high TNF-alpha, low IL-2 producing T cells and also gamma delta T cells are found in patients with active TA compared to inactive TA suggesting an important role for these cells [13, 14].

Two groups have studied an IL-1ra knock out mouse model with enhanced IL-1 signalling. These mice develop inflammation at sites of turbulent blood flow with an infiltrate of monocytes, Th1 cells and dendritic cells [15, 16]. T cells from these mice induce aortitis in nu/nu mice. Suppression of TNF-alpha but not IL-6 prevented development of aortitis, implying that IL-1 and TNF-alpha are key mediators of inflammation in the aorta.

TA has been noted to occur in twins and siblings [17] suggesting that genetic factors may be involved in the pathogenesis, however, only 1% of Japanese TA patients have an affected relative [18]. There are several reports of HLA associations including HLA-DRB1*1502, DPB1*0901, HLA-B*5201, HLA-B*3902 in Japanese patients. HLA-B*5201 appears to be associated with more severe inflammation [reviewed in 19]. In South America the association seems to be with HLA-DRB*1301, HLA-DRB*1602 and DRB*1001.

Pathology

TA is a pan arteritis that typically occurs as focal skip lesions. There is an acute florid inflammatory phase and chronic healed fibrotic phase, both of which may co-exist. During active disease the inflammatory infiltrate is predominantly lymphoblastic with granulomata formation and giant cells involving the media and adventitia. It is characterised by adventitial thickening and cellular infiltration of the tunica media, with local destruction of vascular smooth muscle cells and elastin. The inflammatory lesions originate in the vasa vasorum characterized by perivascular cuffing mainly $\gamma\delta$ T cells, cytotoxic T cells and T helper cells. In the chronic phase, intimal hyperplasia is followed by fibrosis of the tunica media and intima, leading to stenosis [20, 21]. Aneurysm formation may occur following local destruction of the medial layer and an inadequate fibrotic response [21].

4. CLINICAL FEATURES

The presentation of TA is varied and can present with non-specific symptoms depending on which vessels are involved and the stage of the disease. Early reports suggested that TA typically has an early inflammatory phase followed by a late ischaemic/pulseless phase. Some patients do not progress into the occlusive phase and experience a self-limiting monophasic inflammatory episode that does not require chronic immunosuppression. The transition period between the two phases may be over a period of months or years (mean 8 months), although more recent series suggest that these distinct phases are only seen in a minority. Early features include non-specific symptoms of inflammation such as fever, myalgia, arthralgia, weight loss and anaemia. Visual disturbances can be the presenting feature with retinal micro aneurysms, venous dilatation and beading being the most common clinical findings but despite the link to Takayasu's original description serious visual involvement is quite rare. Chronic inflammation of the aorta and its major branches, including the subclavian, common carotid, coronary, pulmonary and renal arteries may result in localized stenosis, vascular occlusion, dilatation and aneurysm formation.

The most common symptoms in Kerr et al's series were therefore related to these findings and included upper extremity claudication, hypertension, pain over the carotid arteries (carotidynia), dizziness and visual symptoms [22]. More than 50% had musculoskeletal symptoms such as myalgia and chest wall pain; synovitis is usually mild.

The most frequent cardiac complication is aortic regurgitation from dilatation of the aortic root. This occurs in approximately 5-55% of patients. Coronary vessel stenosis occurs in up to 25%; other complications include mitral regurgitation, cardiomyopathy and myocarditis. The pulmonary artery may be involved in 50-86% of patients and therefore patients may present with features of pulmonary hypertension. Symptoms such as dizziness, syncope, visual changes, vertigo and arm claudication are more common in studies from Japan and the USA, whereas hypertension is more common in India due to more frequent involvement of the abdominal

aorta and renal artery stenosis. Crescentic glomerulonephritis and acute myocardial infarction have been described. Other rare systemic symptoms include skin lesions (erythema nodosum and pyoderma gangrenosum) and serositis [19].

5. DIAGNOSIS AND INVESTIGATIONS

TA should be considered in the differential diagnosis when any young person presents with large vessel ischaemia and/or hypertension, especially if associated with any systemic symptoms. The diagnosis is often missed or delayed. It is important to note that about 20% of patients are asymptomatic at the time of diagnosis so careful clinical examination is essential looking in particular for bruits over the aorta and its major branches (one third). Reduced or absent pulses of large arteries as well as blood pressure discrepancies of at least 20mm Hg between the arms and/or legs may be seen.

There are no laboratory tests or validated diagnostic criteria for the diagnosis of TA. In contrast to giant cell arteritis, biopsy material is rarely available in patients with TA. Hoffman examined multiple serological tests including ESR, CRP, tissue factor, von Willebrand factor and found that no test reliably distinguished healthy volunteers and patients with TA [23]. Inflammatory markers, such as the ESR and CRP, are raised in 80% of patients with active TA [24]. Patients may have a mild normochromic normocytic anaemia and hyperglobulinaemia but may not have a raised inflammatory response, even in the early inflammatory stages. Complement activity is typically normal and disease specific autoantibodies are characteristically absent. The ACR proposed classification criteria for TA in 1990 and these have remained the most widely applied with three or more of the criteria associated with a sensitivity of 90.5% and specificity of 97.8% [25] (Table 1).

Table 1: ACR Classification criteria for Takayasu's arteritis

Criterion	Definition
1. Age < 40 years old	Development of symptoms or signs related to TA at age < 40 years
2. Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities
3. Decreased brachial arterial pulse	Decreased pulsation of one or both brachial arteries
4. BP difference > 10 mmHg	Difference of > 10mmHG in systolic blood pressure between arms
5. Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
6. Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its proximal branches, or large arteries in the proximal upper or lower extremities, not due to atherosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental.

Note for purposes of classification a patient shall be said to have TA if at least 3 of these 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90.5% and specificity of 97.8%. From Arend et al [25].

Presence of three out of six criteria is required for diagnosis, but by these criteria patients in several Asian countries whose abdominal aorta is predominantly involved would elude diagnosis. Although ophthalmological findings and/or symptoms are excluded, in Japan approximately 35 per cent of patients show abnormal ophthalmological findings including micro aneurysm, retinal haemorrhage, cataract, or glaucoma.

6. DISEASE MONITORING

The critical limitation in managing a patient with TA has been the inability to accurately assess disease activity. Analysis of acute phase response is often an unreliable indicator of disease activity. Specific activity scores and outcome measures have been developed for TA [26].

7. CLINICAL IMAGING

Conventional angiography

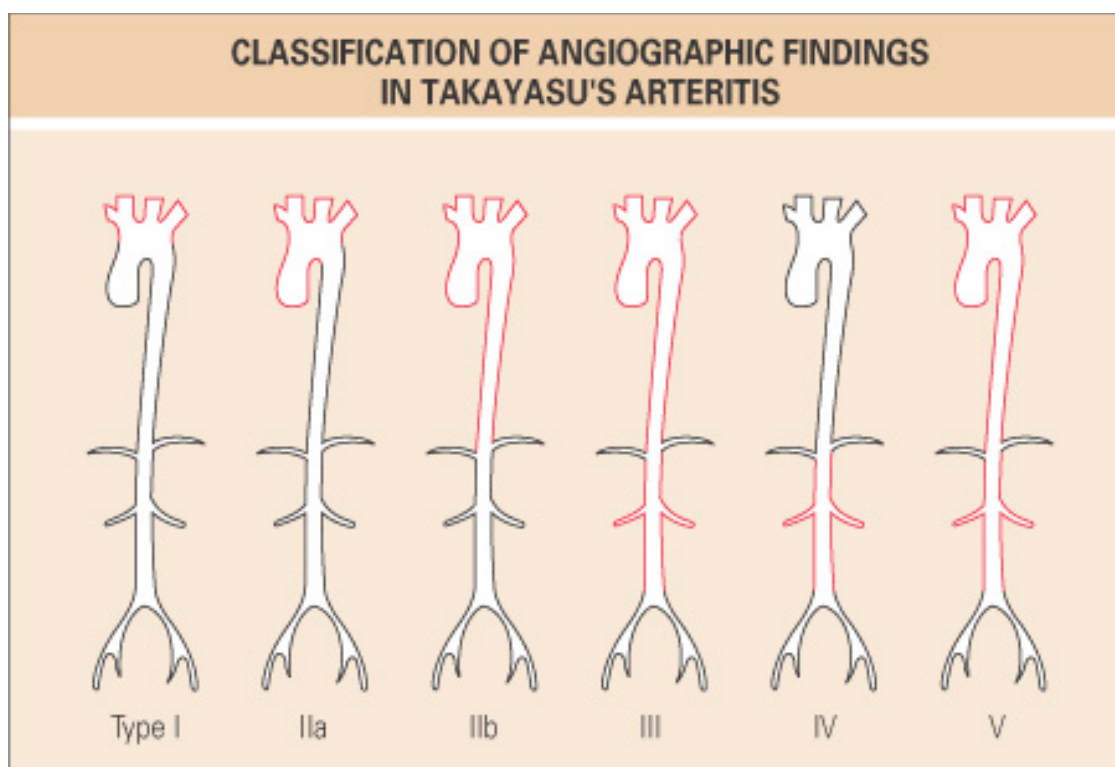
Conventional angiography has been the gold standard investigation for the diagnosis of TA. The commonest angiographic findings are long, smooth vascular stenoses and occlusions, and sometimes aneurysms.

Panangiography is required to determine the extent of disease involvement [21]. Diffuse disease affecting the aorta and its branches above and below the diaphragm is the most common pattern of disease worldwide. (Figures 8, 9 and 10)

However, conventional angiography cannot demonstrate earlier vasculitic changes such as thickening of the vessel wall and mural enhancement, and is thus not useful for early diagnosis. Disadvantages of conventional angiography include its invasive nature and the exposition to ionizing radiation. Furthermore it is contraindicated in patients with impaired renal function and in those allergic to iodine. Hence, other modalities of imaging have been explored in recent years including ultrasound, CT, magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET). For all these reasons, conventional angiography has become a therapeutic procedure for endovascular intervention rather than a diagnostic method [21].

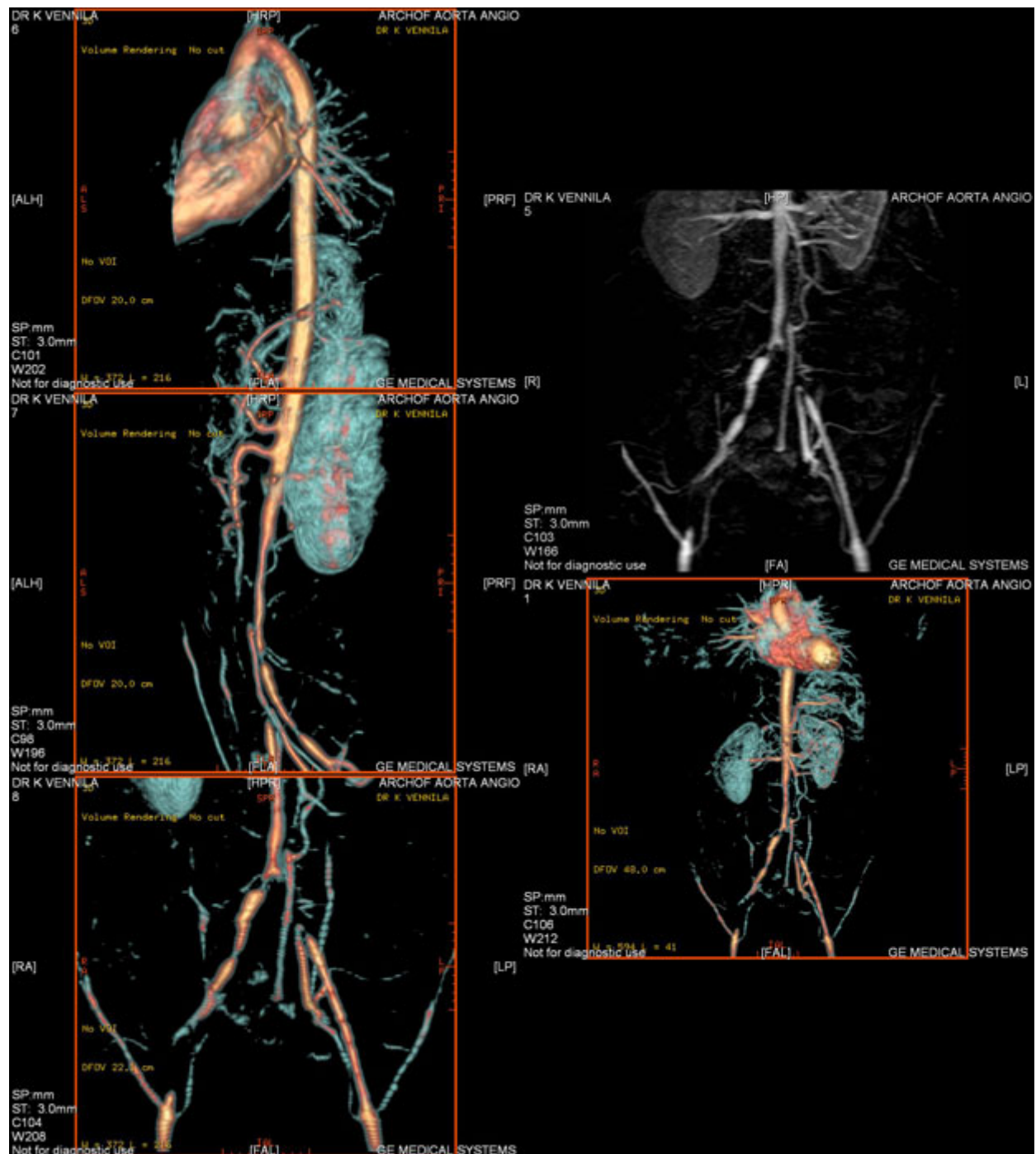
*Figure 8 - Classification of Takayasu's Arteritis***Table 19.1** Classification of Takayasu's arteritis

Type	Site of involvement
I	Branches of aortic arch
IIa	Ascending aorta, aortic arch and its branches
IIb	Ascending aorta, aortic arch and its branches and thoracic descending aorta,
III	Thoracic descending aorta, abdominal aorta and/or renal arteries,
IV	Abdominal aorta and/or renal arteries.
V	Combination of Types IIb and IV

Figure 9 - Diagrammatic representation of the different types of Takayasu's Arteritis

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Figure 10 - Angiogram showing narrowing of lower aorta and marked narrowing of common iliac arteries in a young lady with TA



Magnetic Resonance Imaging (MRI)

MRI is particularly indicated to examine the aorta and the other deep, large vessels without the use of ionizing radiation or iodinated contrast. Increased vessel wall thickness (usually with a diffuse circumferential pattern), associated with vessel wall oedema on T2 and fat-suppressed sequences, and mural contrast enhancement on T1 sequences are early signs of vascular inflammation. Moreover, MRI angiography (MRA) provides luminal information, such as arterial stenosis, occlusion and dilatation [21]. Comparative studies with conventional angiography are encouraging. The potential for MRI to assess disease activity and response to treatment needs to be further explored. Serial assessment of mural thickness may provide evidence of response to treatment. Limitations of MRI/MRA include poor visualization of calcifications and falsely accentuated stenoses. Disadvantages include high cost of the procedure and long acquisition time. Furthermore it is contraindicated in patients with impaired renal function, claustrophobia and in those with some metal devices [21].

High Resolution Doppler Ultrasound

High resolution ultrasound (US) has been reported to be up to 10 fold more sensitive than MR for the assessment of superficial arteries such as the common carotid arteries [27]. Increasingly it is being used to assess involvement in large branches of the aorta. The high resolution of US raise the possibility that it may offer a means by which disease activity and response to treatment may be monitored, but this has yet to be studied. The procedure is also highly operator dependant and requires operators with vascular expertise [21].

CT Angiography

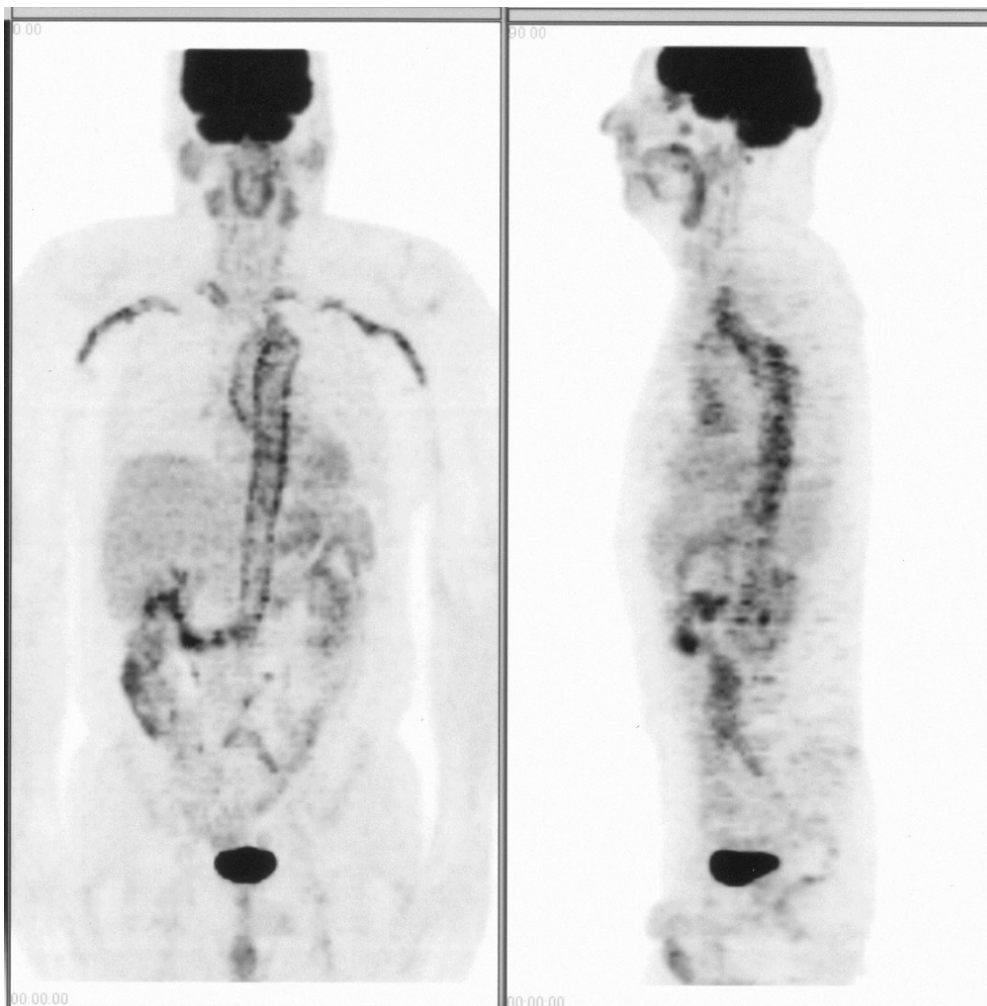
Computed tomography (CT) and CT angiography (CTA) are well suited to detect inflammatory changes in large arteries because of their good spatial resolution and convenient scanning time. CT can measure aortic diameter and detect mural calcifications. CTA can evaluate both the vessel wall and the lumen of the large vessels. CTA has a role in diagnosing early and advanced TA. In early TA, CT may show arterial wall thickening with mural enhancement and low-attenuation ring on delayed images. In late TA the arterial wall is slightly thickened with high attenuation or calcifications. Furthermore CTA may show TA complications such as arterial stenosis, occlusion and dilatation. The role of CTA in monitoring disease activity in TA patients is still unclear. The main disadvantage of CT/CTA is the exposure to a significant amount of ionizing radiation, which limits its repeated use. Furthermore it is contraindicated in patients with impaired renal function and in those allergic to iodine. [21].

¹⁸F-Fluorodeoxyglucose Positron Emission Tomography

¹⁸F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) is a nuclear medicine technique, currently often co-registered with computerized tomography (CT; PET/CT), which assesses the extent and amount of vascular uptake of the radiolabelled glucose analogue FDG by metabolically active cells in infections,

malignancies, and inflammation. In active TA, there is increased FDG uptake by the vessel wall, typically with a smooth linear pattern. PET is able to visualize virtually all vessels larger than 4mm in diameter, but not arteries of smaller calibre such as the renal arteries [21]. Principal advantage of PET is its ability to identify pre-stenotic disease in patients presenting with non-specific symptoms in the early phase of the disease [28-33]. As yet 18F-FDG-PET scanning has only been shown to be of use in the diagnosis of TA. In a recent systematic review and meta-analysis, PET had a sensitivity of 87% and a specificity of 73% for TA [34]. Prospective studies are required to confirm its utility as a tool for assessment of disease activity and for monitoring. Its major limitation is that involves radiation exposure, especially when combined with CT and this limits its serial use. In addition it is expensive and because the isotope has a short half-life its use is limited to a few centres (Fig 11).

Figure 11 - 18F-Fluorodeoxyglucose positron emission tomography (18F-FDG-PET) showing increased uptake in the aorta, subclavian arteries and mesenteric vasculature.



8. MANAGEMENT

The current treatment modalities include glucocorticoids, immunosuppressive therapy and non-medical intervention. There is limited data on which to build an evidenced based approach to the management of TA. EULAR have recently published guidelines on the management of large vessel vasculitis [35].

Glucocorticoids are the mainstay of medical treatment. Improvement /resolution of systemic symptoms has been reported in 25-100% of glucocorticoid treated patients. The optimal dosage has not been clearly defined. There have been no comparative trials to determine the optimal dosage or length of treatment. An initial dose of prednisone 1 mg/Kg/day (maximum 60 mg/day) is recommended in all newly-diagnosed, active TA patients. Initial high-dose GC should be maintained for a month, and then tapered gradually. This starting dose may be lowered in selected individuals at high risk of steroid toxicity. Because around 20% of patients have a self-limited, monophasic inflammatory episode, the systematic prescription of an immunosuppressive agent for all newly-diagnosed TA patients is not essential. If a relapse occurs, treatment with glucocorticoids at the higher previously effective dose is recommended, and adjunctive immunosuppressive agents should be considered [36]. There is not the degree of evidence for the use of immunosuppressive therapies in TA as there is for the ANCA associated vasculitides. Methotrexate is now the first choice second line therapy based largely on small open labelled studies and anecdotal evidence [22, 36-37]. Azathioprine remains a suitable alternative to MTX in TA [36]. Before the widespread use of MTX, cyclophosphamide (CYC) was the agent of choice for corticosteroid-resistant TA. CYC is now largely reserved for life threatening disease or disease unresponsive to synthetic and biological immunosuppressive agents. Mycophenolate has shown some promise as an alternative to MTX in TA [36].

Observational evidence supports the use of anti-TNF- α agents in TA patients with relapsing disease. Infliximab is the most commonly reported anti-TNF agent used. However, anti-TNF- α are not curative, and relapses remain common [36, 38-39]. Preliminary experience with the use of the IL-6 receptors inhibitor monoclonal antibody tocilizumab in TA suggests safety and clinical and radiographic efficacy [36, 38-40]. Both anti-TNF- α agents and TCZ seem equally effective and safe in TA patients with relapsing disease [39]. In case of a relapse under biological therapy, a switch to another biologic agent should be considered [36, 38-39]. Large RCTs are required to generate convincing evidence of efficacy for both anti-TNF- α and anti-IL-6 (-receptor) therapies in TA.

The first multicentre randomized clinical trial in TA has recently been completed. This trial evaluated the efficacy of abatacept in the treatment of TA. The primary endpoint was duration of remission (relapse-free survival, RFS). The RFS at 12 months was estimated to be 22% for those receiving abatacept and 40% for those receiving placebo ($p = 0.853$). In this study, the addition of abatacept to prednisone did not reduce the risk of relapse in patients with TA [41].

As with all chronic rheumatologic conditions there is an increased risk of developing premature atherosclerosis. Cardiovascular risk assessment should be made with careful attention to and treatment of hypertension. Consideration of surgical intervention into renal artery stenosis should be made. Lifestyle factors should be addressed including smoking and dietary habits. All patients should be evaluated for aspirin and a statin prescription unless contraindicated. Osteoporosis is a recognized consequence of high dose and /or prolonged treatment with corticosteroids and prophylaxis should be considered in all patients on treatment for TA [36].

Surgical treatment

Surgical treatment is beneficial in selected cases. Surgery should be performed if possible, when inflammation is quiescent, as aneurysm, graft dehiscence or graft occlusion is more likely in the presence of active arteritis. However surgery to prevent imminent ischaemia of a vital organ should not be delayed because of active inflammation. The operative procedures include bypass of stenosed segments of arteries, resection of aneurysms and replacement of aortic valves. Angioplasty and/or stenting can be effective procedures for some vascular complications of TA, especially for coronary atherosclerosis and renal artery stenosis. [42]

Prognosis

Earlier diagnosis and initiation of treatment has greatly improved the outcome in patients with TA. Non-invasive diagnostic imaging that can enable the assessment of disease activity and hence allow adjustment of treatment accordingly will improve our understanding and management of the disease. However the outcome of patients with TA varies greatly and the most common causes of mortality are congestive cardiac failure, cerebrovascular events, myocardial infarction, aneurysm rupture and renal disease.

Predictors of poor outcome are progressive disease, TA retinopathy, secondary hypertension, aortic valve insufficiency or aneurysms [43]. Overall survival rates of 82.9% at 15 years have been reported from Japan [44]; and Park et al from Korea reported 10 year survival of 87.2% [45]. In a recent US series the overall survival was 97% at 10 years and 86% at 15 years. Mortality was increased compared with the general population (standardized mortality ratio, 3.0; 95% CI, 1.0-8.9) [46]. Mortality directly related to TA usually occurs from congestive cardiac failure, cerebrovascular events, myocardial infarction, aneurysm rupture or renal failure.

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Top references are in bold

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Anca-associated vasculitides and polyarteritis nodosa

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LEARNING OBJECTIVES

- Precisely locate polyarteritis nodosa (PAN) and antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitides in the current definitions of primary systemic vasculitides
- Conduct appropriate investigations to diagnose and evaluate the severity of PAN and ANCA-associated vasculitides
- Adequately manage the treatment of patients with a newly diagnosed form of each of these vasculitides in their more usual presentations
- List the different primary necrotising vasculitides of small vessels, according to the revised Chapel Hill nomenclature, and among them, the ANCA-associated vasculitides, using their recently revised names
- Describe and explain the different clinical phenotypes of granulomatosis with polyangiitis (GPA) (Wegener's) and their respective association with cytoplasmic ANCA positivity with proteinase 3 specificity
- Recognise that microscopic polyangiitis (MPA) has been clearly distinguished from PAN especially since the publication in 1994 of the Chapel Hill criteria and that it is often associated with perinuclear ANCA (pANCA) to myeloperoxidase (MPO)
- Explain that only anti-MPO pANCA have clearly been proved to be pathogenic in animal models and in a single case report of their transplacental transfer resulting in pulmonary-renal syndrome of a new born human infant. However, despite these latter findings and other recent studies, the precise origin and mechanisms leading to the production of ANCA remain undetermined

- Describe the other pathogenic mechanisms that may be involved in ANCA-associated vasculitides, including specific T lymphocyte subsets or dendritic cell dysfunction
- Describe and explain the general lines of treatment for GPA (Wegener's) and MPA—that is, induction therapy followed by a maintenance regimen. Know that the optimal duration of maintenance regimens remains to be determined and that, despite such treatment, the relapse rate remains high
- Evaluate the place of biological agents in the therapeutic armamentarium for patients with GPA (Wegener's) or MPA. Especially, outline the results of recent therapeutic studies using targeted monoclonal B cell therapy—that is, rituximab, which was shown to be non inferior to conventional first-line cyclophosphamide-based induction therapy in patients with active generalised GPA (Wegener's) or MPA, and superior to AZA as maintenance therapy.
- Differentiate eosinophilic GPA (Churg–Strauss syndrome) (EGPA) from the other ANCA-associated vasculitides, based on their clinical and biological manifestations
- Explain that EGPA is associated with pANCA to anti-MPO in 30–40% of patients, and that there are some clinical differences according to their presence or not, suggesting that distinct pathogenic mechanisms may be involved, such as ANCA- and/or eosinophil-mediated cytotoxicity
- Define the treatment for patients with EGPA according to the Five-Factor Score (FFS)
- Describe the overall outcome of patients with EGPA, especially their frequent glucocorticoid dependence
- Recognise that the identification of predictive parameters of relapse might in the future allow adjustment of treatment according to individual patient characteristics. Notably, several studies showed that ANCA increases were not reliable as predictors for relapse, demonstrating that ANCA levels cannot be used to guide immunosuppressive therapy
- Recognise PAN as one of the two medium vessel systemic necrotising vasculitides and describe its main clinical features
- Describe the correct treatment for patients with PAN, especially according to their hepatitis B virus status and the presence or not of poor prognostic factors, according to the FFS
- Recall the global outcome and relapse rate of PAN
- Explain that the original prognostic FFS (1996) can be used to assess the severity of PAN, MPA and EGPA, and that the revised FFS (2010) can now also be applied to patients with GPA (Wegener's)
- Explain that PAN, GPA (Wegener's), MPA and EGPA activity can be evaluated during clinical trials using the Birmingham Vasculitis Activity Score (BVAS) version 3, and know that for patients with GPA (Wegener's) there is a specific GPA-BVAS

1 Background knowledge

For this chapter, readers should be aware of the classification and consensus definitions of the primary necrotising vasculitides, mainly the revised Chapel Hill nomenclature, and the recent changes in the names for some of them. Polyarteritis nodosa (PAN) is a medium vessel vasculitis, whereas granulomatosis with polyangiitis (GPA) (Wegener's), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA, Churg–Strauss) are small vessel vasculitides. Because the last three are often associated with antineutrophil cytoplasmic antibodies (ANCA), they have been grouped under the label of ANCA-associated vasculitides. However, they differ in many clinical and biological aspects and their treatment is also slightly different. No personal experience of these vasculitides is required because the main clinical features of these diseases are described in-depth in this module. However, experience with glucocorticoid and immunosuppressive therapies is necessary to understand their potential benefits and risks for the vasculitides.

Even though the incidence of ANCA-associated vasculitides has substantially increased during the past 10 years for several reasons, including better awareness of these diseases, they remain uncommon, with less than 30 new cases per million population each year. It is therefore probable that every rheumatologist will be confronted at least once in his/her life with an affected patient. The incidence of PAN has decreased over the past decades, along with that of hepatitis B virus (HBV) infection, but cutaneous polyarteritis remains common.

2 Introduction

Systemic vasculitides are a heterogeneous group of diseases characterised by inflammation of vessel walls. They are defined according to the Chapel Hill nomenclature, published in 1994 and revised in 2012 (box 1), which is mainly based on the calibre of the predominantly affected vessels (Jennette et al, 1994; Jennette et al, 2013*). The group of large vessel vasculitides includes giant cell arteritis and Takayasu's disease, while medium vessel vasculitides include Kawasaki disease and PAN. The small vessel vasculitides are divided into two categories, depending on the presence of immune deposits: immune complex small vessel vasculitis and ANCA-associated vasculitis (AAV). The first category, characterised by moderate to marked vessel wall deposits of immunoglobulin and/or complement, is represented by anti-glomerular basement membrane disease, cryoglobulinaemic vasculitis, hypocomplementaemic urticarial vasculitis (anti-C1q vasculitis) and IgA vasculitis (Henoch–Schönlein). By contrast, AAV has few or no immune deposits and is associated with the presence of ANCA specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). Depending on their clinical presentation and ANCA specificity, AAV is divided into three major variants: GPA (Wegener's), MPA and EGPA (Churg–Strauss).

Box 1 2012 Revised International Chapel Hill nomenclature of vasculitides**Large vessel vasculitis**

- Takayasu arteritis
- Giant cell arteritis

Medium vessel vasculitis

- Polyarteritis nodosa
- Kawasaki disease

Small vessel vasculitis**ANCA-associated vasculitis**

- Microscopic polyangiitis
- Granulomatosis with polyangiitis (Wegener's)
- Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

Immune complex

- Anti-GBM disease (Goodpasture's)
- Cryoglobulinaemic vasculitis
- IgA vasculitis (Henoch–Schönlein)
- Hypocomplementaemic urticarial vasculitis (anti-C1q vasculitis)

Variable vessel vasculitis

- Behçet's disease
- Cogan's syndrome

Single organ vasculitis

- Cutaneous leucocytoclastic angiitis
- Cutaneous arteritis
- Primary CNS vasculitis
- Isolated aortitis
- Others

Vasculitis associated with systemic disease

- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

Vasculitis associated with probable aetiology

- Hepatitis C virus-associated cryoglobulinaemic vasculitis
- Hepatitis B virus-associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Drug-associated AAV
- Cancer-associated vasculitis
- Others

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CNS, central nervous system; GBM, glomerular basement membrane.

Adapted from Jennette et al, *Arthritis Rheum* 2013;65:1–11*.

PAN, GPA, EGPA and MPA (as well as other vasculitides such as Kawasaki disease) are classically (but not universally, because of the segmental distribution of the lesions) associated with fibrinoid necrosis of the arterial wall on histology; therefore they are often termed necrotising systemic vasculitides.

3 ANCA-associated vasculitides

3.1 Granulomatosis with polyangiitis (Wegener's)

3.1.1 Classification

GPA, formerly known as Wegener's granulomatosis or disease, was first described in 1931 by Klinger, with the clinical and pathological unique features added to the description in 1936 by Wegener. The disease is characterised by granulomatous necrotising inflammatory lesions of the upper and/or lower respiratory tract, often associated with pauci-immune glomerulonephritis, which in some cases can progress rapidly, resulting in significant loss of renal function. In 1990, the American College of Rheumatology (ACR) proposed four classification criteria for GPA in patients with documented vasculitis, with two being necessary to classify the patient with 88.2% sensitivity and 92.0% specificity (Leavitt et al, 1990).

3.1.2 Epidemiology

The reported incidence of GPA varies from 2 to 12 per million population and the prevalence from 24 to 157 per million people (Lane et al, 2005; Mohammad et al, 2009). There is some geographical variation, GPA being more frequent in northern rather than southern European countries. There appears to be variation in incidence over time, with spikes seen every 6–8 years, at least in the UK, especially for PR3-ANCA-associated GPA (annual incidence rising to 17.4/million/year in 1996–8 and in 2005–7, as compared with only 4.5/million/year between these periods) (Watts et al, 2011). Ethnicity may also be a factor because GPA is rarely seen in African Americans in comparison with whites (Cao et al, 2011). In addition, the annual incidence of GPA in Japan is only 2.1 per million people, compared with MPA at 18.2 per million people, and case series from China also suggest a lower incidence of GPA than MPA. There is no gender predominance in GPA and the peak incidence is in the fourth through sixth decades of life; by contrast, it is very much less common in children and adolescents (Lynch and Tazelaar, 2011).

Epidemiological studies have shown that exposure to some environmental agents such as silica, dust, cattle, hard metals or organic solvents was noted before diagnosis in some patients with GPA but these represented <10% of all cases (Lane et al, 2005).

3.1.3 Clinical manifestations

Clinical manifestations of GPA are summarised in table 1.

Table 1 Frequencies of organ/system involvement or manifestations at diagnosis of granulomatosis with polyangiitis (Wegener's)

Study	Patients (N)	Organ/system involved or manifestation (%)							
		ENT	Lung	Kidney	Heart	GI	Skin	CNS	PNS
Koldingsnes <i>et al</i> , 2003	56	80	61	80	20	5	34	13	23
Fauci <i>et al</i> , 1983	85	91	94	85	12	–	45	–	–
Reinhold-Keller <i>et al</i> , 2000	155	93.5	55	53.5	12.9	–	23.2	–	20.6
Hoffman <i>et al</i> , 1992	158	92	85	72	6	–	46	8	15
Stone, 2003	180	77	60	54	1.7	1.7	20	8.9	
Anderson <i>et al</i> , 1992	265	75	63	60	<4	–	25	–	–
Holle <i>et al</i> , 2010	445	91–98	52–67	44–54	6–24	1–8	20–32	10–12	39–41

CNS, central nervous system; ENT, ear, nose and throat; GI, gastrointestinal; PNS, peripheral nervous system.

3.1.3.1 General symptoms

Constitutional symptoms such as fever, weight loss and fatigue may occur at presentation or during the disease course in 30–80% of patients.

3.1.3.2 Musculoskeletal symptoms

Musculoskeletal symptoms are common, with non-erosive polyarthritis affecting medium- and large-size joints in two-thirds of patients (Lynch and Tazelaar, 2011).

3.1.3.3 Upper airway involvement

Granulomatous ear, nose and throat (ENT) lesions are the most typical manifestations of the disease, noted in more than three-quarters of patients at diagnosis, with crusting rhinitis, sinusitis, chronic otitis media, saddle-nose deformity (figure 1) and/or nasal septum perforation.

Hearing loss may occur (conductive and sensorineural) owing to inflammation of middle ear mucosa, dysfunction of the Eustachian tube or cochlear artery vasculitis. Oral manifestations are uncommon and may present as ulcerative stomatitis or hyperplastic gingivitis, 'Strawberry gingival hyperplasia' (figure 2). Laryngeal involvement can cause hoarseness and lead to subglottic stenosis in up to 15% of cases (Hoffman *et al*, 1992).

Figure 1 Saddle-nose deformity in a patient with granulomatosis with polyangiitis (Wegener's).



Figure 2 Localised hypertrophic and painful gingivitis (or strawberry-like gum) in a patient with granulomatosis with polyangiitis (Wegener's).



3.1.3.4 Pulmonary involvement

Two-thirds of patients have pulmonary involvement, with bilateral parenchymal nodules, cavitated in half of the cases (figures 3–8), and/or alveolar haemorrhage (figures 9-10) in 10–20% of patients being the more characteristic manifestations.

Figure 3 Lung nodule in a patient with granulomatosis with polyangiitis (Wegener's).

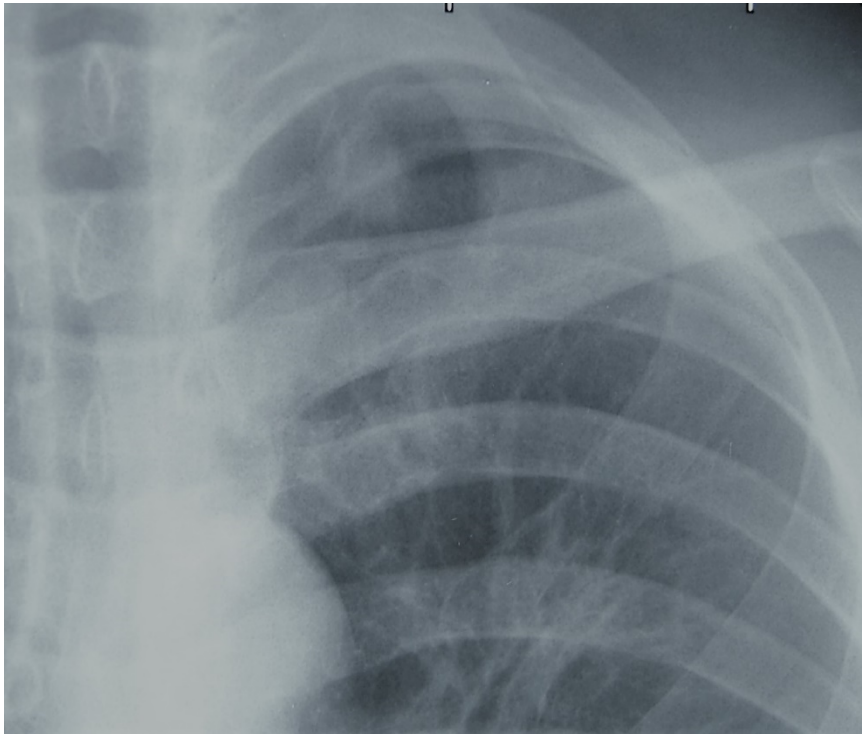


Figure 4 Lung nodule in a patient with granulomatosis with polyangiitis (Wegener's).

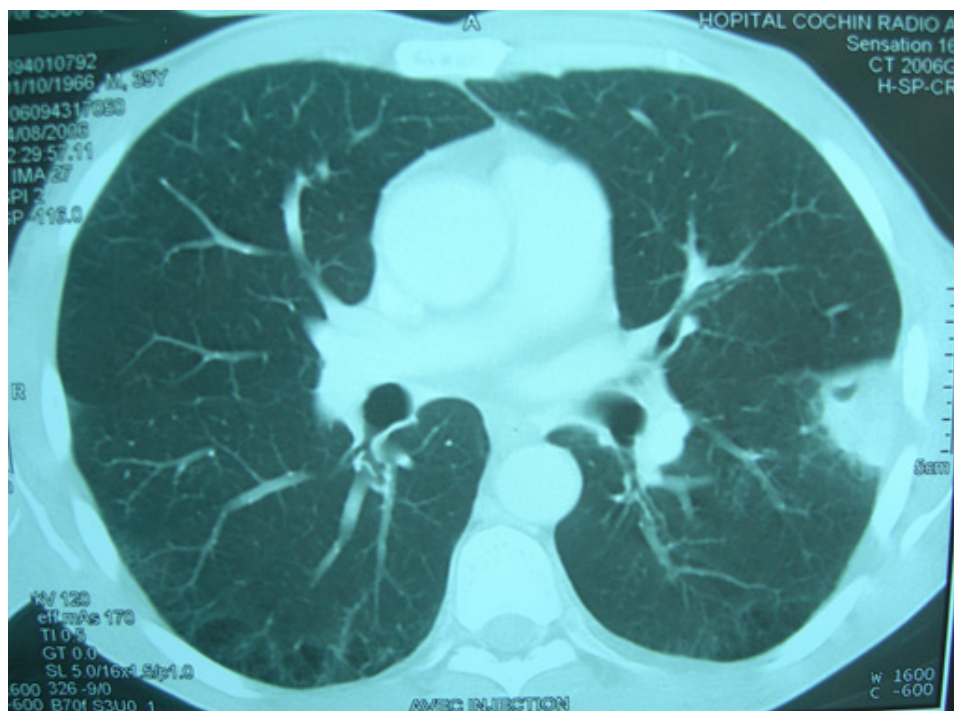


Figure 5 Apical lung nodules in a patient with granulomatosis with polyangiitis (Wegener's) (surrounded by some ground glass infiltrates).

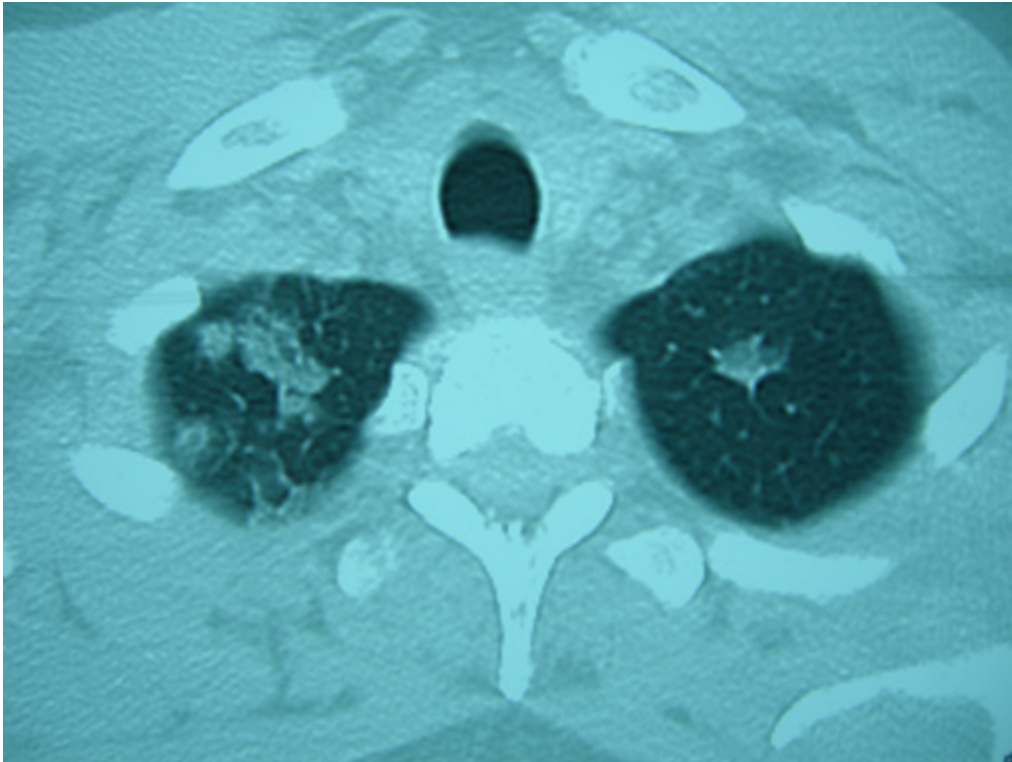


Figure 6 Peripheral lung nodule with surrounding inflammation and ground glass opacity, suggestive of perilesional haemorrhage, in a patient with granulomatosis with polyangiitis (Wegener's).

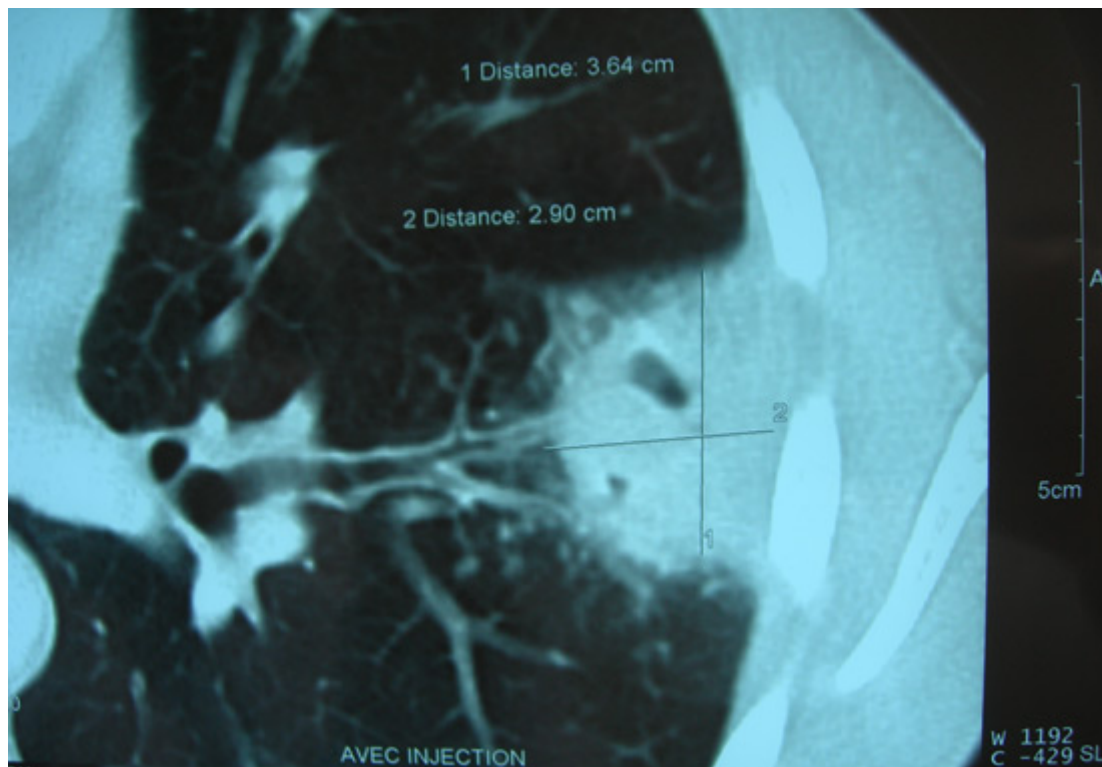


Figure 7 Lung nodules in a patient with granulomatosis with polyangiitis (Wegener's), including a large cavitated nodule.

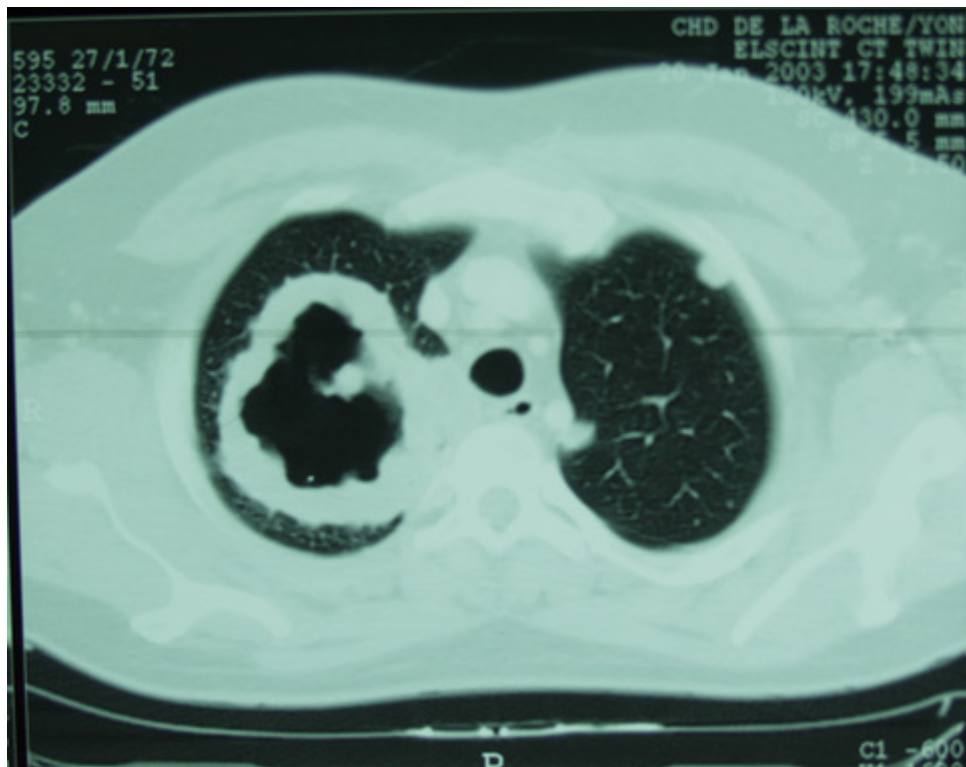


Figure 8 Cavitated lung nodule in a patient with granulomatosis with polyangiitis (Wegener's).

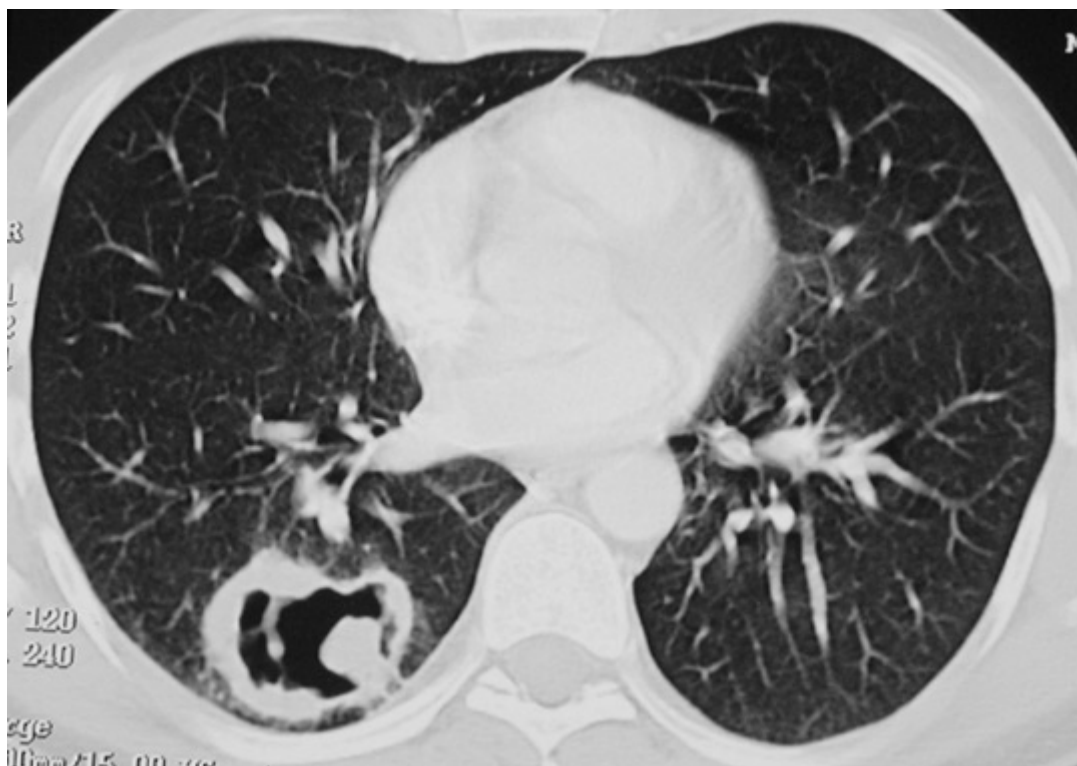
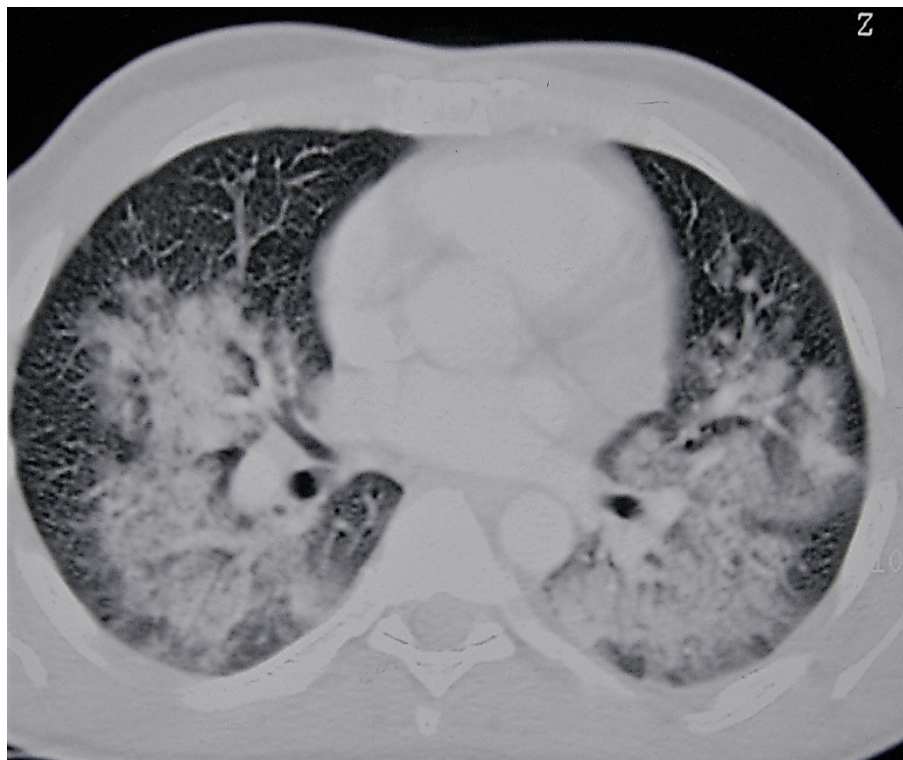


Figure 9 Bilateral lung infiltrate due to alveolar haemorrhage in a patient with granulomatosis with polyangiitis (Wegener's).



Figure 10 Bilateral lung infiltrate due to alveolar haemorrhage in the same patient with granulomatosis with polyangiitis (Wegener's).



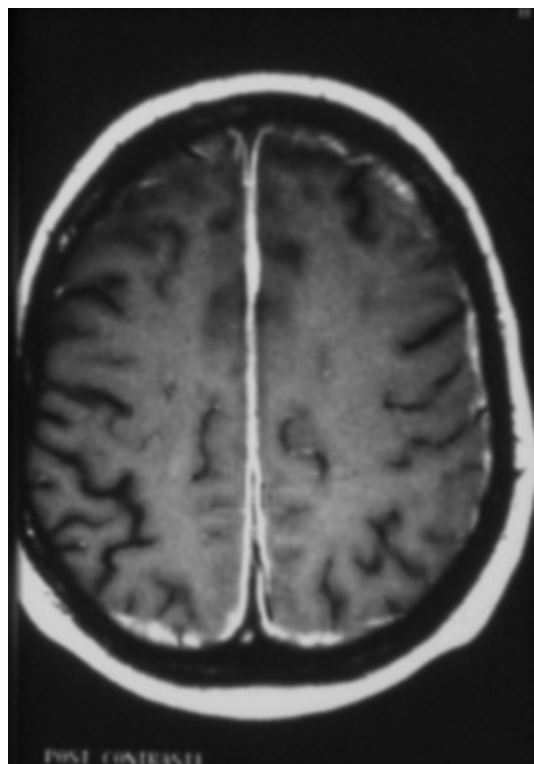
3.1.3.5 Renal involvement

Rapidly progressive glomerulonephritis, also called necrotising crescentic glomerulonephritis or pauci-immune glomerulonephritis, is the third main manifestation of GPA, noted in 40–100% of patients depending on the series (i.e., more commonly in nephrology versus rheumatology series).

3.1.3.6 Neurological involvement

Peripheral nervous system involvement occurs in one-third of patients, mainly represented by mononeuritis multiplex (79% of the patients with peripheral neuropathy), then sensorimotor polyneuropathy. Central nervous system (CNS) involvement is less common and can be seen in 6–13% of patients, usually later in the course of the disease. Initial presentation with pachymeningitis is one of the described CNS manifestations, which is suggestive, but not specific, for GPA (figure 11).

Figure 11 Pachymeningitis in a patient with granulomatosis with polyangiitis (Wegener's). Note the thickened meninges with increased brightness (gadolinium-enhanced T1 sequence).



3.1.3.7 Skin lesions

Skin lesions occur in 10–50% of patients, with palpable purpura of the legs and feet being the most common manifestation. Necrotic papules on the extensor surfaces of the limbs, nodules or extensive and painful cutaneous ulcerations are less common but suggestive of the disease (figures 12–14).

Figure 12 Necrotic and purpuric skin lesions in a patient with granulomatosis with polyangiitis (Wegener's).



Figure 13 Maculopapular, purpuric and necrotic skin lesions in a patient with granulomatosis with polyangiitis (Wegener's).



Figure 14 Distal ischaemic lesions of the fingers in a patient with granulomatosis with polyangiitis (Wegener's).



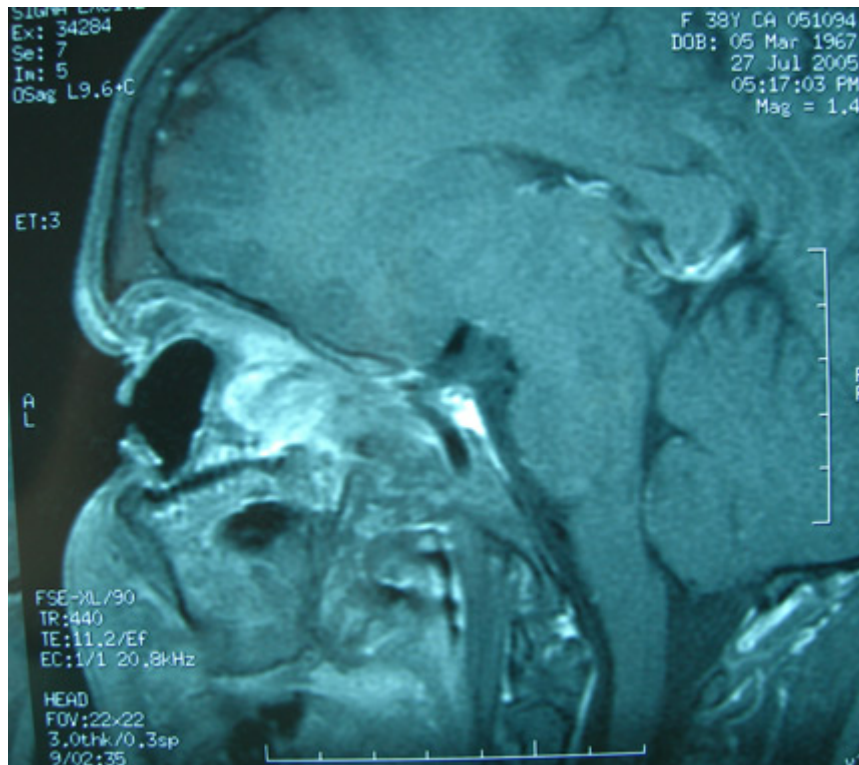
3.1.3.8 Other clinical manifestations

Eye involvement, mainly episcleritis, is also frequent in GPA. Orbital granuloma or pseudo-tumour (which constitutes 15% of the eye involvement) may compress important muscles or nerves (figures 15 and 16). Gastrointestinal involvement is uncommon (usually detected in autopsy studies) (Deniz et al, 2007) and cardiac manifestations are reported with a frequency varying from 0% to 12%.

Figure 15 Left posterior intraorbital (intraconic) granulomatous pseudo-tumour in a patient with granulomatosis with polyangiitis (Wegener's); the patient's left eye had to be surgically removed because of painful ocular compression and ischaemia (horizontal MR image).



Figure 16 Left posterior intraorbital granulomatous pseudo-tumour in a patient with granulomatosis with polyangiitis (Wegener's); the patient's left eye had to be surgically removed because of painful ocular compression and ischaemia (parasagittal MR image).



Some studies have highlighted the higher risk of venous thrombosis in patients with GPA (as well as in MPA and EGPA, but not PAN) during the active phases of the disease. Indeed, the incidence rate of venous thromboses was 7 per 100 patients/year, as compared with 0.3 per 100 patients/year in the general population; this finding would justify closer monitoring of the patients for those events but could not be used to justify systematic prophylaxis with anticoagulation for all patients (Merkel et al, 2005; Stassen et al, 2008; Allenbach et al, 2009).

3.1.4 Phenotypes of GPA

Although to date their precise definitions are not widely accepted, at least two different forms of GPA may be distinguished: systemic/generalised/severe forms and localised/limited/early-systemic forms (Hoffman et al, 1992; Merkel et al, 2005). Systemic GPA is represented by kidney involvement, alveolar haemorrhage, involvement of one or more other vital organ(s) or less severe manifestation(s) but with significant general systemic symptoms, such as fever and/or weight loss. Limited disease corresponds to GPA whose manifestations remain limited mostly to the upper respiratory tract or, more rarely, skin (i.e., not life or major organ threatening manifestations). Notably, these forms seem also to differ histologically, with systemic GPA being associated more often with predominantly vasculitic lesions and localised GPA with marked granulomatous features (Godman and Churg, 1954), possibly because of a more central role of Th2 T lymphocytes in the former and Th1 T lymphocytes in the latter. In addition, whereas 90% of patients with

systemic GPA have cytoplasmic ANCA (cANCA), with a diffuse cytoplasmic pattern on immunofluorescence assay and directed towards PR3 on enzyme-linked immunosorbent assay (ELISA), only 50–80% of those with limited GPA are ANCA positive.

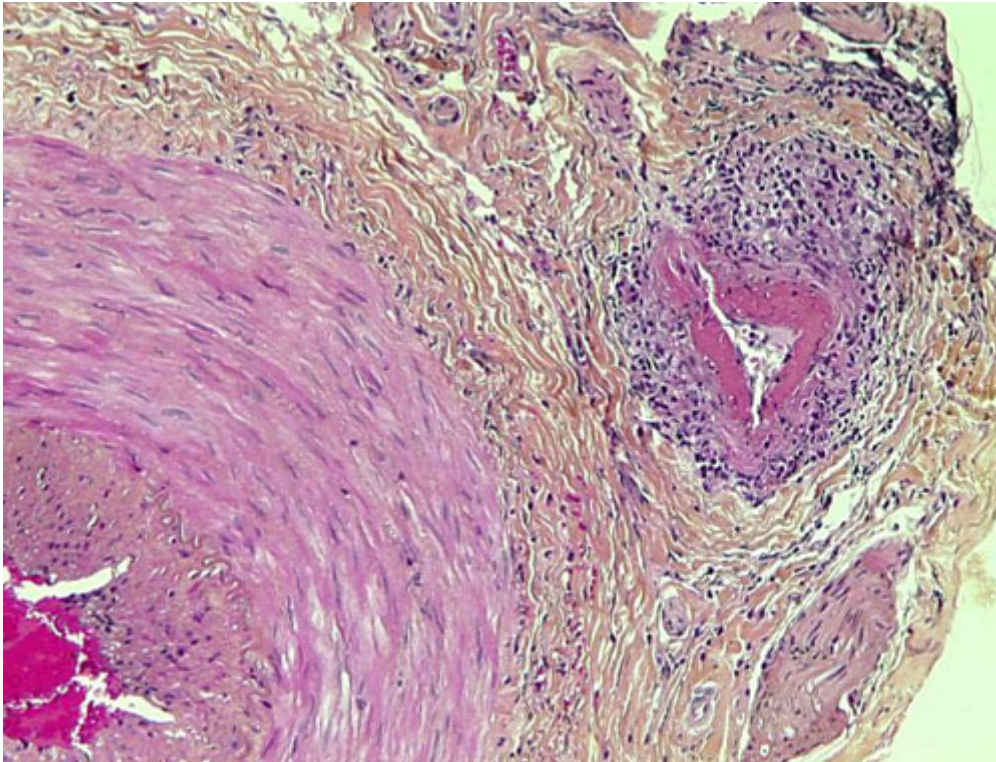
These limited/localised forms represent less than one-third of all GPA cases at diagnosis and especially occur in women, and at a slightly younger age than in those with systemic GPA (Stone, 2003). However, most of them will evolve over time to a more systemic form and patients with persistently and strictly localised GPA are thus rare and represent <5% of all patients with GPA (Holle et al, 2010; Pagnoux et al, 2011). Conversely, once life-threatening manifestations have been treated and controlled, systemic GPA can further evolve as a localised but often persistent form, as evidenced by crusting rhinitis or subglottic stenosis.

3.1.5 Histology

In some patients, the combination of highly suggestive clinical features and the detection of anti-PR3 cANCA can be sufficient to make the diagnosis of GPA and begin treatment. However, histological confirmation of the diagnosis is preferred and it should be performed when there is a suspicion of kidney involvement. It has a prognostic value for renal recovery (Lind van Wijngaarden et al, 2006; Berden et al, 2010). In addition, renal biopsy can also be important to exclude other causes of renal problems, such as drug toxicity.

Nasal and/or sinus biopsy is easy to perform, but only 20% and 50% of such biopsies, respectively, contribute to diagnosis (Devaney et al, 1990; Duna et al, 1995). Cutaneous biopsy often shows small vessel leucocytoclastic vasculitis, which is non-specific. Skin nodules are rare in GPA but can coincide with necrotising or granulomatous vasculitis of medium arterioles or, most often, extravascular granulomas. Bronchoscopy with examination of bronchoalveolar fluid can confirm alveolar haemorrhage, when present, but also, and, more importantly, rule out and/or diagnose associated infection, when suspected. Bronchial biopsy can reveal granulomatous inflammation in a maximum of 25% of cases, but rarely shows vasculitis. Surgical biopsy of lung nodules more often contributes to diagnosis, showing necrotising vasculitis in up to 60% of cases, sometimes in association with vascular or extravascular granuloma, but can sometimes be feasible only with open-lung surgery. In cases of alveolar haemorrhage, lung biopsy may show diffuse alveolar infiltrate and haemorrhage, with varying degrees of necrotising capillaritis and some granulomatous inflammation. Tracheal biopsy in cases of subglottic lesions with stenosis can be dangerous and contributes to diagnosis in less than a quarter of cases. Neuromuscular biopsy, especially of the peroneal muscle and nerve branches, has a diagnostic sensitivity of 60% in patients with clinically diagnosed peripheral nerve involvement (figure 17), but can lead to definitive sensory deficit at the site of the biopsy.

Figure 17 Vasculitis of a small branch of a larger and normal artery on a neuromuscular biopsy sample from a patient with granulomatosis with polyangiitis (Wegener's).



3.1.6 Pathogenesis of GPA

The aetiology and pathogenesis of GPA remain unknown, but as in many other autoimmune conditions, appear to be multifactorial, involving the interaction between a genetically predisposed host, environmental factors and a breakdown of immune tolerance (Jennette and Falk, 2013).

Studies have shown a genetic predisposition in GPA. It has been confirmed that multiple HLA genes are prevalent in different AAV populations, with HLA-DPB1 being over-represented in patients with GPA (Heckmann et al, 2008). In addition, a genome-wide association study has provided evidence for the association of PR3-ANCA disease and SERPINA1 and PRTN3. SERPINA1 encodes α -1 antitrypsin, a serine protease which has PR3 as one of its substrates, and PRTN3 encodes PR3 (Lyons et al, 2012).

A pathogenic role for ANCA has been supported by several in vitro and in vivo animal models. However, unlike MPO-ANCA disease, a robust animal model of PR3-ANCA disease has not yet been developed. PR3 is a 29 kDa neutrophil serine protease encoded by a single gene located on chromosome 19p13.3. This protein is mainly stored in primary granules of human neutrophils and monocytes, but is also present at the cell membrane surface, with genetic regulation of its expression. Following tumour necrosis factor α priming, the ANCA-target antigen expression on the neutrophil membrane surface increases owing to membrane flip-flop with externalisation of the inner membrane-bound PR3, as well as the exocytosis of granule contents, making PR3

more accessible for interaction with ANCA. ANCA thereafter promote neutrophil adhesion to endothelial cells and their lysis. ANCA can also activate monocytes, which results in enhanced production of reactive oxygen species (Jennette et al, 2011a*; Kallenberg, 2011).

Pertinently, in GPA, higher levels of membrane-bound PR3 expression have been demonstrated as a result of its flip-flop following neutrophil activation, which involves interactions with phospholipid scramblase 1 and may interfere with macrophage clearance of apoptotic neutrophils (Kantari et al, 2005). However, the primary mechanisms leading to the synthesis of ANCA and to the shift from natural to pathogenic autoantibodies and, eventually, the mechanisms leading to the formation of granulomas in GPA are not clearly understood. Passive transfer of anti-PR3-ANCA in animal models has been demonstrated relatively little so far, requiring additional costimulation(s) or very specific genetic backgrounds to observe any inflammation or limited vasculitis, with no or almost no granuloma (Pfister et al, 2004*; Primo et al, 2010). Pendergraft et al showed that immunisation with the middle region of the protein derived from the antisense DNA strand of PR3 (cPR3) resulted (in a mouse model) in the production of antibodies not only to cPR3 but also to PR3, which are bound to each other, indicating idiotypic relationships (Pendergraft et al, 2004). The authors suggested, by comparing protein gene sequences, that these anti-cPR3 antibodies might be produced in vivo as a response to various microbial challenges, such as *Staphylococcus aureus*, that would cross-react with the autoantigen (cPR3). In vitro, PR3 can induce the maturation of dendritic cells via the protease-activated receptor-2 pathway (Csernok et al, 2006). These dendritic cells thereby become fully competent antigen-presenting cells and can induce stimulation of specific CD4 T cells, which produce interferon γ , as a Th1-like autoimmune response, potentially favouring granuloma formation.

In addition, Abdulahad et al demonstrated that patients with remitting GPA had an expanded proportion of regulatory T cells, a subset of CD4 T cells that express CD25 (high) and FoxP3, but are functionally defective, potentially further leading to the persistence of the autoimmune response (Abdulahad et al, 2007). Recently, PR3 has been shown to induce platelet shape change, but not aggregation, adding another mechanism to the complex interaction between neutrophils and platelets (Peng et al, 2014).

In addition, PR3 expressed on apoptotic neutrophils impairs resolution of inflammation by interfering with phagocytosis of these cells by macrophages. Recent data have shown how PR3 may disrupt immune silencing associated with clearance of apoptotic neutrophils (Millet et al, 2015). The membrane-bound PR3 perpetuates inflammation through macrophage polarization and effects on plasmacytoid dendritic cell (pDC)–T-cell interactions, suggesting that PR3 expressed on the membrane of apoptotic cells acts as a ‘danger’ signal, and that PR3-ANCA-associated vasculitis might be considered not only as an autoimmune disease, but also as a nonresolving autoinflammatory disease.

Finally, other pathogenic mechanisms or autoantibodies may also be involved in GPA. Some patients with GPA (5%) have perinuclear-labelling pANCA with anti-myeloperoxidase (MPO) specificity, preferentially seen in MPA, rather than anti-PR3 cANCA (the distinction between GPA and MPA can be difficult in those cases). In addition, antibodies against lysosomal membrane protein 2 (LAMP-2) have been reported in AAV, with a prevalence of up to 90% in untreated patients at presentation (Kain et al, 2008; Kain et al, 2012). However, there are still insufficient data about their pathogenicity. Kain et al reported that the immunisation of rats with anti-LAMP-2 induced focal necrotising glomerulonephritis, but no other group has been able to reproduce these results so far (Roth et al, 2012). In these studies anti-LAMP-2 antibodies were generated after immunisation with FimH, a bacterial adhesion of common Gram-negative fimbriated bacteria, such as *Escherichia coli*. This cross-reactivity between FimH and LAMP-2 raises the question as to whether natural infection with fimbriated bacteria might induce AAV. In favour of this hypothesis Kain et al reported that nine of 13 consecutive patients presenting with AAV had had a microbiologically proven infection with a fimbriated organism within the preceding 3 months; and Roth et al reported that 12% of a sample of 105 patients with urinary tract infections had positive assays for LAMP-2 in their ELISA. Currently, the INTRICATE Consortium (<http://www.intricate.eu/>) is conducting a multicentre prospective observational study to determine whether infections with type 1 fimbriated bacteria induce antibodies to LAMP-2 in man, and to study their possible association with AAV (Kain, 2013).

3.2 Microscopic polyangiitis

3.2.1 Classification criteria

MPA did not appear in the classification criteria established in 1990 by the ACR. PAN and MPA were then thought to be different forms of the same disease because some clinical manifestations are very similar and MPA was thus initially considered to be a 'microscopic' form of PAN. MPA was unanimously recognised in the mid-1990s, with the Chapel Hill nomenclature, as a clearly different entity among systemic vasculitides (Jennette et al, 1994). The discovery of ANCA (van der Woude, 1985), which are only present in some small vessel vasculitides and not in PAN, further supported the distinction between MPA and PAN.

3.2.2 Epidemiology

Like all other vasculitides, MPA is a rare disease. Because PAN and MPA have long been grouped together in published studies, valid epidemiological data are sparse and only the more recent studies can be considered reliable for MPA frequencies.

MPA has been reported worldwide and can affect all racial groups, but with a predominance in Caucasians. Men are affected slightly more often, with the male to female ratio ranging from 1.1 to 1.8. The average age at

onset is about 50 years. The total annual incidence is estimated at 3–24 per million population, and the prevalence at 25–94 per million population (Mohammad et al, 2007; Mohammad et al, 2009).

3.2.3 Clinical features

The main clinical features of MPA are listed in table 2.

Table 2 Microscopic polyangiitis: clinical features and organ or system involvement, expressed as percentages of the studied population (N = 235 in total)

Characteristics	Serra et al, 1984	Savage et al, 1985	D'Agati et al, 1986	Adu et al, 1987	Guillevin et al, 1999*
No. of patients	53	34	20	43	85
Mean age (years)	53	50	50	–	57
Sex ratio (male/female)	1.5	1.8	1	1.7	1.2
General signs (fever, asthenia, myalgias, arthralgias)	79	76	–	–	73
Hypertension	26	29	35	21	34
Kidney	100	100	100	100	79
Skin	60	–	35	53	62
Purpura	40	44	–	–	41
Lung	55	–	55	34	25
Haemoptysis	23	32	–	–	–
Infiltrates	30	–	–	–	10
Pleural effusion	19	15	–	–	6
Gastrointestinal tract	51	–	–	56	30
Ear, nose, throat	30	–	–	20	–
Sinusitis	6	9	–	–	11
Eyes	30	–	–	28	–
Nervous system	28	–	–	–	–
Peripheral	19	18	15	14	58
Central	15	18	40	0	12
Heart	15	–	–	9	–

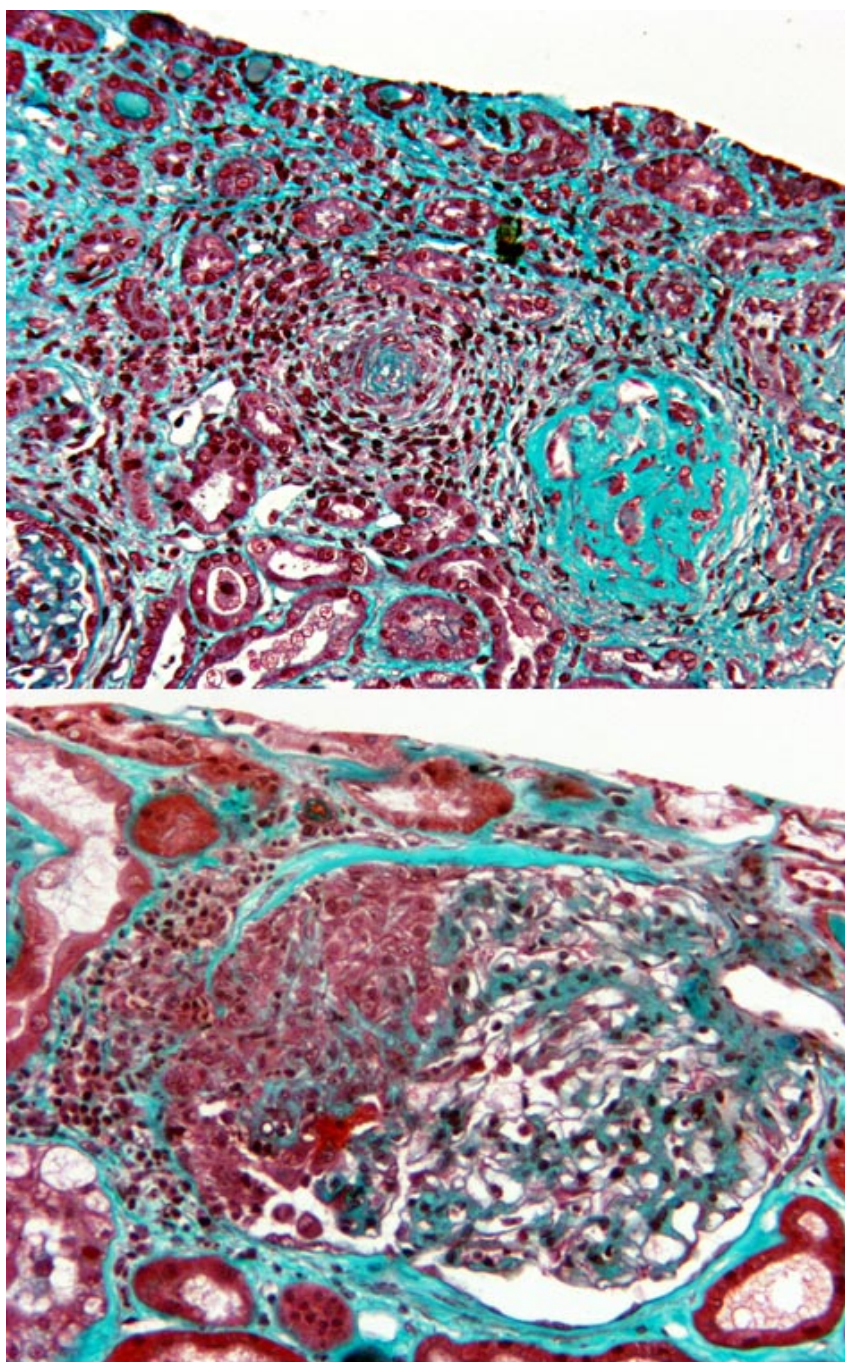
3.2.3.1 General symptoms and clinical presentation at disease onset

Most patients have some general systemic symptoms before MPA is diagnosed, such as myalgias, arthralgias and/or, more rarely, arthritis, that are present in 56–76% of patients at the time of diagnosis. An indolent course of several months, or even years, before diagnosis can be made, with mild general symptoms and/or even episodic, mild and ignored blood stained sputum.

3.2.3.2 Renal involvement

Rapidly progressive glomerulonephritis is a major feature of MPA (figure 18). Renal involvement appeared to be nearly universal in the first series of patients with MPA, but these cases were mainly reported by nephrologists (Primo et al, 2010). Initial renal manifestations are often silent, but detection of microscopic haematuria with or without proteinuria usually precedes renal function deterioration. Patients who have only renal involvement are often referred to as having kidney-limited disease or renal vasculitis. Most of these cases will evolve, if insufficiently treated, to MPA (or GPA).

Figure 18 Renal histology in a patient with microscopic polyangiitis showing vasculitis and glomerular scars.



3.2.3.3 Pulmonary involvement

The classic pulmonary manifestation of MPA is diffuse alveolar haemorrhage caused by pulmonary capillaritis. Moreover, like GPA or anti-glomerular basement membrane disease (Goodpasture), MPA can also be responsible for a pulmonary–renal syndrome. Haemoptysis or moderately bloody expectorations may precede severe pulmonary haemorrhage, which is characterised by dyspnoea and anaemia, and may progress to more diffuse alveolar damage and respiratory distress syndrome (Primo et al, 2010). Bronchial arteritis can also be found during histological examination of a lung biopsy specimen.

Interstitial lung fibrosis is a less well-recognised pulmonary manifestation of MPA, which may or may not follow alveolar haemorrhage. It has also been described as an isolated process confined to the lungs in some patients with anti-MPO pANCA, more frequently in the Japanese population. In a recent report from a Chinese cohort of patients with MPA, 19/67 presented with pulmonary fibrosis (Huang et al, 2014). These patients were older, mainly female and only six had an initially positive MPO-ANCA (the others became MPO-ANCA positive during follow-up).

3.2.3.4 Cutaneous manifestations

Skin lesions are found in half of patients with MPA. Maculopapular purpuric lesions of the lower limbs are the most frequent skin manifestations. Other lesions are vesicles, necrosis, ulcerations, nodules, splinter haemorrhages, livedo reticularis, hand and/or finger erythema, facial oedema and mouth ulcers. On histology, leukocytoclastic, but non-specific, vasculitis of the small vessels of the dermis, can be seen in the lesions.

3.2.3.5 Neurological involvement

Mononeuritis multiplex affects two-thirds of patients with peripheral nervous system involvement, followed by symmetric polyneuropathy. Necrotising vasculitis can be seen in 80% of sural nerve biopsies. CNS involvement and cranial neuropathies have been reported in around 10% of patients.

3.2.3.6 Gastrointestinal involvement

Abdominal pain is the most frequently reported gastrointestinal symptom, present in up to 50% of patients. Sometimes, bleeding or more severe small intestine or large bowel ischaemia, ulcerations and/or perforations may occur.

3.2.3.7 Other clinical manifestations

Cardiovascular complications in MPA are rare. Among 85 patients with MPA heart failure and/or pericarditis occurred at frequencies of 17.6% and 10%, respectively (Guillevin et al, 1999*). Severe acute congestive heart failure has been reported, but rarely with documented myocardial infarction. However, subclinical myocardial

infarctions may be more common. Ocular manifestations, such as eyelid inflammation, retinal cotton-wool spots, retinal vasculitis and/or choroiditis, may be seen in MPA, but rarely. Pertinently, mild, non-granulomatous, non-erosive, and thus non-specific, sinus inflammation may be noted in MPA. However, there is some controversy about even such non-specific ENT involvement, which is sometimes considered to be an excluding feature for the diagnosis of MPA when present and should prompt consideration of GPA as the alternative diagnosis, but this remains controversial.

3.2.4 Laboratory findings and complementary investigations

There is no specific laboratory test for diagnosing MPA. ANCA are detected in 60–80% of patients with MPA. The majority of ANCA detected are pANCA anti-MPO, although anti-PR3 can also rarely be found. Anti-MPO-ANCA are not as specific for MPA as anti-PR3-ANCA are for GPA, partly because they can also be found in EGPA, in about 5% of patients with GPA, in drug-induced AAV and in a variety of other different inflammatory disorders.

As in the other AAV, non-specific markers of inflammation are found in MPA: raised erythrocyte sedimentation rate, C-reactive protein level, platelet and white blood cell counts and low haemoglobin (normochromic normocytic anaemia) and serum albumin.

In patients with renal involvement, microscopic haematuria is present in almost all cases and may reflect disease activity, damage, infection or haemorrhagic cystitis/bladder malignancy due to cyclophosphamide therapy. The presence of red cell casts is highly suggestive of an active glomerulonephritis, but is difficult to detect in daily practice. Proteinuria can be found in >90% of patients, but is usually <3 g per 24 h.

Renal histology in patients with kidney manifestations is characterised by the presence of focal segmental thrombosing and necrotising glomerulonephritis. Extracapillary crescents are present in nearly all renal biopsies and often involve more than 60% of the glomeruli. The severity of renal impairment and the prognosis for renal function has been reported to correlate with the presence of glomerular sclerosis and tubular damage, and active glomerular disease with crescents (Berden et al, 2010).

Visceral angiography is not part of the usual diagnostic investigations of MPA. When performed, and based on the results of earlier series in which patients with MPA and PAN were mixed, it is usually normal in MPA, without stenoses and/or microaneurysms as found in PAN (however, rare cases of anti-MPO-ANCA-positive MPA with visceral microaneurysms have been reported).

3.2.5 Pathogenesis

Animal models (Heeringa et al, 1998; Xiao et al, 2002*) support a direct pathogenic role of anti-MPO pANCA. MPO constitutes about 5% of all neutrophil proteins and is present in the cytoplasmic primary granules at high

concentrations. The experimental model from Xiao et al is based on the passive transfer of anti-murine MPO antibodies or splenocytes, obtained from MPO-deficient mice immunised with murine MPO, into mice lacking T and B cells (with inactivated recombina-activating gene 2—rag2) and into wild-type mice. This resulted in the development of severe necrotising crescentic glomerulonephritis and systemic necrotising vasculitis, including haemorrhagic pulmonary capillaritis, closely resembling human disease. Little et al using an experimental rat model, showed that immunisation of a particular rat strain with human MPO led to the synthesis of antibodies recognising murine MPO and to the development of systemic vasculitis with pauci-immune glomerulonephritis (Little et al, 2006). Subsequently, passive transfer of purified IgG anti-MPO from immunised rats into non-immunised rats also induced systemic vasculitis.

Despite these animal models, evidence that MPO-ANCA alone can be pathogenic in humans remains inconclusive. A case of transplacental transfer of MPO-ANCA has been reported to result in neonatal MPA (Bansal and Tobin, 2004). However, a subsequent case report documents a successful pregnancy of a healthy newborn despite transplacental transfer of MPO-ANCA (Silva et al, 2009).

The potential role of T cells in MPA, as opposed to GPA, is poorly established. The mouse model of Xiao et al described above, showed that vasculitis is caused by anti-MPO alone and not by T cells.

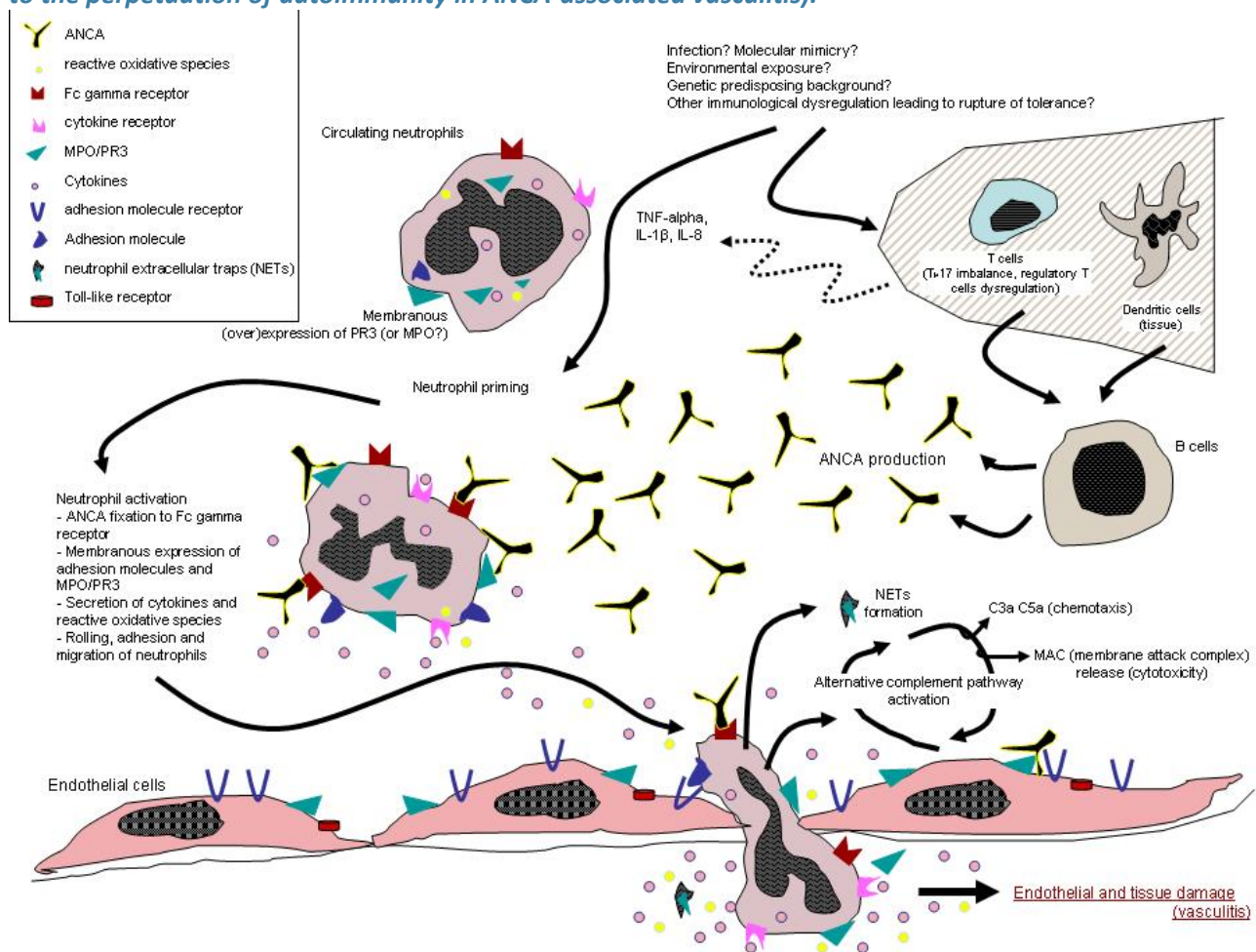
Recent reports have shown that activation of the alternative pathway of complement is required for development of vasculitis. Complement is activated by factors released by neutrophils stimulated by ANCA, and C5a can prime neutrophils to enhance ANCA-induced neutrophil activation (Xiao et al, 2005; Cartin-Ceba et al, 2012). In an animal model, mice lacking the neutrophil receptor for C5a did not develop glomerulonephritis (Schreiber et al, 2009). Thus, the complement system is a potential target for treatment in human AAV (Kallenberg et al, 2013) currently being investigated (Jayne et al, 2017).

In addition, modifications in the Fc gamma receptor, present in neutrophils, have also been involved in the pathogenesis and modulation of the disease (Jennette and Falk, 2013b).

Epigenetic and genetic factors may have a marked influence on the pathogenesis and severity of the disease (Jennette et al, 2011b; Xiao et al, 2013). Recently, a genome-wide association study implicated a genetic influence of HLA-DQ in MPO-ANCA disease, suggesting that GPA and MPA are distinct genetic entities (Lyons et al, 2012).

The main putative pathogenic mechanisms of AAV are shown in figure 19. This schematic representation applies to MPA and probably also to GPA. For EGPA, the role of ANCA is less clear cut, and there is likely to be an important role for the eosinophil in some manifestations.

Figure 19 Schematic representation of the main hypothesised antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis pathogenic mechanisms. IL, interleukin; MPO, myeloperoxidase; PR3, proteinase 3; TNF, tumour necrosis factor. The trigger(s) for neutrophil activation and the production of pathogenic ANCA remain putative. Dysregulated T cells and dendritic cells may play important and/or contributory roles. Once primed, neutrophils become further activated by the fixation of ANCA to MPO (or PR3) and Fc gamma receptors expressed on the cell surface. Surface expression may be constitutively upregulated in patients with granulomatosis with polyangiitis (Wegener's) (and further increased after neutrophil priming). Activated neutrophils are attracted to target vessels and tissues through the expression of several adhesion molecules and possibly other molecular tracking systems, such as toll-like receptors. The release, by activated neutrophils, of reactive oxidative species, proteinases (including PR3 or MPO) and cytokines, results in endothelial and tissue injury (vasculitis). Activated neutrophils also activate an alternative complement pathway and cause the release into the bloodstream and locally injured tissues of neutrophil extracellular traps (NETs) (potentially toxic locally, especially in the kidneys, and/or contributing to the perpetuation of autoimmunity in ANCA-associated vasculitis).



In MPA, there are a substantial number of ANCA-negative patients in whom all these models fail to explain the pathogenesis of their disease. In these cases, anti-LAMP-2 might have a pathogenic role. The presence of anti-endothelial cell antibodies and a predisposed innate immune system may also be associated with the vascular inflammation found in those patients (Damianovich et al, 1996).

3.3 Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

3.3.1 Classification

EGPA (Churg–Strauss) is a disorder characterised by pulmonary and systemic small vessel vasculitis, extravascular granulomas and hypereosinophilia, which characteristically occurs in people with background late-onset asthma and allergic rhinitis. It was first described in 1951 by two pathologists, Churg and Strauss, who established three major histological criteria: tissue infiltration by eosinophils, necrotising vasculitis and extravascular granulomas (Churg and Strauss, 1951). However, these three histological components rarely coexist temporally or spatially in the patients we see today. In 1984 Lanham et al proposed clinical criteria that are useful for the diagnosis of EGPA: the association of asthma, blood eosinophil count $>1500/\text{mm}^3$ and symptoms of systemic vasculitis affecting at least two extrapulmonary sites (sensitivity of 95% and specificity of 95%). In 1990, the ACR proposed six classification criteria for EGPA in patients with documented vasculitis, with four being necessary for diagnosis of EGPA with 85% sensitivity and 99.7% specificity (Masi et al, 1990).

3.3.2 Epidemiology

EGPA is the least common of the AAV. Its annual incidence is between 0 and 4 per million population and prevalence is between 7 and 22 per million population (Mohammad et al, 2009). The mean age at diagnosis of EGPA is around 45–50 years, with a male to female ratio of about 1.

3.3.3 Clinical features

The main clinical features of EGPA are described in table 3.

3.3.3.1 Natural history of EGPA

Lanham et al identified three phases of the disease. The prodromal period may last for over 30 years and consists of asthma and other common and non-specific allergic manifestations (allergic rhinitis and nasal polyposis). The second phase of the disease is characterised by the onset of peripheral blood and tissue eosinophilia with Löffler's syndrome, chronic eosinophilic pneumonia or eosinophilic gastroenteritis; the eosinophilic infiltrative disease may remit and recur over the years before systemic vasculitis appears and defines the third phase of the disease, although these three phases do not necessarily follow one another in this order. Systemic vasculitis emerges a mean of 4–9 years after the onset of asthma, with reports indicating a maximum latency of 30 years.

Table 3 Clinical manifestations of eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

Characteristics	Chumbley <i>et al</i> , 1977	Lanham <i>et al</i> , 1984	Guillevin <i>et al</i> , 1987	Haas <i>et al</i> , 1991	Abu- Shakra <i>et al</i> , 1994	Guillevin <i>et al</i> , 1999	Solans <i>et al</i> , 2001	Comarmond <i>et al</i> , 2013
No. of patients (n)	30	16	43	16	12	96	32	383
Sex (M/F)	21/9	12/4	24/19	12/4	6/6	45/51	9/23	199/184
Mean age (years)	47	38	43	42	48	48	42	50
Age range (years)	15–69		7–66	17–74	28–70	17–74	17–85	
Asthma (%)	100	100	100	100	100	100	100	91
General symptoms (%)			72	100	100	70	69	49
Pulmonary infiltrates (%)	27	72	77	62	58	38	53	39
ENT manifestations (%)	70	70	21	10	83	47		48
Mononeuritis multiplex (%)	63	66	67	75	92	78	44	46
GI manifestations (%)	17	59	37	56	8	33	38	23
Cardiac manifestations (%)	16	47	49	56	42	30	28	31
Arthralgia/arthritis (%)	20	51	28	31	42	41		30
Myalgia (%)		68		43	33	54		39
Skin manifestations (%)	66			68	67	51	69	40
Purpura (%)		48	28	25		31	41	22
Nodules (%)	27	30	21	25		19	6	10
Renal manifestations (%)	20	49	16	31	8	16	13	22
Pleurisy (%)		29		25			19	9

ENT, ear, nose and throat; GI, gastrointestinal.

3.3.3.2 General symptoms

General symptoms, such as fever or weight loss, are present in most patients and their development in patients with asthma should alert physicians to the possibility of EGPA onset.

3.3.3.3 Musculoskeletal symptoms

Arthralgias are frequent and often occur during the first days or weeks. Arthritis with local inflammatory findings is rare, and joint deformity and radiographic erosions do not occur. Although arthralgia can affect all joints, it predominates in larger joints. Myalgias are present in half of patients.

3.3.3.4 Pulmonary manifestations

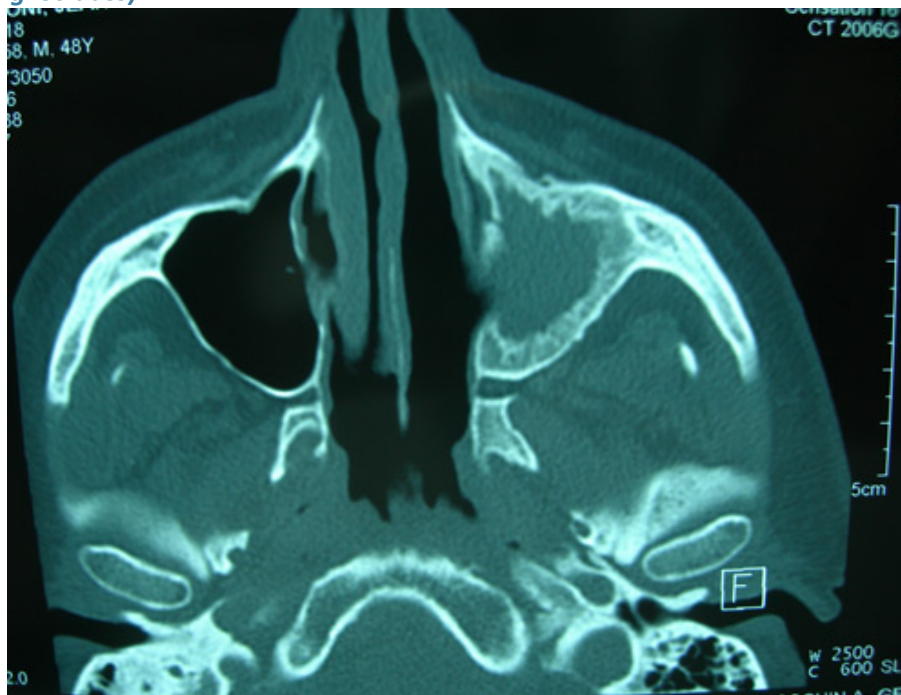
Asthma is the central feature of EGPA and precedes the systemic manifestations in nearly all cases. Unlike common asthma, it appears relatively late, around the age of 35 years. The severity and frequency of the asthmatic attacks usually increase until the onset of vasculitis. Although dramatic remission of asthma may occur when vasculitis emerges, asthma usually becomes more severe during the weeks preceding vasculitis and often glucocorticoid-dependent, with some patients requiring admission to hospital owing to respiratory failure. Chest radiographs are often abnormal and 38–77% of patients have transient and labile pulmonary

infiltrates, which rarely cavitate, in contrast to GPA. Pulmonary infiltrates, when present during the second phase of the disease, and in association with asthma and hypereosinophilia, may mimic chronic eosinophilic pneumonia. According to recent prospective studies, pleural effusion is rarely present at the time of diagnosis and was seen in only 3% of patients, usually as an eosinophil exudate.

3.3.3.5 ENT involvement

Maxillary sinusitis is common and 70% of patients have a history of allergic rhinitis and/or sinus polyposis (figure 20).

Figure 20 *Left maxillary sinusitis with osteoformation in a patient with eosinophilic granulomatosis with polyangiitis (Churg–Strauss).*



3.3.3.6 Neurological involvement

Peripheral neuropathy, usually mononeuritis multiplex, is found in 45–75% of patients, and its occurrence is highly suggestive of the diagnosis in a patient with asthma. CNS involvement is relatively rare. It occurs in 5–10% of patients and includes strokes and pachymeningitis.

3.3.3.7 Cutaneous lesions

Purpura is seen in nearly half of cases and subcutaneous nodules in 30%. Skin biopsies may show extravascular and eosinophilic granulomas. These nodules are the most distinctive skin lesions of EGPA. Other cutaneous manifestations have been reported, including Raynaud’s phenomenon, livedo reticularis, urticarial lesions, patchy skin necrosis, infiltrated papules, vesicles or bullae and toe or finger ischaemia.

3.3.3.8 Cardiac involvement

Cardiac involvement is common in EGPA and one of the hallmarks of the disease, because it is the major cause of death. The reported incidence of cardiac manifestations depends on the method used for their assessment, varying from 17%, when using electrocardiography, to 92%, in post mortem studies.

The spectrum of cardiac features in patients with EGPA includes pericarditis, myocarditis, arrhythmias and, more rarely, angina pectoris, myocardial infarction and sudden death. Echocardiography may show several abnormalities, including diminished contractile parameters, which are not specific for vasculitis. Studies (Marmursztejn et al, 2009; Dennert et al, 2010) have shown that cardiac MRI has a higher sensitivity in detecting cardiac involvement of the disease and it has been proposed for the evaluation of patients, with or without clinical symptoms. However, its prognostic value remains uncertain. For patients with no other signs of cardiomyopathy, cardiac magnetic resonance imaging-detected anomalies do not seem to adversely affect prognosis or outcome (Dunogu   et al, 2015).

3.3.3.9 Gastrointestinal involvement

Digestive tract symptoms, including abdominal pain, diarrhoea and bleeding, occur in 30–60% of patients. Bowel perforation is the most severe GI complication and is one of the major causes of death. Vasculitis and granulomas may be present throughout the GI tract, but occur more often in the small intestine and/or colon (Pagnoux et al, 2005).

3.3.3.10 Other manifestations

Renal disease can be seen but is uncommon in EGPA, especially in comparison with GPA and MPA. Depending on the series, it is usually found in <25% of patients. The glomerular lesion that typifies EGPA is focal segmental glomerulonephritis with necrotising features including crescents, indistinguishable from the other AAV; however, kidney disease is considered less severe, rarely causing renal failure. Other lesions are also possible, such as vasculitis, eosinophilic interstitial infiltrates and granuloma.

The eye can also be involved, and uveitis, retinal vasculitis, episcleritis and/or conjunctival nodules have been described.

3.3.4 Patient subgroups according to ANCA status

EGPA is associated with ANCA, mainly anti-MPO pANCA; however, only 25–40% of patients with EGPA are ANCA-positive. In those patients there is an increased frequency of renal involvement, constitutional symptoms, purpura, alveolar haemorrhage, mononeuritis multiplex and/or CNS involvement.

In ANCA-negative patients vasculitis has been reported less frequently in histological specimens, and eosinophil tissue infiltration is often more prominent. Furthermore, there is a higher incidence of cardiomyopathy, pericarditis, livedo and/or pulmonary infiltrates in those patients (Sable-Fourtassou et al, 2005; Sinico et al, 2005).

After a mean follow-up of 3 years, patient survival and relapse rates did not differ according to patient ANCA status, but long-term follow-up studies suggested a higher relapse rate in ANCA-positive patients and a higher mortality rate in ANCA-negative patients because the latter more often had cardiomyopathy (Baldini et al, 2009; Comarmond et al, 2013).

3.3.5 Complementary investigations and differential diagnosis

Apart from ANCAs, other abnormal findings can be found in EGPA. Eosinophilia is present in active untreated disease and often $>1500/\text{mm}^3$ (97% of patients). The absence of eosinophilia may be explained by prior glucocorticoid administration for asthma. The mean eosinophil count at diagnosis is around $7500/\text{mm}^3$, but the eosinophil count can exceed $50\,000/\text{mm}^3$. The association of eosinophilia $>1500/\text{mm}^3$ with asthma is highly suggestive of a diagnosis of EGPA. Serum IgE is raised in more than 75% of patients.

The presence of isolated eosinophilia should raise the possibility of parasitic infection (especially with nematodes) and allergies (mainly drug allergies). The other main differential diagnosis to consider is hypereosinophilic syndrome, characterised by the presence of persistent peripheral blood eosinophilia $>1500/\text{mm}^3$ and eosinophil-mediated organ damage. Recent techniques have become available to identify certain subtypes of hypereosinophilic syndrome and therefore rule out EGPA. The myeloproliferative subtype is known to be associated with FIP1-like 1 platelet-derived growth factor receptor-alpha (FIP1L1-PDGFR α) and the lymphocytic subtype with T cell antigen receptor rearrangements. In some cases, the differential diagnosis can only be definitively established during follow-up, especially in ANCA-negative patients with no histologically proven vasculitis and negative molecular genetic testing (Ogbogu et al, 2009).

Alternative diagnoses should be considered, particularly in patients with unusual clinical features and/or in those who are resistant to glucocorticoids and/or do not have asthma.

3.3.6 Histology

The two characteristic lesions for the diagnosis of EGPA are vasculitis and extravascular necrotising granulomas, usually associated with eosinophilic infiltrates. Vasculitic lesions may be granulomatous or non-granulomatous, and typically involve small arteries. In the lungs, the histological features of EGPA include necrotising vasculitis and areas resembling eosinophilic pneumonia. Extrapulmonary lesions are more commonly found in the heart and gastrointestinal (GI) tract than in the kidney. The most common histological lesions seen in the heart are granulomatous and/or eosinophilic infiltration of the myocardium and coronary

vessel vasculitis. Vasculitis and granulomas can be present throughout the GI tract, but occur more often in the small intestine and/or colon (Pagnoux et al, 2005). Cutaneous and subcutaneous lesions, even the so-called Churg–Strauss granulomas, lack diagnostic specificity and 50% of such lesions occur in a variety of systemic diseases other than EGPA.

3.3.7 Aetiopathogenesis

The pathophysiology of EGPA can be divided into three aspects, corresponding to the three main phases of the natural history of EGPA: the pathogenic role of T helper type 2 (Th2) lymphocytes in asthma; eosinophils infiltrating tissues; and anti-MPO-ANCA, possibly playing an additional role in the occurrence of some vasculitis lesions in the third of patients who are ANCA-positive. In addition, as in the other forms of AAV, genetic factors influencing the aetiopathogenesis of the disease are likely to be important, such as the association with HLA-DRB4 (Vaglio et al, 2013).

Th2 cells orchestrate the recruitment and activation of the primary effector cells of the allergic response, the mast cells and the eosinophils, through the release of cytokines such as interleukin (IL)-4, IL-5 and IL-13. Activation of these cells results in the release of a plethora of inflammatory mediators that individually or in concert contribute to producing the symptoms of asthma. IL-4 is required for class switching from IgG to IgE, and IL-5, in association with IL-3 and granulocyte/macrophage-colony stimulating factor, is particularly important in regulating eosinophil proliferation. The hypothesis that some allergens or infections (parasitic or bacterial) might trigger CD4 Th2 cells and cause a massive expansion of eosinophils needs to be confirmed. Indeed, desensitisation and vaccinations have been implicated as potential triggering factors for the development of EGPA.

EGPA cases have also been sporadically reported in relation to the use of different drugs, such as macrolides, carbamazepine or quinine. The possible contribution of leukotriene receptor antagonists (LTRA; zafirlukast, montelukast and pranlukast) to the development of EGPA has been highlighted. However, LTRA treatment usually provides the opportunity for a substantial tapering or withdrawal of asthma treatment, especially glucocorticoids, which in turn may unmask an underlying and previously incomplete and unrecognised disease, a ‘forme fruste’ of EGPA. It remains to be determined whether the onset of EGPA following the initiation of omalizumab (anti-IgE monoclonal antibody) in asthmatic patients results from the same mechanism (Puéchal et al, 2008). EGPA has also been reported, but much less frequently, with the use of other systemic glucocorticoid-sparing treatments, such as the long-acting β 2-agonist salmeterol, disodium cromoglycate and inhaled fluticasone, and even just after the onset of tapering of inhaled or oral glucocorticoids, without the combination or the introduction of any other anti-asthma drug. Despite EGPA being considered a Th2-mediated disease, a Th17 increased response and a Th1 decreased frequency have been found in active stages

of the disease, suggesting that Th17 and Th1 may also play important roles in the pathogenesis of EGPA (Saito et al, 2009).

Patients with EGPA usually show marked peripheral blood eosinophilia with various degrees of activation and increased levels of circulating IgE and IgE-containing immune complexes. Eosinophils contain large amounts of highly cationic proteins, respectively named eosinophil cationic protein, major basic protein, eosinophil-derived neurotoxin and eosinophil peroxidase (Roufosse, 2013). These cationic proteins, released after eosinophil activation, have been shown to be cytotoxic and may be directly responsible for some of the classic disease features of EGPA. In addition, eosinophils are major sources of IL-25, a cytokine driving Th2 lymphocytes differentiation (Terrier et al, 2010).

As previously mentioned, ANCA are found in about 25–40% of patients with EGPA, directed towards MPO in most cases. Even though the pathogenic role of anti-MPO-ANCA in systemic vasculitis has been recently shown, their role has not been demonstrated in EGPA and none of the anti-MPO animal models developed features of EGPA, such as eosinophil tissue infiltration. Thus, the respective role of eosinophils, lymphocytes and ANCA may differ in patients with EGPA, based on their ANCA status and the phase of their disease. Other as yet unknown mechanisms may also be involved in EGPA.

3.4 Treatment of ANCA-associated vasculitides

Before the advent of immunosuppressive treatment, AAV carried a 2-year mortality rate of 93%. The introduction of glucocorticoids in the 1950s and cyclophosphamide-based regimens in the 1970s (Fauci et al, 1978), has transformed the survival rates, now approaching 80% at 5 years (Flossmann et al, 2011*) and 75–85% at 10 years (Puechal et al, 2016).

Treatment should be based on several factors after careful analysis of classification, expected outcome, aetiology, pathogenesis, severity, comorbidity and age; however, inducing and maintaining disease remission, using the least cytotoxic drugs, should be the main goal.

To help the clinician choose the most effective treatment and to avoid overtreatment, the French Vasculitis Study Group established the Five-Factor Score (FFS), which has significant prognostic value in PAN, MPA and EGPA (not validated for GPA). The presence of any of the following five factors indicates higher mortality: proteinuria >1 g/day, renal insufficiency (creatininaemia >140 µmol/L), cardiomyopathy, GI manifestations and CNS involvement (Guillevin et al, 1996; Gayraud et al, 2001). When the FFS was 0, mortality at 5 years was 12%, but rose to 46% when the FFS was ≥2. A revised FFS was recently published and includes age >65 years as another measure of poor prognosis and the presence of ENT manifestations as a parameter of good prognosis in GPA and EGPA (table 4). However, this latter revised FFS has not yet been validated on non-French patients, and thus should not be applied when deciding optimal treatment (Guillevin et al, 2011*). The Birmingham

Vasculitis Activity Score (BVAS), a validated tool for small- and medium-vessel vasculitis, can be used to determine the intensity of treatment, with higher scores being associated with higher mortality (Flossmann et al, 2011*). It was validated for assessment of disease activity in systemic vasculitis in 1994 (Luqmani et al, 1994), modified in 1997 for use in collaborative European trials (BVAS v.2) (Luqmani et al, 1997*), in 2001 to produce a disease-specific instrument for GPA (BVAS/Wegener's granulomatosis) (Stone et al, 2001) and again in 2009 with the removal of redundant and/or uncommon items (BVAS v.3) (Mukhtyar et al, 2009b*). The last version consists of a list of 56 items considered to be vasculitis manifestations with a numerical weight attached to each item, and each organ system has a ceiling score (figure 21). These scores reflect the proportional importance of each manifestation and each organ system and are designed to document new or worsening clinically active vasculitis that would be likely to require immunosuppressive therapy or an increased clinical monitoring regimen. In the recent EULAR/ERA-EDTA recommendations and British Society for Rheumatology guidelines for the management of AAV, BVAS is used to define patients' disease states (Yates et al, 2016; Ntatsaki et al, 2014). BVAS is an effective tool in routine care for the management of most patients with active vasculitis. It provides a valuable checklist to help clinicians remember the most common manifestations of vasculitis when assessing patients with suspected or diagnosed disease. It has the advantage of being able to quantify disease activity, and provide qualitative data for each organ system involved. However, one of the limitations of BVAS is the failure to capture grumbling disease lasting for >3 months when there has been no increase in disease activity. (More information on BVAS is given in the EULAR online course on rheumatic diseases—module 24.)

Table 4 Original and revised Five-Factor Score (FFS)

Original FFS items (1996)	Revised FFS items (2009)	Mortality rate at 5 years	
Creatinine >140 µmol/l	Creatinine >150 µmol/l	FFS = 0	12%
		Revised FFS = 0	9%
Proteinuria >1 g/24 h	Age >65 years		
Specific cardiomyopathy	Specific cardiomyopathy	FFS = 1	26%
		Revised FFS = 1	21%
Specific gastrointestinal involvement	Specific gastrointestinal involvement		
Specific central nervous system involvement	Absence of ear, nose and/or throat manifestations (GPA and EGPA only)	FFS = 2	46%
		Revised FFS ≥2	40%

These scores are to be calculated at the time of diagnosis only (not validated at the time of relapse or during follow-up). The original FFS can be applied to patients with polyarteritis nodosa (PAN), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA). It is not validated for granulomatosis with polyangiitis (Wegener's) (GPA). A revised version of the FFS was designed in order to be used also for GPA patients. It is based on the analysis of a large French cohort of patients with PAN, MPA, EGPA and GPA. The ear, nose and throat (ENT) item (absence of ENT manifestations) only applies to patients with GPA and EGPA (for MPA and PAN, only the other four parameters are to be used for the calculation of the score).

Figure 21 Birmingham Activity Score (version 3). RBCs, red blood cells. (Adapted from Luqmani et al, 1994; Luqmani et al, 1997*; Mukhtyar et al, 2009b*)

Birmingham Vasculitis Activity Score (version 3)

Case Number:

Name:

Date of assessment:

Tick an item only if attributable to active vasculitis. If there are no abnormalities in a section, please tick 'None' for that organ-system.		If all abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the PERSISTENT box at the bottom right corner	
Is this the patient's first assessment?		Yes <input type="checkbox"/>	No <input type="checkbox"/>
None	Active disease	None	Active disease
1. General <input type="checkbox"/> Myalgia <input type="checkbox"/> Arthralgia / arthritis <input type="checkbox"/> Fever $\geq 38^{\circ}$ C <input type="checkbox"/> Weight loss ≥ 2 kg <input type="checkbox"/>		6. Cardiovascular <input type="checkbox"/> Loss of pulses <input type="checkbox"/> Valvular heart disease <input type="checkbox"/> Pericarditis <input type="checkbox"/> ♦Ischaemic cardiac pain <input type="checkbox"/> ♦Cardiomyopathy <input type="checkbox"/> ♦Congestive cardiac failure <input type="checkbox"/>	
2. Cutaneous <input type="checkbox"/> Infarct <input type="checkbox"/> Purpura <input type="checkbox"/> Ulcer <input type="checkbox"/> ♦Gangrene <input type="checkbox"/> Other skin vasculitis <input type="checkbox"/>		7. Abdominal <input type="checkbox"/> Peritonitis <input type="checkbox"/> Bloody diarrhoea <input type="checkbox"/> ♦Ischaemic abdominal pain <input type="checkbox"/>	
3. Mucous membranes / eyes <input type="checkbox"/> Mouth ulcers <input type="checkbox"/> Genital ulcers <input type="checkbox"/> Adnexal inflammation <input type="checkbox"/> Significant proptosis <input type="checkbox"/> Scleritis / Episcleritis <input type="checkbox"/> Conjunctivitis / Blepharitis / Keratitis <input type="checkbox"/> Blurred vision <input type="checkbox"/> Sudden visual loss <input type="checkbox"/> Uveitis <input type="checkbox"/> ♦Retinal changes (vasculitis / thrombosis / exudate / haemorrhage) <input type="checkbox"/>		8. Renal <input type="checkbox"/> Hypertension <input type="checkbox"/> Proteinuria $>1+$ <input type="checkbox"/> ♦Haematuria ≥ 10 RBCs/hpf <input type="checkbox"/> Creatinine 125-249 μ L (1.41-2.82mg/dl)* <input type="checkbox"/> Creatinine 250-499 μ L (2.83-5.64mg/dl)* <input type="checkbox"/> ♦Creatinine ≥ 500 μ L (≥ 5.66 mg/dl)* <input type="checkbox"/> ♦Rise in serum creatinine $>30\%$ or fall in creatinine clearance $>25\%$ <input type="checkbox"/> *Can only be scored on the first assessment	
4. ENT <input type="checkbox"/> Bloody nasal discharge / crusts / ulcers / granulomata <input type="checkbox"/> Paranasal sinus involvement <input type="checkbox"/> Subglottic stenosis <input type="checkbox"/> Conductive hearing loss <input type="checkbox"/> ♦Sensorineural hearing loss <input type="checkbox"/>		9. Nervous system <input type="checkbox"/> Headache <input type="checkbox"/> Meningitis <input type="checkbox"/> Organic confusion <input type="checkbox"/> Seizures (not hypertensive) <input type="checkbox"/> ♦Cerebrovascular accident <input type="checkbox"/> ♦Spinal cord lesion <input type="checkbox"/> ♦Cranial nerve palsy <input type="checkbox"/> Sensory peripheral neuropathy <input type="checkbox"/> ♦Mononeuritis multiplex <input type="checkbox"/>	
5. Chest <input type="checkbox"/> Wheeze <input type="checkbox"/> Nodules or cavities <input type="checkbox"/> Pleural effusion / pleurisy <input type="checkbox"/> Infiltrate <input type="checkbox"/> Endobronchial involvement <input type="checkbox"/> ♦Massive haemoptysis / alveolar haemorrhage <input type="checkbox"/> ♦Respiratory failure <input type="checkbox"/>		10. Other <input type="checkbox"/> a. <input type="checkbox"/> b. <input type="checkbox"/> c. <input type="checkbox"/> d. <input type="checkbox"/>	
♦Major items highlighted		PERSISTENT DISEASE ONLY: (Tick here if all the abnormalities are due to persistent disease) <input type="checkbox"/>	

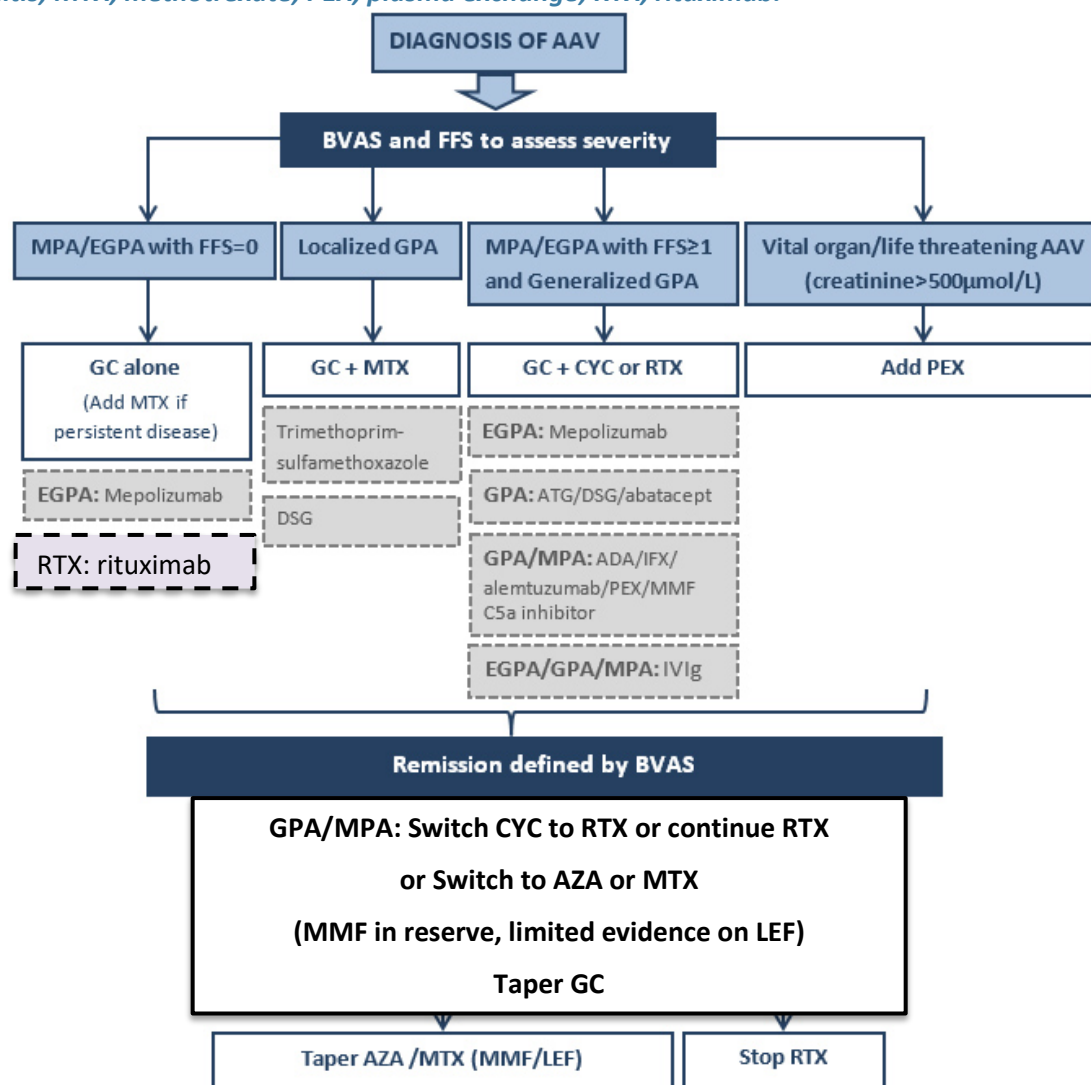
References: Luqmani, RA, et al. (1994). "Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis." QJM 87(11):671-8; Luqmani, RA, et al. (1997). "Disease assessment and management of the vasculitides." Baillieres Clin Rheumatol 11(2): 423-46; Mukhtyar C. et al (2009). "Modification and validation of the Birmingham Vasculitis Activity Score (version 3) ARD 2009 68:1827

Treatment recommendations have been devised by the European League Against Rheumatism (EULAR) and British Society for Rheumatology to help physicians in the management of patients with AAV (Hellmich et al, 2007; Mukhtyar et al, 2009a*; Ntatsaki et al, 2014; Yates et al, 2016).

All current major trials on ANCA-associated vasculitides are listed and detailed on the European Vasculitis Study Group (EUVAS), French Vasculitis Study Group and/or Vasculitis Clinical Research Consortium websites at: <http://www.vasculitis.org>; <http://www.vascularites.org>; and <http://rarediseasesnetwork.epi.usf.edu/vcrc/index.htm>, respectively.

An algorithm for AAV treatment according to disease severity is proposed in figure 22 and a summary of the induction and maintenance treatments is listed in table 5.

Figure 22 Treatment algorithm for ANCA-associated vasculitides. In grey: potential alternative agents or drugs under investigation. AAV, ANCA-associated vasculitis; ADA, adalimumab; ANCA, antineutrophil cytoplasmic antibody; ATG, antithymocyte globulin; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; DSG, deoxyspergualin; EGPA, eosinophilic granulomatosis with polyangiitis; FFS, Five-Factor Score; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; IFX, infliximab; IVIg, intravenous immunoglobulin; LEF, leflunomide; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; PEX, plasma exchange; RTX, rituximab.



Please see in-depth discussion II of the EULAR online course on rheumatic diseases, Module 24, for more details on the current and future use of biologics in AAV.

Table 5 Induction and maintenance treatments available or under investigation for AAV

ANCA-associated vasculitides	Limited GPA	Generalised GPA	MPA (FFS = 0)	MPA (FFS ≥ 1)	EGPA (FFS = 0)	EGPA (FFS ≥ 1)	Life threatening AAV	Refractory/relapsing AAV
Induction therapy								
Glucocorticoids	✓✓	✓✓✓	✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓
Trimethoprim-sulfamethoxazole	✓✓	✓	-	-	-	-	-	-
Methotrexate	✓✓✓	✓✓ ¹	✓✓	-	✓✓	-	-	-
Mycophenolate mofetil	T	T	T	✓✓	✓	-	-	✓✓
Azathioprine			X?		X ³			
Cyclophosphamide	✓✓	✓✓✓	✓✓	✓✓✓	✓	✓✓✓	✓✓✓	✓✓✓
Plasma exchange	-	T	-	T	-	-	✓✓✓*	T*
Rituximab	-	✓✓✓	-	✓✓✓	-	✓✓	✓✓✓	✓✓✓
Adalimumab	-	?	-	?	-	-	-	?*
Infliximab	-	?	-	?	-	-	-	✓*
Etanercept	X ²	X ²	-	-	-	-	X ²	X ²
Abatacept	-	-	-	-	-	-	-	✓✓**
Alemtuzumab	-	-	-	-	-	-	-	T*
Deoxyspergualin	-	-	-	-	-	-	-	✓✓ T**
Antithymocyte globulin	-	-	-	-	-	-	-	✓✓**
C5a inhibitor	-	T	-	T	-	-	-	T*
Mepolizumab	-	-	-	-	✓✓	✓✓	-	✓✓***
Intravenous immunoglobulin	-	✓	-	✓	-	✓	✓	✓✓
Maintenance therapy								
Glucocorticoids	✓✓	✓✓✓	✓✓	✓✓✓	✓✓	✓✓✓	✓✓✓	✓✓✓
Trimethoprim-sulfamethoxazole	✓✓	✓✓	-	-	-	-	-	-
Methotrexate	✓✓	✓✓✓	✓✓	✓✓✓	✓✓	✓✓✓	✓✓✓	✓✓✓
Azathioprine	✓✓	✓✓✓	X?	✓✓✓	X	✓✓✓	✓✓✓	✓✓✓
Leflunomide	-	✓✓	-	✓✓	-	✓	✓	✓
Mycophenolate mofetil	✓✓	✓✓	✓✓	✓✓	-	✓	✓	✓
Cyclophosphamide	✓	✓	✓	✓	-	✓	✓	
Rituximab	-	✓✓✓	-	✓✓✓	-	✓	✓✓✓	✓✓✓
Belimumab	-	T	-	T	-	-	T*	T*
Etanercept	X ²	X ²	-	-	-	-	X ²	X ²
Mepolizumab	-	-	-	-	✓✓	✓✓		✓✓***

✓ Evidence in favour of its use based only on case reports or case series; ✓✓ evidence in favour of its use; ✓✓✓ strong evidence in favour of its use; X evidence against its use; ? Controversial; – not tested; T currently being tested.

*GPA and MPA; **GPA; ***EGPA.

¹In the NORAM trial (de Groot et al, 2005*) methotrexate was not inferior to cyclophosphamide for newly diagnosed patients with early systemic GPA or MPA without organ-threatening or life-threatening disease and a creatinine <150 µmol/L.

²Increased risk of carcinoma (in combination with cyclophosphamide).

³In the CHUSPAN2 trial (Puéchal et al, 2017), azathioprine adjunction to glucocorticoids for remission-induction of nonsevere systemic necrotizing vasculitis did not improve remission rates, lower relapse risk, spare steroids or diminish the EGPA asthma/rhinosinus-exacerbation rate.

3.4.1 Induction therapy

3.4.1.1 Regimen for MPA and EGPA with poor prognostic factors and systemic/severe forms of GPA

Patients with MPA or EGPA with poor prognostic factors (FFS ≥ 1) and patients with systemic/severe forms of GPA should all receive an induction regimen based on the combination of glucocorticoids and an immunosuppressant agent, with cyclophosphamide (CYC) or rituximab (RTX) as first choice.

Methylprednisolone pulses (usually 7.5–15 mg/kg intravenously over 60 min repeated at 24 h intervals for 1–3 days) are still used at the start of treatment for some patients with severe forms of vasculitis because of their rapid action and relative short-term safety, although the evidence for their use is poor and there is growing concern about their cumulative effects. Oral glucocorticoids are given at a dose of 1 mg/kg/day of prednisone-equivalent, usually as a single morning dose. After 3 weeks of the full dose, the glucocorticoid dose should be progressively tapered and, in the absence of relapse, glucocorticoids can be stopped after 9–18 months. However, the optimal duration of glucocorticoid therapy is debated, and there is concern about the toxicity of glucocorticoids, especially with regard to the risk of infection (Walsh et al, 2010).

CYC, an alkylating immunosuppressant agent, can be given orally and continuously or using an intravenous bolus. Comparison of the two CYC regimens (i.e., oral vs intravenous) shows them to be equally effective at controlling disease activity without differences in survival, but pulse CYC therapy is associated with a lower cumulative dose and toxicity (Guillevin et al, 1997; de Groot et al, 2009*). However, pulse CYC may expose the patient to a higher subsequent risk of relapse (Harper et al, 2012). The CYC dose, as well as the total number and frequency of pulses when administered intravenously, should be adjusted according to the patient's condition, especially age, renal function and haematological data. Initial pulse doses used range from 0.5 g to 1.2 g at intervals of 2 weeks initially for one month, then every 3 weeks until achievement of remission. In the EUVAS trials, the CYC pulse dose is of 15 mg/kg (max 1.2 g) every 2 weeks for the first 3 pulses, followed by infusions every 3 weeks for the next 3–6 pulses. The oral CYC dose is 2 mg/kg/day, usually with a maximum of 200 mg/day. Sufficient hydration is mandatory to limit the risk of bladder toxicity of CYC metabolites (especially acrolein). The use of sodium 2-mercaptoethane sulfonate (mesna) and a total of 2–3 litres of fluid

are recommended during pulse therapy. Oral CYC should be taken in the morning with a large glass of water and the patient should remain well hydrated over the next 24 h.

CYC has been the usual induction agent for decades and most physicians treating vasculitis are familiar with its use, including the management and prevention of its potential late-onset adverse events, which are closely related to the given cumulative dose. However, RTX, a genetically engineered chimeric murine/human IgG1k monoclonal antibody directed against the CD20 antigen expressed on the surface of B lymphocytes, is now considered an equally effective alternative treatment.. The RAVE and RITUXVAS trials have shown that RTX is not inferior to CYC for inducing remission in generalised ANCA-positive GPA, MPA and renal limited vasculitis (Jones et al, 2010*; Stone et al, 2010*). RTX was given in these two studies in combination with glucocorticoids and at a dose of 375 mg/m² every week for a total of four injections. However, an alternative might be 1 g every 2 weeks, for a total of two injections (Guerry et al, 2011). Notably, the frequency of infections, mainly bronchitis and pneumonia, was no worse than with CYC-based induction, possibly related to the concomitant use of high doses of glucocorticoids. There have been rare cases of progressive multifocal leukoencephalopathy due to the JC virus in patients with vasculitides, both with and without RTX treatment, suggesting that RTX may be selectively associated with JC virus infection (Molloy and Callabrese, 2009; Molloy and Callabrese, 2012). In addition, there is controversy about patients with GPA with granulomatous manifestations, in whom therapeutic responses may be slower and less dramatic (Aries et al, 2006; Aouba et al, 2008). There are no controlled prospective studies using RTX in patients with ANCA-negative disease, but successful RTX treatment in ANCA-negative GPA has been reported (Khan et al, 2010), highlighting the possible pathogenic role of other antibodies (Chen et al, 2009). Some case reports and small series also suggested that RTX might have some efficacy in refractory EGPA (ANCA-positive and -negative) (Cartin-Ceba et al, 2011; Thiel et al, 2013); prospective randomised trials are ongoing (REOVAS, ClinicalTrials.gov Identifier: NCT02807103).

There is no strong evidence for mycophenolate mofetil (MMF) as an induction agent in AAV. Two small studies involving a total of 76 Chinese patients with mostly mild to moderate kidney involvement but not severe lung haemorrhage or central nervous system involvement (>98% MPA) suggested that it might be a useful alternative in patients with generalised disease (Hu et al, 2008; Han et al, 2011). A randomised controlled trial involving 140 patients with new-onset of early systemic and generalised GPA/MPA compared MMF to intravenous CYC as an induction agent (MYCYC, ClinicalTrials.gov identifier: NCT00414128). Preliminary 6-month results were unable to show non-inferiority of MMF and a standard glucocorticoid taper, in comparison to CYC. However, MMF and a non-fixed dose of glucocorticoids demonstrated non-inferiority. In addition, the relapse rates after 6-months were higher in patients who had received MMF, but confined to the PR3-ANCA subgroup. Therefore, these studies suggest that MMF induction may be considered in patients with MPA / MPO-ANCA associated vasculitis without severe renal manifestations (Jones and Walsh, 2012; Jayne and Rasmussen 2015).

3.4.1.2 Regimen for MPA or EGPA without poor prognostic factors and for localised/early-systemic forms of GPA

It was shown that patients with MPA or EGPA without factors for poor prognosis (FFS = 0) at the time of diagnosis can be successfully treated with prednisone alone, with immunosuppressant agent(s) given only as a second-line treatment if disease activity persists or a relapse occurs despite glucocorticoid therapy.

Traditionally, glucocorticoids are started orally at a dose of 1 mg/kg/day of prednisone or equivalent. As described above, after 3 weeks of the full dose, the glucocorticoid dose should be gradually tapered. The relapse or failure rate seen in patients with MPA or EGPA treated with prednisone alone is high, but the 7-year survival rate is 79%. The addition at diagnosis of an immunosuppressant agent may lower the relapse rate of these patients with FFS = 0, but the balance between benefits and toxicity is narrowed and study results do not favour the systematic first-line use of CYC in combination with glucocorticoids (Ribi et al, 2008; Ribi et al, 2010). Azathioprine (AZA) - a less toxic drug - has been investigated in a study recruiting patients with EGPA, MPA and PAN (Puéchal et al, 2017). However, it failed to demonstrate a decrease in treatment failure or relapse, did not show a steroid-sparing effect and did not lower EGPA patients' rate of asthma/sinonasal disease exacerbations. Alternative therapies, such as MTX, need evaluation.

In contrast to MPA and EGPA, the combination of glucocorticoids and an immunosuppressant agent is required in all patients with GPA. Patients with a localised/early-systemic form of GPA can be treated initially with glucocorticoids and methotrexate (MTX), achieving similar responses to CYC. Although, MTX was shown to be inferior to CYC in preventing a relapse in the EUVAS NORAM trial (de Groot et al, 2005*), this was possibly explained by the trial protocol, which required withdrawal of MTX after 12 months. Thus, when effective, it should be continued for several years. Non-randomised studies suggested that co-trimoxazole (trimethoprim-sulfamethoxazole) could be used for remission induction in GPA for upper airway disease or localised disease. However, in a study evaluating 26 patients with localised GPA, initial treatment with trimethoprim-sulfamethoxazole was not sufficient in three-fourths of them due to failure or progression to early systemic or generalised disease (Holle et al, 2010).

3.4.2 Maintenance treatment

Once remission is achieved with CYC, patients can be switched to a less toxic immunosuppressant agent for maintenance, often AZA or MTX, neither one being clearly better than the other (Pagnoux et al, 2008b*), or RTX which has been shown to be superior to AZA at maintaining remission of GPA and severe MPA in a randomized controlled trial (Guillevin et al, 2014*).

The AZA dose is 2 mg/kg/day and the MTX dose is 0.3 mg/kg, delivered once weekly, up to 25 mg/week, orally or subcutaneously. It remains uncertain whether changing to AZA after 3–6 months of induction with CYC is as

effective as changing after 12 months (Walsh et al, 2014), but patients are usually switched to maintenance treatment after six to nine intravenous pulses or 3–4 months of oral CYC (Jayne et al, 2003*). The recently published REMAIN trial has compared different lengths of maintenance therapy with AZA (2 vs 4 years of maintenance) in GPA, MPA and renal-limited vasculitis patients achieving complete remission after induction with CYC and corticosteroids (Karras A et al, 2017). A longer course of AZA and prednisone has been found to be associated with a lower relapse rate (62.7% vs 22.0%), especially in those patients with ANCA persistently positive after induction therapy.

RTX for maintenance of remission in AAV has been investigated in a prospective randomised controlled study (MAINRITSAN) comparing RTX with AZA (Guillevin et al, 2014*). The primary end point was the rate of major relapses at 28 months. One hundred and fifteen patients were included after remission achievement with CYC infusions. The RTX group received pre-emptive fixed low-dose maintenance re-treatment every 6 months (500 mg RTX, five infusions over 18 months) and was compared with the group receiving maintenance treatment with AZA (2 mg/kg/day for 12 months, 1.5 mg/kg/day for 6 months, then 1.0 mg/kg/day for last 4 months). In the RTX arm, 7/55 (12.7%) patients compared with 26/54 (48.1%) patients in the AZA arm had at least one major relapse. In the long-term analyses of MAINRITSAN-trial patients, RTX remained superior to AZA at maintaining remission of ANCA-associated vasculitides over 60 months, with no safety differences with AZA (Terrier et al, 2016). The cumulative glucocorticoid use was comparable between the 2 arms. RTX maintenance was associated with better overall survival, and ANCA-specificity and month-12 persistence were associated with higher subsequent relapse risk.

The best treatment schedule (RTX injection on demand or driven by surrogate markers such as CD19 level and/or ANCA titer), and its duration are being investigated in 2 randomized controlled trials. MAINRITSAN 2 (Clinicaltrials.gov identifier: NCT01731561) has compared two RTX regimens: 500 mg infusions according to ANCA status/titer and/or circulating CD19 B-cell reappearance versus systematic 500 mg infusions at fixed intervals of 6 months (controls) (Charles et al, 2016). AAV relapse rates for patients given individually tailored or systematic RTX-infusion schedules did not differ significantly. However, the experimental arm patients received fewer infusions and lower total RTX doses. The objective of the ongoing MAINRITSAN 3 trial (ClinicalTrials.gov identifier: NCT02433522) is to determine the optimal duration of the RTX maintenance treatment to prevent relapses (2 years or 4 years). In addition, RITAZAREM (ClinicalTrials.gov identifier: NCT01697267) is comparing a different RTX regimen (1 g every 4 months until month 20) with AZA for maintenance treatment (2 mg/kg daily for 24 months) in relapsing AAV patients after achievement of remission with RTX.

In addition, prospective randomised trials are ongoing to assess the role of RTX as maintenance therapy in EGPA patients (MAINRITSEG, ClinicalTrials.gov Identifier: NCT03164473).

Leflunomide (LEF) is another alternative to MTX or AZA. One study, involving 54 patients with GPA, compared LEF 30 mg/day with MTX up to 20 mg/week and showed significantly higher rates of relapse in the MTX group. However, this was balanced by an increased frequency of adverse events in the LEF group (Metzler et al, 2007). A recent systematic review and network meta-analysis of all randomised trials comparing non-biological remission maintenance treatments in adult patients with GPA or MPA showed comparable efficacy of MTX, AZA or LEF, and even suggested, albeit indirectly, that LEF might be best (Hazlewood et al, 2014). Further prospective randomised trials with LEF are needed for confirmation.

MMF 2 g/day was compared with AZA 2 mg/kg/day for the maintenance of remission in 156 patients with AAV after CYC induction in the IMPROVE trial. Relapses were more common in the MMF group and adverse event rates were similar between the groups. Therefore MMF should be considered only in patients who cannot tolerate the usual maintenance drugs (Hiemstra et al, 2010*).

Trimethoprim-sulfamethoxazole 960 mg twice daily has also been proposed as a maintenance agent in GPA and a small randomized study has shown that treatment with co-trimoxazole in monotherapy may reduce the incidence of relapses in GPA patients in remission (Stegeman et al, 1996); however, it may not be effective in maintaining remission, particularly in generalized GPA (Reinhold-Keller et al, 1996).

Other maintenance strategies, based on B cell depletion, are currently being evaluated. Belimumab, a human monoclonal antibody that inhibits B lymphocyte stimulator (BLyS), is being tested as maintenance treatment in MPA and GPA (BREVAS, ClinicalTrials.gov identifier: NCT01663623). The optimal duration of glucocorticoid treatment, and its effect on disease flares and/or relapses, is also being currently evaluated for GPA in the prospective TAPIR trial, where 60 patients in remission are randomized to either reduce their prednisone dose to 5 mg or 0 mg a day.

3.4.3 Adjunctive treatments

Prevention of opportunistic infections, such as *Pneumocystis jiroveci* pneumonia, with trimethoprim-sulfamethoxazole 960 mg three times a week, is mandatory in patients receiving CYC, throughout the CYC therapy and for 2–4 months after its discontinuation, and should also be considered in those receiving glucocorticoids and RTX.

All patients receiving treatment with glucocorticoids should follow local guidelines for the prevention of glucocorticoid-induced osteoporosis (Mukhtyar et al, 2009a*). Gastro-protection with proton pump inhibitors is also advisable.

Supportive care is also a very important part of the treatment of patients with vasculitis. Pain control, prevention of pressure sores and physical therapy are needed in the case of mononeuritis multiplex.

Introduction of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists has been beneficial in patients with severe hypertension due to renal vasculitis.

3.4.4 Other treatments

Interest in the use of intravenous immunoglobulins (IVIg) to treat systemic vasculitis was stimulated by their successful prevention of coronary artery aneurysms in Kawasaki disease. The obvious advantage of IVIg is that they generate few severe side effects, which is unfortunately counterbalanced by their high costs and only short-term benefits. IVIg have been used in GPA, MPA and EGPA, especially in patients refractory to several immunosuppressant agents and high-dose glucocorticoids and/or those with a concomitant and severe infection or pregnant (Jayne et al, 2000; Martinez et al, 2008).

Plasma exchange can improve the outcome of patients with AAV and severe renal failure (serum creatinine $>500 \mu\text{mol/L}$ or 5.65 mg/dL). It has been shown to increase the rate of renal recovery and enable dialysis to be stopped at 1 year; however, it has no effect on longer-term renal function or survival and is not commonly undertaken in patients with plasma creatinine $<500 \mu\text{mol/L}$ (Jayne et al, 2007; Casian and Jayne, 2011). Plasma exchange (seven sessions over 14 days) is often used in patients with alveolar haemorrhage, based on the usual treatment for Goodpasture syndrome, but its benefit is still uncertain. A recent meta-analysis concluded that more data are needed to establish the long-term benefit of this treatment (Walsh et al, 2011). The aim of a current international prospective controlled trial (PEXIVAS, ClinicalTrials.gov identifier: NCT00987389) is precisely to better evaluate the place of plasma exchange in patients with AAV with less impaired renal function and/or alveolar haemorrhage.

CCX168 - an oral inhibitor of the complement C5a receptor has been evaluated in a limited number of AAV patients. The CLEAR study was designed to assess if different regimens of glucocorticoids, added to a standard induction with CYC or RTX, could be replaced by CCX168 without compromising efficacy in patients with mild-to-moderate renal involvement (Jayne et al, 2017). 86% of patients receiving CCX168 + low dose glucocorticoids and 81% of patients receiving CCX168 + no glucocorticoids had a non-inferior $\geq 50\%$ BVAS reduction at 12 weeks versus 70% of patients in the standard care group of high dose glucocorticoids. In another phase II study evaluating two different dose regimens of CCX168 plus standard high-dose glucocorticoids and either RTX or CYC, 30 mg CCX168 twice daily confirms to be an appropriate for further study in patients with AAV (Merkel et al, 2016).

Other agents have been tested and/or are under investigation in refractory GPA or MPA. The antithymocyte globulin has been used in patients with refractory GPA in the SOLUTION trial, achieving a 75% remission rate, but with a high number of adverse events (Schmitt et al, 2004). The humanized anti-CD52 monoclonal antibody, alemtuzumab (CAMPATH-1H), has led to sustained treatment free remissions in a group of 71 patients with relapsing and refractory GPA and MPA, but it is strongly immunosuppressive and has been found

to be associated with severe adverse events (Walsh et al, 2008). In addition, the SPARROW trial (ClinicalTrials.gov identifier: NCT01446211) is currently evaluating the efficacy of guselimumab (15-deoxyspergualin) in relapsing and refractory GPA and the ABROGATE trial (ClinicalTrials.gov identifier: NCT02108860) is evaluating the use of abatacept (CTLA4-Ig) for the treatment of relapsing, non-severe, GPA.

Inflammatory cytokines are important components in the disease development of AAV (Furuta and Jayne, 2014). TNF- α is associated with disease activity in AAV and its inhibition has already been tested. Complete or partial remission was obtained with infliximab in patients with refractory GPA in the early 2000s. However, after infliximab was stopped, relapses often occurred (Josselin et al, 2008). Etanercept, another TNF-blocking agent, has also been tested in AAV in conjunction with conventional treatment, including CYC, with the aim of reducing the relapse rate. It had no advantage for the prevention of relapse and, more importantly, six cancers were diagnosed during the trial, all in the etanercept arm (WGET, 2005). Eight additional solid malignancies developed in the patients receiving etanercept and five in the control group after the end of the trial (Silva et al, 2011). Adalimumab has also been proposed as an adjunctive and glucocorticoid-sparing agent for the treatment of severe AAV, but further studies are required (Laurino et al, 2010). TNF inhibitors are not currently recommended in the treatment of AAV.

Other inflammatory cytokines have shown to be increased in AAV, making them potential therapeutic targets. IL-6 serum levels were found significantly increased in patients with AAV, and treatment with tocilizumab was able to induce sustained disease remission in a patient with severe multisystem MPA, requiring further evaluation of this treatment option (Berti et al, 2015). Moreover, serum IL-17A and IL-23 levels were found highly elevated in acute AAV patients (Nogueira et al, 2010), supporting the importance for testing their inhibition with ustekinumab (anti-IL-12/23) and secukinumab (anti-IL-17A) in a formal trial setting.

In EGPA, the role of mepolizumab, a monoclonal anti-IL-5 agent, has been tested in two small pilot studies with a total of 17 patients (Kim et al, 2010; Moosing et al, 2011). In both studies a decrease in disease activity and a glucocorticoid-sparing effect was seen. However, this benefit was not sustained after switching to maintenance treatment with MTX (Herrmann et al, 2012). A double-blind, randomised, placebo-controlled study has investigated the efficacy and safety of a 300 mg dose of mepolizumab (administered subcutaneously every 4 weeks) compared with placebo over a 52-week study treatment period in patients with relapsing or refractory EGPA receiving standard of care treatment (Wechsler et al, 2017*). Mepolizumab led to significantly more accrued weeks of remission than placebo (28% vs. 3%), a higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%), and allowed to receive a daily dose of prednisolone or prednisone of 4 mg or less per day in a significantly higher number of patients (44% vs 7%). The benefit of the anti-IL-5 agent was mostly due to a better control of asthma and ENT manifestations in those patients and more uncertain of the vasculitis relapse rate. Therefore, it remains to be determined whether mepolizumab efficacy against EGPA mainly acts on asthma symptoms or also controls extrapulmonary vasculitis manifestations (Guillemin 2017).

Figure 23 Vasculitis Damage Index (VDI). BP, blood pressure; GFR, glomerular filtration rate.

VASCULITIS DAMAGE INDEX (VDI)		
<p>This is for recording organ damage that has occurred in patients since the onset of vasculitis. Patients often have co-morbidity before they develop vasculitis, which must not be scored. Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS). A new patient should usually have a VDI score of zero, unless: (a) they have had vasculitis for more than three months of onset of disease and (b) the damage has developed or become worse since the onset of vasculitis</p>		
1. Musculoskeletal	No	Yes
None	<input type="checkbox"/>	
Significant muscle atrophy or weakness		<input type="checkbox"/>
Deforming/erosive arthritis		<input type="checkbox"/>
Osteoporosis/vertebral collapse		<input type="checkbox"/>
Avascular necrosis		<input type="checkbox"/>
Osteomyelitis		<input type="checkbox"/>
2. Skin/Mucous membranes	No	Yes
None	<input type="checkbox"/>	
Alopecia		<input type="checkbox"/>
Cutaneous ulcers		<input type="checkbox"/>
Mouth ulcers		<input type="checkbox"/>
3. Ocular	No	Yes
None	<input type="checkbox"/>	
Cataract		<input type="checkbox"/>
Retinal change		<input type="checkbox"/>
Optic atrophy		<input type="checkbox"/>
Visual impairment/diplopia		<input type="checkbox"/>
Blindness in one eye		<input type="checkbox"/>
Blindness in second eye		<input type="checkbox"/>
Orbital wall destruction		<input type="checkbox"/>
4. ENT	No	Yes
None	<input type="checkbox"/>	
Hearing loss		<input type="checkbox"/>
Nasal blockage/chronic discharge/crusting		<input type="checkbox"/>
Nasal bridge collapse/septal perforation		<input type="checkbox"/>
Chronic sinusitis/radiological damage		<input type="checkbox"/>
Subglottic stenosis (no surgery)		<input type="checkbox"/>
Subglottic stenosis (with surgery)		<input type="checkbox"/>
5. Pulmonary	No	Yes
None	<input type="checkbox"/>	
Pulmonary hypertension		<input type="checkbox"/>
Pulmonary fibrosis		<input type="checkbox"/>
Pulmonary infarction		<input type="checkbox"/>
Pleural fibrosis		<input type="checkbox"/>
Chronic asthma		<input type="checkbox"/>
Chronic breathlessness		<input type="checkbox"/>
Impaired lung function		<input type="checkbox"/>
6. Cardiovascular	No	Yes
None	<input type="checkbox"/>	
Angina/angioplasty		<input type="checkbox"/>
Myocardial infarction		<input type="checkbox"/>
Subsequent myocardial infarction		<input type="checkbox"/>
Cardiomyopathy		<input type="checkbox"/>
Valvular disease		<input type="checkbox"/>
Pericarditis ≥ 3 mths or pericardectomy		<input type="checkbox"/>
Diastolic BP ≥ 95 or requiring antihypertensives		<input type="checkbox"/>
Name:		
Case Number:		
Date:		
7. Peripheral vascular disease		No
None		<input type="checkbox"/>
Absent pulses in one limb		<input type="checkbox"/>
2 nd episode of absent pulses in one limb		<input type="checkbox"/>
Major vessel stenosis		<input type="checkbox"/>
Claudication >3 mths		<input type="checkbox"/>
Minor tissue loss		<input type="checkbox"/>
Major tissue loss		<input type="checkbox"/>
Subsequent major tissue loss		<input type="checkbox"/>
Complicated venous thrombosis		<input type="checkbox"/>
8. Gastrointestinal		No
None		<input type="checkbox"/>
Gut infarction/resection		<input type="checkbox"/>
Mesenteric insufficiency/pancreatitis		<input type="checkbox"/>
Chronic peritonitis		<input type="checkbox"/>
Oesophageal stricture/surgery		<input type="checkbox"/>
9. Renal		No
None		<input type="checkbox"/>
Estimated/measured GFR ≤ 50%		<input type="checkbox"/>
Proteinuria ≥ 0.5g/24hr		<input type="checkbox"/>
End stage renal disease		<input type="checkbox"/>
10. Neuropsychiatric		No
None		<input type="checkbox"/>
Cognitive impairment		<input type="checkbox"/>
Major psychosis		<input type="checkbox"/>
Seizures		<input type="checkbox"/>
Cerebrovascular accident		<input type="checkbox"/>
2 nd cerebrovascular accident		<input type="checkbox"/>
Cranial nerve lesion		<input type="checkbox"/>
Peripheral neuropathy		<input type="checkbox"/>
Transverse myelitis		<input type="checkbox"/>
11. Other		No
None		<input type="checkbox"/>
Gonadal failure		<input type="checkbox"/>
Marrow failure		<input type="checkbox"/>
Diabetes		<input type="checkbox"/>
Chemical cystitis		<input type="checkbox"/>
Malignancy		<input type="checkbox"/>
Other		<input type="checkbox"/>
Total VDI Score. Record the number of positive items (1 point for each). The VDI score can either increase or remain the same over time.		<input type="text"/>
Remember to carry forward any previous items of damage.		

3.5 Outcomes

In addition to the usual outcome measures (i.e., relapse and mortality rates), damage and quality of life should also be taken into account. Damage includes disease-related sequelae such as peripheral neuropathy or renal insufficiency, late drug-related adverse events, like CYC-induced bladder cancer and infertility, and other

problems such as premature atherosclerosis, where the underlying mechanism is less clear and/or multifactorial (Bourgarit et al, 2005; Pagnoux and Guillevin, 2005a). Damage can be evaluated using the Vasculitis Damage Index (VDI), which is a comprehensive and validated clinical checklist that records the accumulation of damage since the vasculitis onset (figure 23) (Exley et al, 1997). The damage items are often the direct result of previous disease activity, its treatment or other comorbidities. This is quite separate from BVAS and gives no indication of current disease activity. The VDI has been recommended by EULAR as an outcome parameter in clinical trials (Hellmich et al, 2007). Recently, Robson et al (2013) described up to 12 months of VDI data from 735 patients with AAV and up to 7 years of VDI data from 535 patients with AAV, all from the EUVAS trials. The long-term data showed that around one-third of patients had five or more items of damage, highlighting the importance of including damage as an outcome measure and raising awareness of potential comorbidities and treatment side effects when managing a patient with AAV. (in-depth discussion I of the EULAR online course on rheumatic diseases—module 24.)

3.5.1 GPA and MPA

A few patients die early during the first months of the disease from multivisceral involvement because treatment cannot control the disease (Pagnoux et al, 2008a; Flossmann et al, 2011*). Septicaemia can also develop during the first months of treatment owing to the intense initial treatment and indeed seems to be the major cause of early mortality in AAV. Viral infections usually arise later and result from the profound immunosuppression induced by the drugs prescribed to control the vasculitis. Rare cases of *Pneumocystis jiroveci* pneumonia have been described, mostly in lymphopenic patients ($<200/\text{mm}^3$).

Long-term causes of mortality and morbidity include cardiovascular disease, estimated at 14% within 5 years of diagnosis, as the possible consequence of vessel inflammation and long-term treatment with glucocorticoids; and malignancies, with an incidence ratio of 1.6–2.0 compared with the general population (higher risk in GPA than in MPA), as the possible consequence of long-term immunosuppressive therapy and, more hypothetically, underlying predisposition (Gaffo, 2013; Mahr et al, 2013).

Among all vasculitides, the relapse rate is probably highest in GPA, affecting up to 50–60% of patients at 5 years. All forms of GPA may relapse at any time, sometimes after several years or even decades of remission. Relapses also occur in MPA, reaching around 35% at 5 years, which is more than in PAN but less than in GPA. Relapse does not necessarily involve the same features as those at the original presentation and other organs can be involved; however, relapses are usually less severe than initial manifestations, mainly because the diagnosis tends to be made earlier.

The presence of PR3-ANCA (as compared with MPO-ANCA) carries a 1.62-fold greater risk of relapse (Walsh et al, 2012*). However, change of ANCA titre over time is not a useful predictor of relapse, and should not be used without clinical evidence of active disease to guide treatment (Finkelstein et al, 2007; Tomasson et al,

2012). A rapid reduction of glucocorticoid therapy of >0.8 mg a month was associated with a greater risk of relapse in a Japanese study of patients with MPA (Wada et al, 2012), but this was not reproduced in a Caucasian population (McGregor et al, 2012).

Relapses occur more frequently after maintenance treatment is stopped (two-thirds of relapses), but can also occur during treatment (Pagnoux et al, 2008b*; Hiemstra et al, 2010*). Conversely, excessively prolonged remission treatment can be harmful and not all patients relapse. Hence, the optimal maintenance regimen, its duration and the parameters on which it can be individually adjusted remain to be determined.

Patients with GPA presenting with ENT involvement and/or granulomatous manifestations (orbital pseudo-tumour, lung nodules) seem to relapse more often than those with renal vasculitis.

3.5.2 EGPA

The prognosis of EGPA has improved dramatically since the introduction of glucocorticoids and, when indicated, cytotoxic drugs. With adequate treatment, remission is rapidly obtained in $>80\%$ of patients. During follow-up, relapses occurred in 25–35%—half during the first year and later in the others—after a mean follow-up of 5 years. The 10-year survival rate is around 75–80%. Cardiac involvement is, and remains, the primary cause of death in patients with EGPA.

The EGPA Task Force recommendations defined relapse as the new appearance, recurrence or worsening of clinical EGPA manifestation(s), excluding asthma and/or ENT symptoms, requiring the addition, change or dose increase of glucocorticoids and/or other immunosuppressants (Groh et al, 2015*).

Indeed, asthma usually persists after recovery from vasculitis and $>75\%$ of the EGPA survivors in long-term remission have persistent asthma requiring maintenance treatment with low doses of prednisone (<10 mg/day) and/or inhaled glucocorticoids (Cohen et al, 2007; de Groot et al, 2009*). The availability of mepolizumab could represent a great opportunity to lower the need of corticosteroids in EGPA patients with refractory asthma.

4 Polyarteritis nodosa

4.1 Introduction

PAN was first described by Küssmaul and Maier in 1866 (Kussmaul and Maier, 1866). This necrotising systemic vasculitis predominantly involves medium arteries and can affect most organs in the body. The causes of primary and secondary PAN can be distinguished, since PAN can be the consequence of HBV infection (Trepo and Thivolet, 1970; Prince and Trepo, 1971) and sometimes other aetiological agents, like human immunodeficiency virus or, more controversially, hepatitis C virus (Saadoun et al, 2010). Among the vasculitides, PAN is now less common than in the past for reasons that will be discussed later.

4.2 Classification criteria

In 1990, the ACR established criteria for PAN classification, with 82.2% sensitivity and 86.6% specificity (Lightfoot et al, 1990), but did not distinguish between PAN and MPA. However, there are major differences between these two entities, as clarified and clearly established in definitions from the 1994 Chapel Hill nomenclature. PAN predominantly affects medium vessels, whereas MPA affects small vessels, especially arterioles, capillaries and venules. MPA is responsible for glomerulonephritis and lung capillaritis, while PAN is characterised by vascular nephropathy and never affects the lungs. ANCA are usually present in MPA and absent in PAN (Henegar et al, 2008).

4.3 Epidemiology

PAN is a rare disease that affects all racial groups. The HBV immunisation programmes and screening tests, as well as the changes in the classification of vasculitis and the better recognition of AAV as a separate identity, have resulted in a substantial reduction in the incidence of PAN. In Australia a small study reported a decrease in the temporal incidence of PAN: from 2.3 per million per year in the period of 1995–1999 to 1.1 per million per year in 2000–2004 (Ormerod and Cook, 2008). A study comparing the incidence of PAN in three European regions showed an annual incidence of 4.4–9.7 per million by the ACR criteria versus 0–0.9 per million by the Chapel Hill Consensus Conference (CHCC) definition (Watts et al, 2001).

PAN may be found in patients of all ages, including children and the elderly, but predominates in the 40–60-year-old age group. The male to female ratio is approximately equal.

4.4 Clinical features

4.4.1 General symptoms

A poor general condition is common. Weight loss and fever are present in two-thirds of patients (Pagnoux et al, 2010*). Symptoms occur early during the course of the disease and may be present at its onset. These symptoms can be isolated and the diagnosis is made only when other systemic manifestations occur. The characteristics of fever vary from one patient to another (high, remittent, with chills or intermittent).

4.4.2 Myalgias and arthralgias

Half of the patients have myalgias. These may be intense, diffuse, spontaneous or occur only after pressure is applied. Muscle enzymes are usually normal or slightly raised. Conversely, amyotrophy can be marked, but mostly reflects weight loss, sometimes of >20 kg, with some patients being bedridden owing to the intensity of pain and amyotrophy. Muscle biopsy can contribute decisively to the diagnosis of PAN when performed at this time. Arthralgias predominate in the knees, ankles, elbows and wrists, rather than the shoulders or hips. Synovitis is rarely seen and joints are usually not eroded nor deformed.

4.4.3 Neurological manifestations

Whereas peripheral neurological symptoms are frequent, CNS involvement is rare. Peripheral neuropathy is the most common finding in patients with PAN (50–75%), and in 23–33% is the earliest symptom of disease. Indeed, one of the variants of PAN exclusively involves peripheral nerve and muscle (Pagnoux and Guillevin, 2005b). Onset is usually acute, but may be more progressive, particularly in the elderly. Sensory signs are responsible for hypoaesthesia or hyperaesthesia, dysaesthesia or frank pain as the prominent and earliest features. Motor signs can occur thereafter. The first manifestations often affect the lower limbs, with one particular nerve involved. Later, other nerves become affected, with this pattern being referred to as mononeuritis multiplex. Indeed, mononeuritis multiplex affects 56.5–61.5% of patients. Mononeuritis (simplex) is less often seen. The pattern is usually distal and asymmetrical. The following nerves are preferentially involved: superficial peroneal, sural, radial, cubital and/or median nerves. In its late stage, so many nerves can be affected that mononeuritis multiplex can be mistaken for a symmetrical process. Cerebrospinal fluid, when analysed, is generally normal. Electromyography typically shows axonal neuropathy. Motor and sensory nerve action potential amplitudes are markedly decreased, or even absent, in the most severely affected nerves, while motor nerve conduction velocities are normal or only slightly diminished.

With treatment, mononeuritis multiplex in PAN progressively improves and patients may recover without sequelae. However, 12–18 months are often required before maximal recovery occurs. The degree of recovery is variable and unpredictable because, in some patients, severe neuropathy with extensive palsies may regress completely, whereas in others, minor palsies or sensory symptoms may never totally disappear. Sensory symptoms, usually paraesthesiae, persist longer and sometimes indefinitely. Moreover, several unpredictable peripheral neuropathy flares may occur.

CNS involvement (especially ischaemic, or more rarely haemorrhagic, stroke, seizure or confusion) is much less common and it is usually a late manifestation of the disease. Cranial nerve palsies are rare, being found in around 1% of patients with PAN, and affect the oculomotor (III), trochlear (IV), abducens (VI), facial (VII) and/or acoustic (VIII) cranial nerves. Vasculitis of the optic nerve, optic chiasm and/or occipital cortex has also been described. However, blurred vision or visual loss may also occur as a result of choroiditis, retinitis or brain parenchymal arteritis. The cerebrospinal fluid is usually normal but, in a few cases, an increased protein concentration, without increased cellularity, may be present.

4.4.4 Skin manifestations

Theoretically, cutaneous or subcutaneous nodules are the hallmarks of PAN, occurring in 8–27% of patients. They occur in clusters along the trajectories of superficial arteries and often disappear spontaneously within a few days, before new ones develop. Necrotic purpura is also common, and hence cannot be considered a

distinctive feature of MPA (Kluger et al, 2008). The main other differences between PAN and small vessel vasculitides are reported in table 6.

Ulcerations and livedo are less frequent. Local rupture of superficial arteries may lead to cutaneous haematoma or ecchymosis. A biopsy of infiltrated and/or central lesion zones can show vasculitis.

Other manifestations have been reported, such as bullous purpura and vesicles that may precede necrosis, urticaria, transient erythema or erythema annulare fugax, superficial phlebitis, Raynaud's phenomenon and splinter haemorrhages.

4.4.5 Renal manifestations

Renal artery involvement can be responsible for mild to severe and malignant arterial hypertension and/or vascular ischaemic nephropathy with renal insufficiency. Angiography, if performed, may show renal parenchymal infarcts and/or multiple stenoses and microaneurysms of branches of coeliac-mesenteric and/or renal arteries. Microaneurysms can occasionally rupture, spontaneously or after renal biopsy, which is therefore strongly contraindicated in the presence of microaneurysms. However, the main renal manifestation of AAV (glomerulonephritis) is never found in PAN; if this is reported on a biopsy, the diagnosis should be questioned because the patient actually has AAV.

4.4.6 Arterial hypertension

Hypertension is present in a mean of 40% of patients with PAN and is usually mild; however, it should be kept in mind that it can be triggered or adversely affected by glucocorticoids. Severe and malignant hypertension is detected in 4% of patients.

4.4.7 Cardiac manifestations

Cardiac involvement was reported with frequencies ranging from 10% in clinical investigations of patients with PAN to 40% when considering radiological and/or electrocardiographic anomalies, to 78% in a histopathological study.

Congestive heart failure is the main clinical feature, occurring in 6–57% of patients with PAN, but usually less often than in EGPA. Angiography can demonstrate coronary involvement in 85% of patients with clinical signs of infarction. In the remaining 15%, infarction may be due to arteritis in small coronary vessels or spasms.

Table 6 Main differences between polyarteritis nodosa (PAN) and ANCA-associated vasculitis

Disease characteristics	Polyarteritis nodosa	Microscopic polyangiitis	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)	Granulomatosis with polyangiitis (Wegener's)
Size of vessels predominantly involved	Medium	Small	Small	Small
ENT manifestation	No	Few patients, not specific, not destructive and not granulomatous	Allergic rhinitis, sinus polyposis (not destructive)	Frequent, crusting rhinitis, destructive sinusitis, saddle-nose deformity, nasal septum deformity, otitis media
Asthma	No	No	Yes (~100%)	No
Lung involvement	No (rarely, pleural effusion)	Frequent (60–80%), alveolar haemorrhage	Asthma in all. Frequent (50%), transient patchy infiltrates, eosinophil pleural effusion, rarely nodules	Frequent (60–80%), lung plain and/or excavated nodules, alveolar haemorrhage, bronchial and/or subglottic stenosis
Peripheral neuropathy (mononeuritis multiplex)	Very frequent (70%)	Frequent (35%)	Very frequent (65–75%)	Frequent (25%)
Kidney involvement	Reno-vascular involvement (hypertension, ischaemic renal lesions, 30–55%) but no glomerular disease	Very frequent, glomerulonephritis (necrotising extracapillary, 80%)	Not frequent, glomerulonephritis (necrotising extracapillary, 20%)	Frequent, glomerulonephritis (necrotising extracapillary, 70–80%)
Eosinophilia	No (or minor)	No (or minor)	Yes, often >3000/mm ³	No (or minor)
Microaneurysms on renal and/or coeliac angiography	Yes (65% of patients)	Rare (few case reports)	No	Rare (few case reports)
Granuloma on histology	Rare	Rare cases only	Yes, including eosinophils (frequent)	Yes (frequent but not always)
ANCA	No	Yes (60–80%), mainly anti-MPO	Yes (30–40%), mainly anti-MPO-ANCA	Yes (90% of those patients with systemic disease), mainly anti-PR3-ANCA
Relapse rate at 5 years (%)	<25	>50	>50	>60

ANCA, antineutrophil cytoplasmic antibodies; ENT, ear, nose and throat; MPO, myeloperoxidase; PR3, proteinase 3.

4.4.8 Aortic dissection and peripheral vascular manifestations

Aortic dissection is a rare complication, resulting from diffuse vasculitis of the aorta vasa vasorum. Dissection of other large arteries such as the carotid, hepatic, renal or splenic arteries, has also been reported. Peripheral arterial occlusions may be responsible for distal gangrene of the toes or fingers. Angiography can demonstrate the presence of stenoses and/or microaneurysms. Raynaud's phenomenon when present can remain isolated or be complicated by necrosis.

4.4.9 Gastrointestinal manifestations

GI tract involvement is one of the most severe manifestations of PAN, and is reported in 40–60% of patients, more often in HBV-related PAN (Pagnoux et al, 2005). GI manifestations are usually associated with other systemic manifestations of PAN, but they can be the first presenting signs in 2–16% of patients. They are the major cause of death within the first year after PAN onset, and thereafter are the third most common cause, just after infections and heart disease.

GI haemorrhages and small intestine perforations are the most feared manifestations, and are reported in 20–50% and 2–40% (mean 5%) of patients with PAN, respectively. When present, ischaemic vasculitis mainly affects the small bowel, and then, more rarely, the colon or stomach. In some cases, in the absence of disease manifestations, the diagnosis of vasculitis may be based on the histological findings after cholecystectomy or appendectomy. Patients with these localised GI forms usually have a good prognosis after prompt combined medical and surgical treatment. By contrast, acute necrotising or, less commonly, chronic pancreatitis, sometimes with pseudo-cysts, carries an extremely poor prognosis, because of the regular association with severe small intestine ischaemia and/or perforations. However, its incidence is low (seen in about 2–3% of patients).

Digestive malabsorption and exudative enteropathy have been reported on rare occasions. The liver and spleen can be involved, even in the absence of HBV infection, with infarct(s) and/or haematoma(s).

4.4.10 Orchitis

Orchitis is one of the most characteristic manifestations of PAN and was retained as one of the classification criteria established by the ACR. When treated immediately with glucocorticoids, orchitis may regress. In other cases, the ischaemia can be irreversible.

4.4.11 Pulmonary manifestations

The lungs are spared in PAN, in contrast to other vasculitides, such as MPA, EGPA or GPA. When pulmonary symptoms occur, infection should be looked for first, and is usually found.

4.4.12 Bone manifestations

Periosteal changes can be seen, which develop mainly in the legs. Localised oedema and pain are common symptoms. A few cases of bone necrosis have also been reported.

4.4.13 Ophthalmological signs

The eye can be affected in PAN, sometimes severely, as with unilateral or bilateral choroiditis, iritis, iridocyclitis, retinal detachment and/or retinal vasculitis

4.4.14 Localised forms of polyarteritis

Cutaneous PAN (cPAN) is relatively common, as opposed to other types of localised polyarteritis. In 1931 it was described as a distinct entity separate from systemic PAN, limited to the skin, adjacent muscles, nerves and joints. cPAN does not have any specific criteria; its diagnosis is based on clinical and histopathological findings. It has a more favourable prognosis, but relapses are very frequent. Evolution of cPAN into systemic PAN is possible but rare, patients should be kept under regular follow-up (Furukawa, 2012).

Isolated involvement of one skeletal muscle or a muscle group, and isolated neuropathy (mononeuritis multiplex or simplex) without systemic symptoms, have been described, such as occasional cases involving only one organ—the appendix, gallbladder, testis, breast or uterus. These forms usually also have good prognoses.

4.4.15 PAN in childhood

PAN is the third most common childhood vasculitis, after Kawasaki disease and IgA vasculitis (Henoch–Schönlein) (Ozen et al, 2006*). It is associated with fewer relapses and less mortality than adult PAN. In a review of 110 children who had been diagnosed with PAN, 30% were classified as cPAN, 57% as systemic PAN, 8% as MPA associated with ANCA and only 5% had classic PAN associated with hepatitis B surface antigen (Ozen et al, 2004).

4.5 Laboratory tests and angiographic investigations

4.5.1 Laboratory findings

Inflammatory features are found in the majority of patients. An erythrocyte sedimentation rate >60 mm during the first hour (78–89% of patients), raised C-reactive protein, raised white blood cell count (45–75% of patients) and normochromic anaemia (34–79% of patients) are common laboratory findings. Sometimes, a slightly raised eosinophil count of up to 1500/mm³ can be seen. The presence of HBsAg should be systematically sought. Unlike classic PAN, hypocomplementaemia can be found in patients with HBV-associated PAN.

ANCA are supposedly negative in PAN and if present should really challenge the diagnosis. The presence of ANCA giving a cytoplasmic or perinuclear labelling pattern, primarily directed against myeloperoxidase (anti-MPO) in ELISA, should be taken as an argument in favour of MPA rather than PAN.

4.5.2 Angiography

Medium-size arterial stenoses and microaneurysms can be seen on coeliac-mesenteric and renal angiography in PAN. Arterial saccular or fusiform aneurysms range in size from 1 to 5 mm and are predominantly seen in kidneys, mesentery and liver (figure 24). Less often, involvement of lumbar and intercostal arteries can also occur (figure 25). The lesions may disappear with effective vasculitis therapy. Although microaneurysms are not pathognomonic, they are commonly present (>60% of patients) in PAN. Conversely, they can be seen in endocarditis or artery fibrodysplasia, and, very rarely, in ANCA-associated vasculitides. Although conventional angiography still remains the 'gold standard' for detecting microaneurysms (having a higher sensitivity for their detection), because of its associated morbidity, CT or magnetic resonance angiography are now more commonly used in daily practice.

Figure 24 Renal angiography showing multiple microaneurysms in a patient with polyarteritis nodosa.



Figure 25 Angiogram of a 27-year-old woman with polyarteritis nodosa showing aneurysms of the intercostal arteries.



4.6 Histopathology

The histological lesion defining PAN is focal segmental necrotising vasculitis of medium arteries, less commonly arterioles, and only rarely, and not predominantly, capillaries and venules. The lesion may occur in any artery of the body, but involvement of the aorta and/or other large elastic arteries and/or pulmonary arteries has been described very rarely. The acute phase of arterial wall inflammation is characterised by fibrinoid necrosis of the media and an intense pleomorphic cellular infiltration, with predominantly neutrophils and variable numbers of lymphocytes and eosinophils. The normal architecture of the vessel wall, including the elastic laminae, appears to be completely disrupted and/or erased, and replaced by a band of amorphous eosinophilic material, resembling fibrin when stained. Arterial aneurysms and thromboses can occur at the site of the lesion. Arterial healing is characterised by fibrotic endarteritis that may lead to aneurysm regression or, when too abundant, to vessel occlusion. One of the characteristic histological features of PAN is the coexistence of necrotising vasculitis and a healed lesion or normal arteries in different tissues or in different parts of the same tissue.

Several potential biopsy sites can be diagnostic for PAN. Biopsies of the skin nodules are the most effective, enabling diagnosis in 95% of cases (dropping to 50% once they ulcerate). In patients with myalgias with or without concomitant mononeuritis multiplex, or presenting with general symptoms, a muscle biopsy is often useful. It should be performed at the myalgia site or in the gastrocnemius or peroneal muscles. The sensitivity of biopsies performed in proximal muscles (deltoid or quadriceps) is lower than in distal muscles. Nerve biopsy

in a sensory branch of the sciatic peroneal nerve can also be performed when the patient has distal mononeuritis multiplex in its sensory or motor-sensory form, with a sensitivity of about 50%. When patients do not have sensory signs in a candidate region for biopsy, the results have low sensitivity. Nerve biopsy can often prove the presence of vasculitis but cannot easily provide a diagnosis of PAN (vs MPA or other small vessel vasculitis) because nerve arteries are usually small. Furthermore, the biopsy itself can cause a permanent sensory deficit. Because renal involvement results from ischaemia, and not glomerular endothelium involvement, and because of the risk of haematoma due to traumatic rupture of a microaneurysm, renal biopsy is not relevant or recommended in cases of suspected PAN. Occasionally, temporal artery biopsy can show necrotising vasculitis, a histological finding that is rather uncommon in typical giant cell arteritis but has been seen in a few patients with AAV.

4.7 Aetiology and pathogenesis

The aetiology remains elusive for most patients. Nevertheless, in a few cases, infections, mainly viral, have been recognised as being responsible for PAN. Although viral antigens or immune complexes have rarely been found in the vessel walls of patients with PAN, a close relationship has been demonstrated between PAN and HBV infection. HBV infection through contaminated blood transfusion has now almost disappeared, with intravenous drug abuse and sexual transmission of HBV now the major causes of HBV-related PAN. The development of vaccines against HBV and their administration to those at risk, as well as the increased safety of blood transfusions, explain the dramatic decrease of the number of new cases seen since 1989. The frequency of HBV infection fell from 38.5% during 1972–1976 to 17.4% during 1997–2002, with a peak of 48.8% between 1982 and 1986. Over the past few years, the frequency of HBV-related PAN has declined to 20% (Pagnoux et al, 2010*).

Some other viruses have also been associated with PAN, but only explain a small number of cases. A few cases associated with hepatitis C virus (HCV) or parvovirus B19 infections have been described. Other viruses have been incriminated in PAN, and there are anecdotal reports of human immunodeficiency virus infections. Herpes zoster can also be responsible for vasculitis, like some members of the Herpes viridae family.

In addition to infectious causes, PAN-like disease has been described in association with malignancies. The closest relationship has been established with hairy-cell leukaemia. Malignancies are, for the most part, associated with small vessel vasculitides and very few cases of malignancies in true PAN have been reported.

Hence, the immunopathogenic mechanisms leading to vascular injury in PAN are probably heterogeneous. To date, there is no reliable animal model of the disease. The PAN-like disease in cynomolgus macaques, which is similar to the human disease, occurs only sporadically. The mechanism of vascular inflammation implicated most often, based on animal models but also some human studies (Trepo and Guillevin, 2001), is an immune-complex induced lesion. Pertinently, almost all cases of HBV-related PAN are associated with wild-type HBV,

HBe antigenaemia and high HBV replication, supporting the concept that lesions may result from the deposition of soluble viral antigen (Ag)–antibody (Ab) complexes in Ag excess, possibly involving surface antigen (HBsAg) and/or HBeAg. According to this hypothesis, immune complexes would activate the complement cascade, whose activated products would, in turn, attract and activate neutrophils. However, no recent study has explored the pathogenic mechanisms of PAN unrelated to HBV, which remain largely unexplained.

4.8 Treatment of PAN

4.8.1 Treatment of HBV-related PAN

In chronic hepatitis B, glucocorticoids and immunosuppressive agents have deleterious effects and enhance viral replication, despite having proved to be beneficial against the symptoms of vasculitis. Over the long term they perpetuate chronic HBV infection and facilitate progression towards cirrhosis, which may be complicated later by hepatocellular carcinomas.

Thus, the duration of glucocorticoid use must be short to rapidly control the most severe life-threatening manifestations of PAN, which are common during the first weeks of the disease. Glucocorticoids must then be abruptly stopped after 2–4 weeks to enhance immunological clearance of HBV-infected hepatocytes and favour HBeAg to anti-HBeAb seroconversion. The second part of the treatment consists of plasma exchange to clear circulating immune complexes and is usually prescribed until HBeAg to anti-HBeAb seroconversion is achieved. Antiviral agents must also be given to control viral replication as the third part of the treatment, beginning in the first weeks. At present, a combination of antiviral agents (e.g., tenofovir and/or entecavir) is best, using interferon α 2b, lamivudine and/or other newer antiviral drugs (Guillevin et al, 2005; Pagnoux et al, 2006). Owing to the rarity of the disease now, no study will be able to determine which antiviral combination is the most efficient, but therapeutic advances in chronic HBV infection can probably be transposed to HBV-related PAN.

Treatment for other virus-related PAN should also rely on the combination of short courses of glucocorticoid therapy and antiviral agents, together with plasma exchange when manifestations are severe. For HCV-related vasculitis, RTX should be considered, as suggested for the treatment of HCV-associated cryoglobulinaemic vasculitis (Saadoun et al, 2010). PAN associated with parvovirus B19 can respond to intravenous immunoglobulin therapy.

4.8.2 Treatment of non-viral PAN

In PAN, and in AAV, it seems reasonable to adapt the initial treatment to the severity of the vasculitis and not to systematically propose a standard treatment. To help the clinicians choose the most effective treatment, the FFS and BVAS should be used (see AAV treatment, section 3.4).

No robust data is available supporting the use of plasmapheresis in non-viral PAN, regardless of its prognosis; however, it may be useful in refractory PAN (Puéchal and Guillevin, 2013; de Luna et al, 2015).

After successful induction of disease remission in severe diseases, the switch from CYC to AZA or MTX is extrapolated from the AAV maintenance regimens; there are still no consistent data available for use of these drugs for PAN (de Menthon and Mahr, 2011).

Few data are available for the treatment of cPAN. Mild cases may resolve with non-steroidal anti-inflammatory drugs or colchicine; however, if ineffective, treatment with systemic glucocorticoids (0.5–mg/kg/day of oral prednisone or equivalent) and other drugs, such as dapsone or hydroxychloroquine, may help to achieve adequate responses. AZA, MTX and CYC are reserved for more severe cases unresponsive to glucocorticoid therapy (de Menthon and Mahr, 2011). In addition, there have been some reports of patients resistant to systemic glucocorticoids and immunosuppressive therapy successfully treated with IVIg or infliximab (Vega Gutierrez et al, 2007; Lobo et al, 2008).

In childhood PAN, there is a current randomised controlled trial comparing MMF with CYC for the induction treatment of the disease (MYPAN, ClinicalTrials.gov identifier: NCT00414128). It is the first randomised controlled trial examining the treatment of systemic PAN. Biological agents, such as infliximab, adalimumab, etanercept and rituximab, have also been explored (Eleftheriou et al, 2009).

4.9 Outcome and prognosis of PAN

In its systemic form, PAN is an acute disease, which can be severe and cause death if timely adequate treatment is not implemented. In historical series, only about 13% of untreated patients survived. Since the introduction of glucocorticoids, and their later combination with immunosuppressant agent(s), antiviral therapy for HBV-related PAN and plasma exchange, when appropriate, the prognosis of PAN has improved and overall survival rates have increased to more than 76–89% for PAN and 64–70% for HBV-related PAN (Guillevin et al, 1996). Although treatment can now control the outcome for most patients, some relapse and/or die of disease-related or treatment-related causes.

4.9.1 Relapses

Once remission has been obtained, PAN recurs much less frequently than other systemic vasculitides. In a study of 348 patients with a mean follow-up exceeding 5 years, 11% of patients with HBV-related PAN and 28% of those with non-HBV-related PAN relapsed, with mean times to first relapse of 43 and 26 months, respectively (Pagnoux et al, 2010*).

4.9.2 Deaths

In the above study of 348 patients with PAN, overall mortality was 25% after 5 years (20% for non-HBV-related PAN versus 34% for HBV-related PAN), with age >65 years, hypertension and abdominal surgery being independent predictors of death (Pagnoux et al, 2010*). In addition, the presence of any of the factors from the FFS indicates higher mortality rates: when FFS was 0, mortality at 5 years was 12%, when FFS was 1, mortality was 26%, and when FFS was ≥ 2 , mortality was 46%.

Although the causes of death vary from one vasculitis to the other, they can be divided into two categories: deaths attributable to the vasculitic process and those due to treatment side effects, with infections favoured by glucocorticoids and/or cytotoxic agents being one of the leading causes of death.

A few patients die during the first months of the disease from multivisceral involvement often caused by uncontrolled vasculitis because treatment cannot control the disease (Bourgarit et al, 2005). Typically, death occurs during the course of disease characterised by fever, rapid weight loss, diffuse pains and one or several major organ involvement. For PAN, deaths are often the consequence of GI involvement.

The deaths occurring in the following years may be the consequence of treatment side effects. These adverse events emphasise the importance of tailoring the therapeutic regimen after careful analysis of parameters predictive of outcome, such as those included in the FFS (Guillevin et al, 1996).

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SUMMARY POINTS

- Granulomatosis with polyangiitis (GPA) (Wegener's), microscopic polyangiitis (MPA) and eosinophilic GPA (Churg–Strauss) are primary necrotising vasculitides of small vessels, which can be defined using the Chapel Hill nomenclature and are associated in many patients with the presence of antineutrophil cytoplasmic antibodies (ANCA).
- Patients with GPA (Wegener's) can have a systemic generalised form of the disease associated with cANCA positivity with proteinase 3 specificity (but not exclusively) or a more localised form associated with ANCA in only about 50–75% of cases. Progression from one form to the other is possible throughout the disease, with persistently localised disease being rare (<5% of all patients).
- MPA is associated with pANCA to myeloperoxidase (MPO) in nearly 75% of cases.
- Treatment for GPA (Wegener's) and MPA relies on a combination of glucocorticoids and immunosuppressant agents (i.e., intravenous cyclophosphamide pulses or continuous oral cyclophosphamide or rituximab) for induction therapy, followed by a maintenance regimen with glucocorticoids and another less toxic immunosuppressant agent, such as rituximab, azathioprine or methotrexate, for a total duration of treatment of not less than 18 months.
- Rituximab is a newer and non-inferior alternative to cyclophosphamide for inducing remission in patients with generalized GPA (Wegener's) or severe forms of MPA and is superior to AZA as maintenance treatment.
- Despite staged induction–maintenance treatment, the relapse rate remains as high as 35% at 3 years for GPA (Wegener's), being slightly lower for MPA. The identification of parameters predictive of relapse might in the future help treatment to be adjusted according to the characteristics of individual patients. The identification of new strategies and new agents may also help to further improve patient outcomes.
- Eosinophilic GPA (Churg–Strauss) is associated with ANCA, mainly pANCA to anti-MPO, in only 30–40% of patients, and there are some clinical differences according to their presence or not, suggesting that distinct pathogenic mechanisms may be involved, such as ANCA and/or eosinophil-mediated cytotoxicity.
- Treatment for patients with eosinophilic GPA (Churg–Strauss syndrome) without poor prognostic factors can consist of glucocorticoids alone, whereas those with at least one poor prognostic factor according to the Five-Factor Score must receive a combination of glucocorticoids and immunosuppressant agent. Mepolizumab has been demonstrated to provide a better control of the asthmatic and ENT manifestations once vasculitis remission has been achieved but its effect on vasculitis remains uncertain.
- Polyarteritis nodosa (PAN) is a medium vessel systemic necrotising vasculitis. Its frequency has dramatically decreased during the past two decades, in parallel with that of hepatitis B infection (HBV).
- Patients with HBV-related PAN must receive a short course of glucocorticoids to control the vasculitic manifestations, antiviral agents and plasma exchange. Patients without HBV infection should receive glucocorticoids systematically, in combination with an immunosuppressant agent, mainly cyclophosphamide, when poor prognostic factors are present.

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module

EULAR on-line course on Rheumatic Diseases

Anca-associated vasculitides and polyarteritis nodosa

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A previous version was coauthored by Raashid Luqmani, Christian Pagnoux and Cristina Ponte

IN-DEPTH DISCUSSION I

**Assessment of disease activity and damage in small and
medium vessel vasculitis**

I introduction

There are no universally applicable serological markers to assess disease activity or determine chronic sequelae in most forms of vasculitis. Inflammatory markers such as CRP and ESR are not specific to vasculitis; although they are useful additional test when determining disease activity, they are also affected by other causes especially infection, which may mimic vasculitis or co-exist in patients with established vasculitis. Rising ANCA titres using highly sensitive new capture and anchor ELISA methods may prove to be of clinical relevance in predicting relapse, but this technology is still in its infancy and cannot yet be recommended in this setting (Roggenbuck et al, 2009). Furthermore, rising titres may occur in up to 40% of patients who do not subsequently demonstrate any change in clinical features to suggest reactivation of disease. Imaging modalities which can guide disease activity in large vessel vasculitis such as PET scanning are not useful in small vessel vasculitis. Instead, the best current method of determining disease activity and measuring chronic damage is to use clinical tools developed and validated for this purpose. Their main role is to guide treatment decisions, but they can also be of great value in clinical studies as outcome measures and to record the natural history of disease. We will review the concepts of disease activity and disease damage and provide an overview of the clinical tools available.

II Disease activity

The European League Against Rheumatism (EULAR) recommends the use of the Birmingham Vasculitis Activity Score (BVAS) to standardise the assessment of disease activity in clinical trials involving the systemic vasculitides (Hellmich et al, 2007; Yates et al, 2016). The BVAS has largely superseded the use of other scales of activity such as the Groningen Index (Kallenberg et al, 1990) the Disease Extent Index (DEI) (De Groot et al, 2001) and the Vasculitis Activity Index (VAI) (Whiting-O'Keefe et al, 1999) which are described in Table 1, but are not discussed further.

BVAS formalised the assessment of active vasculitis in one section for general features (systemic) and eight specific organ systems: cutaneous, mucous membranes/eyes, ear, nose and throat, chest, cardiovascular, abdominal, renal, and neurological (Luqmani et al, 1994). Symptoms and signs of organ involvement were recorded only if they could be attributed to new or worsening features of vasculitis and not another cause such as infection or side effects from medications. The items were designed to be easy to determine through taking a history and performing a standard examination of the patient together with a few simple investigations such as urinalysis and serum creatinine (Luqmani et al, 1994). Plain chest radiographs are recommended at first assessment of most patients with vasculitis as part of standard care, but do not need repeating at each visit unless clinically indicated. Repeat biopsies which had been required in the previous Groningen Index of activity in patients with granulomatosis with polyangiitis (Wegener's; GPA) (Kallenberg et al, 1990) were excluded on ethical and practical grounds. We tested the BVAS on 213 consecutive patients

with different types of vasculitis. BVAS was feasible to use and had content validity (comprehensiveness) and face validity (credibility) when trialled by a group of physicians with expertise in vasculitis. The BVAS also made biological sense (construct validity) when measured against other scores of disease activity and was sensitive to change when measured serially in 30 patients observed during episodes of both disease activity and inactivity (Luqmani et al, 1994). The BVAS score was weighted (by physician driven consensus) more towards items representing objective evidence of organ involvement, (e.g. significant rise in serum creatinine) as opposed to more subjective and less organ threatening symptoms (e.g. arthralgia) (Luqmani et al, 1994).

The design of the BVAS evolved through its use by the European Union Study Group of Therapeutic Trials in Systemic Vasculitis (ECSYSVASTRIAL) in clinical studies (Luqmani et al, 1997). Minor adjustments were made to the items included and for the first time the presence of persistent, low-grade disease, i.e. not new or worse but grumbling activity was recorded separately, as were the results of specialist opinions from ENT, cardiology or ophthalmologists (Luqmani et al, 1997). The BVAS has been used in several large clinical trials to assess disease activity and define remission and relapse (De Groot et al, 2009; De Groot et al, 2005; Jayne et al, 2003; Jayne et al, 2007). The latest version of BVAS (v.3) has further optimised the items included, excluding items with low specificity for vasculitis and grouping those due to the same pathological processes under the same headings (Flossmann et al, 2007; Suppiah et al, 2011). A single box for “persistent only disease” has replaced the second column to record ongoing active features to simplify the scoring system (Flossmann et al, 2007). Initial variation in scores between different physicians highlighted the need for adequate training to ensure that only items due to active vasculitis (rather than from infection or previous damage) are scored (Flossmann et al, 2007). The BVAS (v.3) forms, training manual and glossary sheet are available online at the EUVAS website (<http://www.vasculitis.org>). The BVAS (v.3) has been validated for assessment of activity of patients with systemic vasculitis, is reproducible and sensitive to change and demonstrates convergence with CRP, physician global assessment and treatment decisions (Mukhtyar et al, 2009). The BVAS has also been adapted for use in trials involving only patients with GPA (BVAS/WG) by concentrating on clinical features specific for patients with GPA (e.g. subglottic involvement) and excluding items less relevant to GPA (e.g. bruits or loss of pulses) (Stone et al, 2001). The BVAS/WG index has been validated in simulation exercises and actual patients with GPA, is sensitive to change with good inter and intra-observer reliability and correlates with the physician’s global assessment (Stone et al, 2001). An exercise applying different assessment tools to paper cases with GPA and microscopic polyangiitis, found a high correlation in scores between the BVAS/WG, BVAS, Physician global assessment and the DEI (Merkel et al, 2009). The BVAS/WG is not recommended for use in non-GPA vasculitis patients because it is yet to be clinically validated in this group.

III Disease Damage

The principle of disease damage in vasculitis is to measure chronic changes or scarring that has resulted since a diagnosis of vasculitis was made. The cause of the damage is not considered to be as important as the fact that

the patient has developed damage. Clearly for some features, the vasculitis itself, or its treatment are responsible. In other cases, co-morbidity from chronic disease or from an aging population is the cause. The most important aspect of recording damage in patients with vasculitis is that we actually ignore causation and only focus on the damage item itself. By definition, damage can only occur after the onset of vasculitis, and represents “permanent” effects (permanence is carefully defined in this context as an item that has lasted at least 3 months, or in the case of a single event, has occurred at least 3 months prior to the current assessment), even though the actual problem may have resolved (e.g. a myocardial infarction, from which the patient has made an apparent full recovery still represents permanent scarring in the myocardium). One of the important concepts of damage is to recognise components of disease that will not respond to immunosuppressive treatment and therefore, by categorising the item as damage, this should prevent inappropriate use of potentially harmful therapy. The concept is intuitive, but for accuracy, reproducibility and to monitor change over time we need an easy and well-defined method of measuring damage. The Vasculitis Damage Index (VDI) is the most widely used and validated method, and recently compared very favourably to a newer tool called the Combined Damage Assessment index (CDA) (Suppiah et al, 2011). An older damage tool called the Systemic Necrotising Vasculitis (SNV) damage index is summarised in Table 1, but it is no longer used and therefore not discussed further (Abu-Shakra et al, 1994). The other tool that is sometimes considered in this category is the five-factor score (FFS) which was proposed by the French Vasculitis Study Group, but this is a prognostic score rather than a detailed damage assessment (Guillemin et al, 1996).

IV Vasculitis Damage Index

The VDI is a generic tool created by the Birmingham Vasculitis Group (UK) in 1997 and is designed to be used with all types of systemic vasculitis (Exley et al, 1997). The principles guiding damage assessment, the items included and the glossary of terms for the VDI were developed by consensus of experts in vasculitis. The VDI comprises 64 items grouped into 11 organ systems. An arbitrary time limit of ≥ 3 months is used as the cut off for scoring an item of damage. For consistency, items such as stroke or myocardial infarction which are discrete events are still only scored after 3 months from the initial episode. Each item is scored as present or absent irrespective of the underlying cause as long as it has occurred after the onset of vasculitis. The intention is to capture damage due to disease or treatment but it is possible that other problems relating to an ageing population contribute to an increasing VDI score over time. There is no weighting of items; each item scored as present counts towards the total score (maximum possible = 64). Several groups have shown that the VDI score is an important prognostic marker (Koldingsnes et al, 2002; Exley et al, 1997). A score ≥ 1 on the VDI at time of first starting immunosuppression is a predictor of higher mortality [HR 6.1 (95% CI 1.7-22.1)] in GPA (Koldingsnes et al, 2002). A score of ≥ 5 at 6 months in a cohort of mixed primary and secondary vasculitis showed a much higher risk of mortality by 2 years [HR 12.3 (95% CI 4.2-36.9)] (Exley et al, 1997). Studies using the VDI have shown that the greatest accumulation of damage occurs in the first 6 months following a

diagnosis of vasculitis (Koldingsnes et al, 2002; Exley et al, 1997). The VDI has been used as an outcome measure in most of the major clinical trials in ANCA associated vasculitis over the past decade (De Groot et al, 2009; De Groot et al, 2005; Jayne et al, 2003; Jayne et al, 2007; WGET, 2005).

V Combined Damage Assessment

The ANCA-associated Vasculitis Instrument of Damage (AVID) is currently being assessed against the VDI in the RAVE trial (Rituximab for ANCA associated Vasculitis Trial); although initial RAVE results have been published, the results of the comparison of damage indices are not yet published. At the same time, we have revised the VDI to be more specific for ANCA-associated vasculitis. Considerable overlap was noted between the 2 separate efforts and therefore the group decided to merge both projects to create a new tool, the Combined Damage Assessment index (CDA).

The CDA comprises 135 items grouped into 17 categories; includes laterality for damage to the eyes and ears and records gradation of severity for 8 items (Seo et al, 2007). The extra components (e.g. striae, easy bruising and weight gain) in the CDA (compared to the VDI) derive from information previously recorded in the 'other' category on the VDI for patients enrolled in the WGET trial (Seo et al, 2005) and also distinguishes between left and right for damage to the eyes and ears (Seo et al, 2007). A survey of 50 experts in vasculitis covering all relevant specialties has shown that malignancy, renal failure, severe respiratory compromise, cardiovascular disease and blindness should have the greatest importance whereas items such as muscle atrophy, bruising, mouth ulcers, striae and alopecia should have the lowest (Seo et al, 2009). The other difference between the CDA and the VDI are that the time cut off for damage is defined as ≥ 6 months and the item of damage must be attributable to vasculitis or its treatment. A recent study has compared the CDA to the VDI in a cross sectional study of 285 patients with primary and secondary causes of vasculitis; the majority of patients (70%) had ANCA associated vasculitis. Attribution to cause of damage was not applied and the ≥ 3 -month time point was used for both the VDI and CDA. The findings were that although the CDA was more sensitive at detecting damage, it was more time consuming and had lower inter- and intra-observer reliability than the VDI due to its complexity (Suppiah et al, 2011).

VI Functional assessment

With improvement in immunosuppressive therapy for the treatment of systemic vasculitis, patients are now surviving for longer, but the effect of pain and other disease symptoms can result in significant impairment to their function and quality of life (Koutantji et al, 2003). Self-reported assessment tools to measure quality of life such as the SF-36), and the HAQ to measure levels of physical functioning and disability are established for use in patients with chronic disease and have been used in patients with vasculitis (Koutantji et al, 2003; Hoffman et al, 1998; Pincus et al, 1999; Walsh et al, 1999).

The OMERACT Vasculitis Working Group has recognised that developing vasculitis- specific patient reported outcome measures (PROMs) is an essential area for future research, because generic tools such as the SF-36 may not be precise enough to accurately measure change in this set of chronic complex multisystem diseases (Merkel et al, 2009).

VII Conclusion

There is no gold standard for assessment of disease activity and damage in patients with systemic vasculitis. However, current methods have been important in standardising the approach to individual patients and also been the cornerstone of the assessment and treatment decisions in many recent clinical trials in vasculitis. These tools will always be imperfect and need ongoing review and revision. Nevertheless, their use is recommended and endorsed by OMERACT (Merkel et al, 2011). In future, new biomarkers may be incorporated into, or surpass these instruments. Emerging issues are the patient perspective in these chronic relapsing diseases; so far little attention has been paid to this area, but it is increasingly apparent that issues which are important to physicians are not the same as the issues considered most important to patients.

Table 1: Summary of Vasculitis Assessment tools.

Assessment tool	Description	Comments	Reference
Disease activity tools			
Groningen Index	Scored on clinical signs and histology.	Impractical for serial assessment because it requires repeat biopsies to provide histological evidence of activity, developed in GPA.	Kallenberg <i>et al</i> , 1990
Vasculitis Activity Index (VAI)	Nine rating scales for separate organ system involvement (graded 0-4) combined with laboratory tests.	Easy to complete but highly subjective.	Whiting-O'Keefe <i>et al</i> , 1999
Disease Extent Index (DEI)	Signs and symptoms, and diagnostic procedures to be performed to confirm active vasculitis in 10 organ systems (each scoring 2) plus constitutional symptoms (scores 1).	Assessment of current damage and activity, designed for use in WG. Weighting used.	De Groot <i>et al</i> , 2001
Birmingham Vasculitis Score (BVAS)	9 organ based systems. Physician consensus derived weighting for each individual item and maximum totals applied to each system.	Physician must decide if items due to new or worse active vasculitis; persistent disease could be documented in the later version but increases complexity of evaluation.	Luqmani <i>et al</i> , 1994; Luqmani <i>et al</i> , 1997

BVAS (v. 3)	66 clinical features grouped into nine organ systems. Weighting according to perceived clinical relevance. Inclusion of some items requiring specialist opinion or further tests.	Physician must decide if items due to active vasculitis, persistent disease indicated by single box (only if all items are persistent).	Mukhtyar <i>et al</i> , 2009
BVAS/WG	Addition of “other section” to nine organ systems used in BVAS. 34 separate disease items, chosen as more specific for GPA, further classified into major (organ- or life- threatening) or minor items.	Only validated for use in GPA although shown to correlate with BVAS for other vasculitides.	Stone <i>et al</i> , 2001

Damage assessment tools

Systemic necrotizing Vasculitis (SNV) Damage Index	34 items. Scoring occurs if damage present for ≥6 months except for irreversible items such as stroke and myocardial infarction which are scored immediately. Some items have double weighting. Does not include items of damage in the ENT system.	Superseded by VDI.	Abu-Shakra <i>et al</i> , 1994
Vasculitis Damage Index (VDI)	Generic tool for all types of vasculitis. 64 items grouped into 11 organ systems. No weighting of items in current version.	1 page tool, easy to use. Validated and widely used.	Exley <i>et al</i> , 1997
ANCA Vasculitis Index of Damage (AVID)	Specific for ANCA associated vasculitis. Left and right sides scored separately for damage to eyes and ears.	Undergoing validation.	Seo <i>et al</i> , 2007
Combined Damage Assessment index (CDA)	Specific for ANCA associated vasculitis. 135 items in 17 organ systems. Left and right side scored separately for damage to eyes and ears. Weighting of items is planned for the future.	Shown to be inferior to VDI.	Seo <i>et al</i> , 2007; Suppiah <i>et al</i> , 2011

Prognostic tools

Five factor score (FFS)	Prognostic factors in polyarteritis nodosa (PAN), microscopic polyangiitis (MPA) and eosinophilic GPA (Churg-Strauss). The parameters of the original FFS are: renal failure, proteinuria, cardiomyopathy, GI tract and CNS involvement. The revised FFS allows also identification of prognostic factors in GPA patients. It includes age >65 years as another measure of poor prognosis and the presence of ENT manifestations as a parameter of good prognosis in GPA and EGPA.	FFS=0, 5 year mortality 11.9%; FFS=1, 5 year mortality 25.9%; FFS>2, 5 year mortality 45.95%.	Guillevin <i>et al</i> , 1996; Guillevin <i>et al</i> , 2011 for revisited version
Vasculitis Damage Index (VDI)	Several studies have shown that the VDI score at different time points can be an important prognostic marker for future death and morbidity.	A VDI score ≥ 5 at the 6 month time point has a HR of 12 for death at 2 years compared to those with a lower score.	Exley 1 <i>et al</i> , 1997

Functional assessment tools (No vasculitis specific tools currently available)

Health Assessment Questionnaire (HAQ)	Self-assessment form to measure levels of physical functioning and disability.	Designed for use in RA, now generic use as tool in chronic diseases.	Pincus <i>et al</i> , 1999; Koutantji <i>et al</i> , 2003
Short form 36 (SF-36)	Self-assessment generic measure of health status. 36 questions. Dimensions: physical function, role limitation (physical or emotional), mental health, social functioning, energy, pain and perception of general health.	Generic use in chronic disease.	Hoffman <i>et al</i> , 1998; Koutantji <i>et al</i> , 2003

The BVAS, BVAS (v.3) and the VDI forms, training manual and glossary sheets are available online on the EUVAS website (<http://www.vasculitis.org/>).

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24

module

EULAR on-line course on Rheumatic Diseases

Anca-associated vasculitides and polyarteritis nodosa

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A previous version was co-authored by Raashid Luqmani, Christian Pagnoux and Cristina Ponte

IN-DEPTH DISCUSSION II

The role of biologics in ANCA-associated vasculitis

INTRODUCTION

In this in-depth discussion we review the role of biologics in the treatment of ANCA associated vasculitides (AAV), and the therapeutic developments expected to occur in the near future.

GRANULOMATOSIS WITH POLYANGIITIS (GPA) and MICROSCOPIC POLYANGIITIS (MPA)

Rituximab

Rituximab (RTX) is a chimeric monoclonal antibody against CD20, a receptor found on the membrane of mature B cells. Many arguments support the use of anti-B-cell drugs in AAV. RTX has been shown to be useful in induction and maintenance of remission in generalised GPA and severe MPA patients.

Two randomized controlled trials (RCT) pointed out the non-inferiority of RTX in inducing remission compared with cyclophosphamide (Stone et al, 2010; Jones et al, 2010). The remission rates were not different in the 2 treatment groups and the short term safety profile was similar, leading to its registration by the EMA and FDA in those patients. In addition, rituximab was found to be superior to conventional induction therapy in relapsing patients (Stone et al, 2010) and may also be effective in refractory disease after failure of induction treatment (Miloslavsky et al, AR 2013). Rituximab should be preferred for women of child bearing age. A recent retrospective study has shown that the malignancy risk in patients with AAV was lower in RTX-treated patients than in cyclophosphamide-treated patients (van Daalen et al, 2017).

Furthermore, RTX has changed the standard of care for maintenance therapy in those patients. RTX superiority to azathioprine to maintain remission was demonstrated in a study comparing pre-emptive low dose RTX with azathioprine after remission achieved with a combination of cyclophosphamide and glucocorticoids (Guillevin et al, 2014). Overall, 57 patients received RTX maintenance re-treatment every 6 months (500 mg RTX, five infusions over 18 months) and 58 patients were treated with AZA (starting at 2 mg/kg/day). The primary end point was the rate of major relapses at 28 months: major relapse had occurred in 3 patients in the RTX group (5%) and in 17 patients in the azathioprine group (29%) ($P=0.002$). The frequencies of severe adverse events were similar in the two groups. At month 60, major-relapse-free survival rates were 71.9% and 49.4% ($P=0.003$); minor-and-major relapse-free survival rates were 57.9% and 37.2% ($P=0.012$); and cumulative glucocorticoid use was comparable (Terrier et al, 2018).

The best treatment schedule (RTX injection on demand or driven by surrogate markers such as CD19 level and/or ANCA titer), and its duration are being investigated in 2 RCT. The former has compared two RTX regimens: 500 mg infusions according to ANCA status/titer and/or circulating CD19 B-cell reappearance versus systematic 500

mg infusions at fixed intervals of 6 months (controls) (Charles et al, 2018). AAV relapse rates for patients given individually tailored or systematic RTX-infusion schedules did not differ significantly. However, the experimental arm patients received fewer infusions and lower total RTX doses. The objective of the latter ongoing trial is to determine the optimal duration of the RTX maintenance treatment to prevent relapses (2 or 4 years) (ClinicalTrials.gov identifier: NCT02433522).

In addition, RITAZAREM is comparing a different RTX regimen (1 g every 4 months until month 20) with AZA (2 mg/kg daily for 24 months) for maintenance treatment in relapsing AAV patients after achievement of remission with RTX (ClinicalTrials.gov identifier: NCT01697267).

Despite the achievement of a better disease control with RTX, late disease flares still occur, mainly in patients with a history of relapse, in those with positive anti-PR3 at baseline or with a positive test for ANCA 12 months after RTX therapy (Specks et al, 2013).

Case series and uncontrolled studies have suggested that granulomatous manifestations respond less or slower to RTX. (Holle et al, 2012).

Most of the adverse events occurring during the therapy with RTX are infections. Few cases of *Pneumocystis jiroveci* pneumonia have been reported, so that a prophylaxis treatment with trimethoprim-sulfamethoxazole (400 mg/80 mg per day) is therefore advised until complete B repopulation (Charles et al, 2013). Moreover, a few cases of progressive multifocal leukoencephalopathy (PML) due to the JC virus have been also described (Molloy 2012, et al). Great caution is therefore needed when considering RTX therapy, in patients exposed to alkylating agents or having fewer than 200 CD4 cells/mm³. There is no evidence of an increased cancer risk with RTX (van Daalen et al, 2017). Cases of RTX induced neutropenia or vasculitis have been reported. Finally, RTX does not impair fertility in both male and female patients.

Anti-TNF alpha agents

TNF- α is associated with disease activity in AAV and its inhibition has been evaluated (Furuta et al, 2014). However, TNF inhibitors are not currently recommended in the treatment of AAV.

Infliximab has been used in refractory GPA, with no concomitant immunosuppressive treatment. Despite small open-label trials showing remission in infliximab-treated patients (Mukhtyar et al, 2005), a trend towards a lower efficacy of infliximab compared to RTX was observed in a long-term follow-up pilot study (de Menthon et al, 2011).

There is no place for etanercept in the management of patients with GPA or MPA. In the only available RCT, etanercept did not show any additional benefit to conventional therapy and was associated with a worse safety profile: six cancers were diagnosed during the trial, all in the etanercept arm (The Wegener's Granulomatosis Etanercept Trial Research Group, 2005).

Adalimumab has also been proposed as an adjunctive and glucocorticoid-sparing agent for the treatment of severe AAV, but further studies are required (Laurino et al, 2010).

Anti-T cells agents

The encouraging results observed with abatacept (CTLA4-Ig) treatment in a small open label study with non-severe relapsing GPA (Langford et al, 2014) await to be confirmed in an ongoing RCT (ABROGATE, ClinicalTrials.gov identifier: NCT02108860).

Alemtuzumab is an antibody targeting the CD52 antigen on lymphocytes. Its use in few patients with severe refractory vasculitides was associated with a good response, but relapse and adverse events were common (Walsh et al, 2008).

Other biologics

The role of tocilizumab, an IL-6 receptor antagonist, has been recently investigated in a small uncontrolled study, where it was administered in monotherapy with no glucocorticoids in MPA patients (Sakai et al, 2016). Complete remission was achieved in two of six patients at 6 months and three patients at 12 months. Larger studies are needed to better define its efficacy.

Belimumab, a human monoclonal antibody that inhibits B lymphocyte stimulator (BLyS), has been evaluated as maintenance treatment in ANCA-positive MPA and GPA (BREVAS, ClinicalTrials.gov identifier: NCT01663623).

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

In EGPA, most of the available literature relies on small uncontrolled studies due to the rarity of the disease.

Mepolizumab

The only published RCT has recently demonstrated the efficacy of mepolizumab (a monoclonal anti-IL-5 agent) compared with placebo in EGPA patients with relapsing or refractory disease over a 52-week follow-up period (Wechsler et al, 2017). Mepolizumab, administered subcutaneously every 4 weeks (300 mg dose), led to significantly more accrued weeks of remission than placebo (28% vs. 3%), a higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%), and allowed to receive a daily dose of prednisolone or prednisone of 4 mg or less per day in a significantly higher number of patients (44% vs 7%). The efficacy of mepolizumab in this trial was mainly due to a better control of asthmatic and ENT manifestations whereas its efficacy in vasculitis remains unclear. This biologic will help controlling the disease in those patients with recurrent and refractory asthma or ENT manifestations.

Rituximab

Pivotal RCT investigating RTX in AAV excluded EGPA patients because this disease is rarer and positive ANCA tests are less frequent than in GPA or MPA.

In the largest available series, 41 EGPA patients have been treated with RTX mostly for refractory or relapsing disease (Mohammad et al, 2016). Patients with positive ANCA testing were significantly more likely to achieve remission at 12 months (80% ANCA-positive vs 36% ANCA-negative). Apart infections, other safety issues included infusion reactions, among which some were severe (Mohammad et al, 2016; Bouldoyre et al, 2009). Very few patients have been described to have received RTX as maintenance therapy.

The French Vasculitis Study Group recommended that RTX can be prescribed to some EGPA patients with refractory disease responding only to high-dose glucocorticoids, particularly those with forms characterized by predominant inflammatory vascular disease (extracapillary glomerulonephritis, alveolar haemorrhage) and with positive anti-MPO ANCA (Charles et al, 2013).

Two RCT of the French Vasculitis Study Group aiming to determine the efficacy of RTX for inducing (REOVAS, ClinicalTrials.gov identifier: NCT02807103) or maintaining remission (MAINRITSEG, ClinicalTrials.gov identifier: NCT03164473) are ongoing in patients with EGPA.

Omalizumab

Omalizumab, an anti-IgE monoclonal antibody, is indicated in patients with convincing IgE mediated asthma. Small case series have suggested its usefulness for the control of refractory asthma and as steroid sparing agent in EGPA patients (Jachiet et al, 2016). However, further studies are needed before considering that omalizumab has no role in the onset of EGPA or in the vasculitis flares that have been observed during therapy.

CONCLUSION

The amount of evidence that biologics play a pivotal role in the treatment of AAV is rapidly increasing. RTX represents a good alternative to cyclophosphamide for inducing remission in patients with generalised GPA and severe MPA without increasing the risk of infertility and cancers. It has changed the standard of care for maintenance of remission in those patients. The best way to treat patients over time with this agent is object of ongoing studies and should probably be individually tailored according to the factors associated with relapse. Mepolizumab can be considered in EGPA patients with refractory asthma or ENT manifestations.

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Behçet's disease, relapsing polychondritis, and eye symptoms in Rheumatic Diseases

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LEARNING OBJECTIVES

Part 1: Behçet's disease

- To recognise the signs and symptoms of Behçet's disease
- To describe the distinct geographical distribution of the syndrome, which is related to the ancient Silk Road, and its special place among the vasculitides
- To suggest a differential diagnosis, which is especially important for areas where the syndrome is rare
- To describe the natural course and prognosis of the various manifestations
- To evaluate treatment modalities, giving due consideration to evidence from the relatively few formal studies
- To plan an individual treatment strategy according to age, gender and the sites involved

Part 2: Relapsing polychondritis

- To recognise relapsing polychondritis (RP).
- To list and describe the diseases associated with RP.
- To recognise that RP may be a benign or a very severe disease.
- To manage different disease presentations.

Part 3: Eye involvement in rheumatic disease

- ➞ To describe, explain and investigate the various eye manifestations observed during the course of rheumatic diseases.
- ➞ To differentiate the prognoses of the different eye manifestations.
- ➞ To identify conditions where an ophthalmologic consultation is appropriate.

1 Behçet's disease

Although there has been global interest in Behçet's disease (BD) during the past two decades, the condition has been recognised since antiquity and was described by Hippocrates. The seminal paper by Hulusi Behçet, a professor of dermatovenereology at the University of Istanbul, was published in the 1930s. He followed up three patients for 17 years and defined the syndrome as the tri-symptom complex of oral aphthae, genital ulcerations and hypopyon uveitis. Later work showed that many other organ systems are also involved (Akman-Demir et al, 2011*).

There is debate about whether the entity described by Behçet is better designated as a disease or a syndrome (Direskeneli, 2006*). The authors prefer the latter given that we do not know the pathogenesis and there is no definitive diagnostic test.

1.1 Epidemiology

The pooled prevalence of BD is currently estimated at 10.3/100 000 inhabitants, as resulting from a global summary of data currently available in countries where epidemiological studies have been conducted on BD. However, BD has a distinct geographical distribution. Most cases come from countries around the Mediterranean basin and from Japan, while the syndrome is quite rare in Northern Europe, Northern Asia, most of continental Africa, Australia or the Americas. Specifically, pooled estimates of prevalence proportions expressed as cases/100 000 inhabitants is 119.8 for Turkey, 31.8 for the Middle East, 4.5 for Asia and 3.3 for Europe (Maldini, 2017*). Travel along the Silk Route has been implicated as the mechanism through which an etiological agent (eg, genetic or environmental) was spread.

Although it can affect every age group, onset before puberty or after the sixth decade is relatively rare. The usual onset is in the third decade. Sex distribution is roughly equal, but a male predominance has been described in some Middle Eastern and Mediterranean countries, while a female predominance has been reported in Japan and Korea.

A study carried out using the capture–recapture method among North African and Asian immigrants in Paris showed that: (a) the prevalence of BD was almost as high as that of other primary vasculitides (polyarteritis nodosa, Wegener's, etc) combined; (b) the prevalence was higher in immigrants than in the in-dwelling European population; and (c) BD risk was not related to age at immigration, suggesting a hereditary basis (Kirino et al, 2013a*). The prevalence of the disease was also low in the Armenian population of Istanbul, suggesting the role of genetic factors (Remmers et al, 2010*).

Some of the manifestations of BD also show regional differences. Gastrointestinal findings are common in Japanese patients (up to 58% of patients), but rather infrequent in Middle East and Turkey (1.4% to 3% of patients). The same is true for pathergy, the non-specific hypersensitivity of the skin to a needle prick, which is less commonly positive in European and US patients. Uveitis due to BD is also more common in countries where BD is more prevalent. A study has investigated potential ethnicity-related differences relative to phenotype and prognosis of patients with BD in a French multi-ethnic country (Savey et al, 2014*). They included 769 consecutive patients fulfilling the international criteria of classification for BD, in the three largest ethnic groups of our cohort (European (n = 369), North African (n = 350) and sub-Saharan African (n = 50)). Sub-Saharan African patients with BD had a higher frequency of central nervous system (CNS) involvement (48% vs 32.3% vs 29.5%, $p = 0.035$), a higher rate of death (12% vs 6% vs 3.5%, $p = 0.029$) and a lower frequency of the HLA-B51 allele (29.4% vs 49.2% vs 55.8%, $p = 0.009$) than those from North Africa and Europe, respectively. Multivariate analysis showed that male gender (HR = 5.01, 95% CI 1.51 to 16.65), cardiovascular involvement (HR = 2.24, 95% CI 1.15 to 4.36) and sub-Saharan African origin (HR = 2.62, 95% CI 0.98 to 6.97) were independently associated with mortality. The 15-year mortality rate was 19%, 9% and 6% in sub-Saharan African, North African and European patients with BD, respectively ($p = 0.015$).

1.2 Clinical spectrum

Skin and mucosa lesions, uveitis, major vessel disease and musculoskeletal, neurological and gastrointestinal manifestations are seen in varying combinations (Ideguchi et al, 2011*). The diagnosis is clinical and a course characterised by remissions and exacerbations is typical. The intensity of the attacks decreases with the passage of time.

BD is usually described as a systemic vasculitis that affects many organs. However, in many instances (eg, parenchymal CNS disease) a true vasculitis cannot be demonstrated. Thus, a better designation would be to describe the condition as a 'systemic inflammation'. In this regard, BD has recently been included among polygenic and multifactorial autoinflammatory diseases also on the basis of clinical presentation, that resembles the clinical framework of monogenic autoinflammatory disorders (Vitale et al, 2016a*).

Table 1 shows the frequency of the main clinical manifestations.

Table 1 Frequency of clinical manifestations of Behçet's disease

Manifestation	Frequency (%)
Oral ulcers	97–99
Genital ulcers	85
Genital scar	50 (probably more prevalent in men)
Skin lesions	
Papulopustular lesions	85
Erythema nodosum	50
Pathergy reaction	60 (Mediterranean countries and Japan)
Uveitis	50
Arthritis	30–50
Subcutaneous thrombophlebitis	25
Deep vein thrombosis	15
Arterial occlusion/aneurysm	5–10
Central nervous system involvement	20
Epididymitis	5
Gastrointestinal lesions	1–58 (more prevalent in Japan)

1.3 Mucocutaneous manifestations

1.3.1 Oral ulcers

Oral ulcers are seen in 97-99% of patients and are often the first disease manifestation (figure 1). They resemble ordinary aphthae but are more frequent and multiple. They often appear as erythematous, circular and slightly raised areas evolving into oval or round ulcers within 48 h.

Figure 1 Oral ulcers in Behçet's disease.

They have traditionally been defined as minor, major and herpetiform according to their size and location; >90% are of the minor type. They are <10 mm in diameter and are often seen on the mucous membranes of the lips, gingiva, cheeks and tongue, perhaps more posterior than ordinary aphthae, and are seen in 15% of the normal population. They usually heal in about 15 days without scarring. Tobacco use decreases their frequency and severity, whereas stopping smoking seems to exacerbate them.

Less frequently, oral ulcers can present as major aphthae, which are larger than 10 mm and usually require a longer healing process (weeks or months) often resulting in scarring. Finally, herpetiform aphthae are smaller (1-3 mm), grouped or coalescent and heal over 1 to 4 weeks.

1.3.2 Genital ulcers

Genital ulcers are usually located on the scrotum in men and on the major and minor labiae in women. Less common locations are the shaft and glans penis and the vaginal and cervical areas. The inguinal area, pubis and perineum are occasionally affected in both sexes. They usually begin as papules or pustules that ulcerate after a short time (figure 2). Compared with oral ulcers, they are larger, deeper, less recurrent and more resistant to healing. They usually heal in 10–30 days if they are not secondarily infected, and leave scars in about 60% of patients. Scar formation is more common if the diameter of the ulcer is >1 cm. Genital scarring is usually good evidence of BD in a patient suspected of having this syndrome.

Figure 2 Genital ulcers in Behçet's disease.



1.3.3 Other skin lesions

The other types of skin lesions can be divided into three broad categories: (a) erythema nodosum-like lesions and superficial thrombophlebitis; (b) papulopustular lesions and (c) other lesions such as skin ulcers and Sweet's syndrome. Erythema nodosum-like lesions are seen in 50% of patients and morphologically resemble the idiopathic or secondary variants (figure 3). Histopathology shows more evidence of vasculitis in lesions associated with BD than in lesions due to other causes.

The superficial thrombophlebitis looks like erythema nodosum. It is more common in men and is characterised by a thrombosed vein on biopsy. Ultrasonography may differentiate the two lesions.

Figure 3 Erythema nodosum-like lesion in Behçet's disease.



The papulopustular lesions resemble ordinary acne (figure 4). They are seen at the usual acne sites such as the face, upper chest and back, and additionally on the legs and arms. They are usually colonised by *Staphylococcus aureus* and *Prevotella* species and are more common in a subgroup of patient with arthritis. Skin ulcers and Sweet's syndrome may occasionally be seen.

Figure 4 *Ostiofolliculitis in Behçet's disease.*



1.4 Pathergy

The pathergy phenomenon is a non-specific hyper-reactivity in response to minor trauma. Although it has a moderate sensitivity ($\approx 50\%$), it is highly specific for BD ($>95\%$). It is usually used as a diagnostic test and is performed by inserting a 20 gauge needle into the dermis of the forearm of the patient. The test is positive when the development of a papule or pustule is observed at the needle-prick site after 24–48 h (figure 5). The rate of positivity is not related to the severity or the site of involvement, although male patients tend to have stronger reactions. It also has a limited reproducibility and may vary in intensity in the same patient if performed repeatedly. It is a useful test in Mediterranean, Near Eastern and Far Eastern countries, although it may be less so in continental Europe or the Americas. Interestingly, increasing evidences suggest a decline in the positive rate of skin pathergy test over the past four-five decades worldwide. This could be related to racial differences as well as different methodology used to perform the pathergy test, including the use of disposable needles instead of blunt, reusable, sterilized needles.

Figure 5 Positive pathergy reaction.

1.5 Eye involvement

Eye involvement in BD causes serious morbidity and is a common cause of blindness in the Mediterranean basin, Middle East and Far East. It is found in 50% of patients, but the frequency reaches 70% in young men aged <25 years. It is usually seen during the first 2 years of the syndrome and is bilateral in 70–80% of patients. The most frequent pattern is a non-granulomatous panuveitis not infrequently accompanied by a retinal vasculitis. Hypopyon formation (figure 6), which is a collection of pus in the anterior segment, is seen in about 20% of patients with eye involvement and is nearly always accompanied by additional posterior inflammation. Isolated anterior involvement is uncommon and conjunctivitis, corneal ulcerations and scleritis are rare occurrences. Recurrent bouts of inflammation lead to structural damage characterised by posterior synechiae, complicated cataracts, optic atrophy and macular degeneration. Total loss of vision is seen in 20% of cases with uveitis, even after treatment.

Ophthalmological consultation with indirect ophthalmoscopic and slit lamp examination must be performed for every patient with vision problems, since correct diagnosis and the prevention of ocular attacks are the most effective means of avoiding blindness.

Figure 6 Hypopyon uveitis in a patient with Behçet's disease. Patient consent obtained.



1.6 Central nervous system disease

Neurological involvement is seen in 5% of patients with BD. It usually occurs after the first 5 years of disease and almost never as a presenting feature. Two main patterns of involvement are seen: vascular and parenchymal. Parenchymal disease leads to inflammatory lesions in the brain stem, diencephalon, basal ganglia and, less frequently, the spinal cord and cerebellum. The cerebral cortices seem to be spared. It usually manifests as bilateral pyramidal signs, unilateral hemiparesis, behavioural changes, sphincter disturbances and headache. Brainstem signs and sensory disturbances are less common. Abnormal cerebrospinal fluid findings, such as pleocytosis and increased cellularity, are found in 60% of patients with parenchymal involvement. Magnetic resonance imaging (MRI) is more sensitive than CT for imaging and the characteristic lesion is a pathological signal with contrast enhancement in the brainstem and basal ganglia regions (figure 7).

Figure 7 Magnetic resonance image of parenchymal central nervous system involvement in a patient with Behçet's disease.



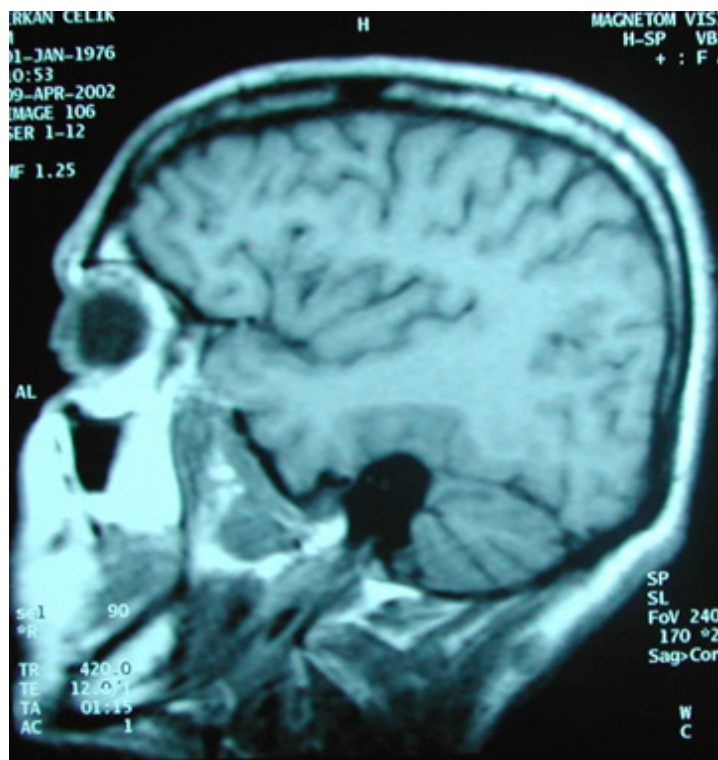
A recent study has claimed that susceptibility-weighted imaging—an MRI modality sensitive to microhaemorrhages and venous flow—performs better than standard sequences in detecting parenchymal neurological disease.

Frequent attacks, a progressive course and abnormal cerebrospinal fluid findings indicate a bad prognosis. About 25% of patients in this category will have some disability in 10 years' time.

The second pattern of neurological involvement is dural sinus thrombosis (figure 8), mainly characterised by headache and papilloedema. It is usually associated with deep vein thrombi in other areas and has a better prognosis than parenchymal involvement.

Sensorineural hearing loss has recently been found to be a common underrated feature of BD, especially in patients with cutaneous plus articular involvement, but there are no studies evaluating the histological basis of inner otologic involvement (Sota et al, 2016*).

Figure 8 Magnetic resonance image of a dural sinus thrombosis in a patient with Behçet's disease.



The presence of headache in a patient should not be ascribed to neurological involvement unless it is associated with neurological symptoms, since tension type headaches are common in patients with BD.

Cognitive impairment in the form of 'frontal' executive dysfunction is also common.

1.7 Major vessel involvement

BD can affect both venous and arterial vessels, the former being more common than the latter. Venous thrombosis is seen in about 20% of patients with BD, throughout the disease course. According to studies on Turkish patients, major vessel involvement is more frequently seen in men and overall is found in up to 40–50% of patients; 60–80% of these lesions are venous thromboses of the deep veins of the lower extremities. Conversely, large-vessel involvement is less frequent in Japan.

The involvement of inferior and superior vena cavae, dural sinuses and axillary, brachial, hepatic and portal veins is a less frequently described event (Espinosa et al, 2002*).

Chronic recurrent thrombosis of the lower extremities leads to erythema, dermatitis, hyperpigmentation and, subsequently, crural ulcers (figure 9). Many patients with chronic venous insufficiency report claudication-like lower extremity pain on walking despite the absence of arterial obstruction (i.e., venous claudication). Chronic obliteration of the caval system leads to venous collaterals on the thoracic and abdominal walls. Obstruction of the superior vena cava may also cause oesophageal varices, chylothorax and chylous pericardial effusions.

Figure 9 Chronic thrombosis and a skin ulcer in a patient with Behçet's disease with longstanding deep vein thrombosis.



Budd–Chiari syndrome resulting from hepatic vein occlusion presents with ascites and liver failure. It is a rare complication of BD, but carries a high death rate. One should be aware that venous thrombi may precede and be an impending sign of arterial inflammation in BD.

Systemic artery involvement may be seen in 1.5–7.5% of patients. The typical lesions are aneurysmal, or uncommonly, occlusive. The abdominal aorta is the most frequently affected site followed by the iliac, femoral, popliteal, carotid and subclavian vessels. Renal, cerebral or coronary arteritis and abdominal visceral ischaemia are uncommon.

Peripheral arterial involvement may translate into reduced or absent pulses with intermittent claudication, cold extremities or even gangrene. Abdominal aortic aneurysms sometimes produce abdominal pain. Bruits can be heard over the affected large arteries and a pulsating mass may be found. Most patients with arterial lesions have constitutional signs and symptoms, such as fever and weight loss.

Pulmonary arterial aneurysms are the most devastating arterial involvement in BD (Hamuryudan et al, 2004*). They are usually seen in the young male patient, who often has thrombosis of the leg veins or the vena cavae, and are manifested by recurrent haemoptysis, dyspnoea and pleuritic chest pain. Pulmonary aneurysms had a death rate of 50% in the 1980s but this figure has decreased to 20% in recent years owing to earlier recognition and better use of immunosuppressive drugs.

These lesions are usually suggested by parahilar or perihilar non-cavitating opacities found on chest X-ray examination (figure 10) and CT scan, and pulmonary angiograms show single or multiple aneurysms in the

pulmonary arteries. Isolated thrombosis of the peripheral segments of pulmonary arteries with or without aneurysms can also be seen. Mediastinal lymphadenopathy, nodules, cavities and consolidations are also seen and are often confused with secondary infections in an immunocompromised patient.

Figure 10 *Chest radiograph of a patient with Behçet's disease with bilateral pulmonary artery aneurysms.*



One should be aware that, in such cases, the ventilation–perfusion scan may mimic pulmonary embolism. The thrombi in BD do not embolise, presumably owing to their sticky nature and their tight adherence to inflamed veins.

1.8 Musculoskeletal manifestations

Arthritis or arthralgia is seen in about 50% of patients during the course of the disease. It may precede the other findings by months or years and usually manifests as an oligoarthritis involving, in decreasing order, the knees, ankles, hands and wrists. It is usually a self-limiting synovitis with an acute onset and resolves in a couple of days to weeks. Deformities are not usual, although they may rarely occur. Synovial fluid examination shows a mild inflammation dominated by polymorphonuclear leucocytes, but the mucin clot is normal.

Sacroiliitis is not a prominent part of the clinical picture, but the coexistence of acne, arthritis and enthesopathies suggests that at least a subgroup of patients may present with spondyloarthritis-like features. However, the co-existence of BD and ankylosing spondyloarthritis is to date yet relegated to an increasing number of case reports, not sufficient to draw firm conclusions on a possible association between the two clinical entities.

Fibromyalgia and local inflammatory myositis confined to the leg are possibly seen. According to a recent study conducted on 30 Egyptian patients, the frequency of fibromyalgia was 3.33 (El-Rabbat et al, 2017*), but previous studies had identified higher frequencies ranging from 9.2% to 18% in Turkish studies (Melikoglu et al, 2013*) and to 37.1% in a Korean study (Lee et al, 2005*).

1.9 Gastrointestinal involvement

Gastrointestinal involvement is seen in 6% of patients, being a frequent finding in the Far East, whereas it is usually not a prominent manifestation in patients from the Middle East. Patients usually present with mild symptoms including abdominal pain, diarrhoea, nausea or vomiting. Conversely, gastrointestinal bleeding and inflammatory bowel disease-like symptoms are more rare. Mucosal ulcerations resemble those found in inflammatory bowel diseases with normal intervening mucosa. Three-quarters of the ulcerations are found in the terminal ileum and the caecum, with the remainder being found in the oesophagus, stomach and duodenum. Rectal involvement is rare. Patients complain of vomiting, abdominal pain and diarrhoea. A mass is often palpable in the abdomen during exacerbations, and ileocaecal perforations may occur.

It is sometimes difficult to distinguish the findings of gastrointestinal BD from those of Crohn's disease. The presence of oral and genital ulcerations, with round, focal and isolated intestinal ulcers on endoscopy and frequent perforations favour the former, whereas perianal disease, fistula and stricture formation, the occasional presence of a granuloma in histopathology and longitudinal, diffuse and segmental ulcerations in endoscopy favour the latter.

The occasional patient with isolated findings of bowel inflammation and the absence of other manifestations of BD should be followed up meticulously since the diagnostic criteria are usually fulfilled after considerable follow-up. Younger age at diagnosis is associated with a more severe clinical course and a poorer prognosis.

A disease activity index for gastrointestinal BD has been developed with the aim to differentiate quiescent, mild, moderate and severe disease (Cheon et al, 2011*). Table 2 shows this index.

Table 2 shows the disease activity index for patients with gastrointestinal BD proposed by Cheon et al (Cheon et al, 2011). The table has been drawn by Cheon et al, 2011. The gastrointestinal is severe for scores ≥ 75 , moderate for scores ranging between 40 and 74, mild for scores between 20 and 39, quiescent for scores ≤ 19 . Symbols : * Score 5 for oral ulcer, genital ulcer, eye lesion, skin lesion, or arthralgia; score 15 for vascular involvement or central nervous system involvement. † Fistula, perforation, abscess, or intestinal obstruction.*

Item	Score
General well-being for 1 week	
Well	0
Fair	10
Poor	20
Very poor	30
Terrible	40
Fever	
< 38°C	5
$\geq 38^\circ\text{C}$	10
Extra intestinal manifestations	*
Abdominal pain in 1 week	
None	0
Mild	20
Moderate	40
Severe	80
Abdominal Mass	
None	0
Palpable mass	10
Abdominal tenderness	
None	0
Mildly tender	10
Moderately or severely tender	20
Intestinal complications†	10 per item
Number of liquid stools in 1 week	
0	0
1-7	10
8-21	20
22-35	30
≥ 36	40

1.10 Urological problems

The three problems related to the genitourinary system in BD are epididymitis, cystitis and erectile dysfunction. Epididymitis is seen in up to 20% of male patients and manifests as testicular pain. A patient with BD may have neurogenic bladder with or without demonstrable involvement of the spinal cord. Erectile dysfunction occurs in two-thirds of patients with neurological involvement. The frequency of varicocele is also increased among patients with BD.

1.11 Other manifestations

The heart is rarely affected during the course of BD, although various conduction abnormalities and valvular problems are occasionally seen. One peculiar manifestation is right-sided endomyocardial fibrosis with intracardiac thrombi—a finding seen in men with widespread vascular disease.

Glomerulonephritis is occasionally seen, with pathology ranging from immunoglobulin A (IgA) nephropathy to rapidly progressive inflammation. Immune complexes are not commonly found.

Secondary amyloidosis of the AA type has been reported in 0.04–3% of patients. It is predominantly seen in men, is closely associated with large vessel disease and arthritis, and has a death rate of >50% within 3.5 years after onset.

1.12 Histopathology

No specific cell type dominates in vasculitic lesions. In fact, neutrophils and mononuclear cells with high predominance of T lymphocytes (mostly CD4⁺ cells), and few B lymphocytes, NK and macrophages cells can be observed at immunohistochemical analysis of vascular infiltrates in BD inflammatory lesions. Predominance of cytotoxic CD8⁺CD56⁺NKT cells and of CD8⁺CD56⁻ T cell have been described in the eye involved by inflammatory BD lesions.

The histology of oral aphthae is similar to the aphthae present in recurrent oral stomatitis. Arterial and venous vessels of all sizes may be affected in BD with a peri- and intra-vascular inflammatory infiltrate eventually provoking stenosis, blood clots, and aneurysms. Direct injury to the vessel wall can sometimes be seen, such as in oral and genital ulcers, erythema nodosum-like lesions and local myositis. In erythema nodosum lesions histology generally show characteristics of septal panniculitis with infiltration of neutrophils. However, lobular panniculitis with vasculitis can also be seen in some cases, while granuloma formation is rarely seen.

Vascular injury is also found in uveitis and major vascular disease such as arterial aneurysms or major vein occlusions. On the other hand, for some lesions direct evidence of injury to the vascular wall cannot be shown. Among these are the acne lesions of the skin, where histology is no different than for ordinary acne, and in parenchymal lesions of the brain, where direct vessel wall injury is difficult to demonstrate.

Histology of the synovial membrane shows features of nonspecific synovitis

1.13 Pathogenesis

The pathogenesis of BD remains unclear. The relative risk of having BD in the siblings of affected individuals has been estimated to be between 11 and 53, implying a genetic influence on disease development. Although an autosomal recessive inheritance pattern has been suggested among paediatric patients, Mendelian inheritance patterns seem not to be operative. Genetic anticipation in the form of earlier disease onset in the second generation compared with their affected parents has also been reported. HLA-B51 has been the most consistently reported HLA association, and has been shown in many ethnic groups, although with differing risk ratios, and has lately been confirmed in a whole genome analysis in 2430 cases and 2660 controls along with interleukin (IL)-10 and IL23R-IL12RB2 loci (Mizuki et al, 2010*). Imputation analyses of genome-wide association studies showed new associations such as ERAP-1, CCR1-CCR3, KLRC4 and STAT4. The absence of concordance in monozygotic twins, however, suggests that other factors are also involved in pathogenesis.

BD does not exhibit the properties of a true autoimmune disease: it lacks consistent autoantibodies, there is no secondary Sjögren's syndrome and the prevalence of autoimmunity is not increased. Nor is it a typical autoinflammatory disease. However, a targeted resequencing study among patients with BD found variants of IL-23R, IL1R1 and NOD2 among the Japanese and IL-23R, TLR4, MEVF (M694V) and NOD2 among the Turks, suggesting that certain autoinflammatory aspects may be operative (Kirino et al, 2013b*). Consequently, the latest approach to BD pathogenesis supports the idea that both the innate and adaptive immune systems have a role in the induction of the disease. Actually, numerous pathogenetic evidences support the autoinflammatory hypothesis, especially about role of the primed state of neutrophils IL-1 that has been found significantly higher in patients with both active and inactive BD compared to healthy controls (Keller et al, 2005*). In addition, IL-1 production by monocytes stimulated with lipopolysaccharide is even higher in BD patients compared to subjects with familial Mediterranean fever (FMF), the prototype of IL-1 related autoinflammatory disease (Mege et al, 1993*). Also, single nuclear polymorphisms of IL-1 gene have shown to be significantly more represented in BD patients than healthy (Liang et al, 2013*). In support of these findings, IL-1 inhibition has revealed to be a good therapeutic option for BD patients.

Interestingly, toll-like receptors (TLRs)-2, -4 and -9, which are involved in both innate and acquired immunity, are implied in the pathogenesis of BD. In particular, TLR-2 and TLR-4 up-regulate IL-1 β production in active BD patients through a ROS-NLRP3 inflammasome pathway, while TLR-9, whose polymorphisms are significantly more frequent in BD patients, is involved in different autoimmune and autoinflammatory disorders (Sakamoto et al, 2012*). The higher expression of the P2X7 receptor (P2X7r) in monocytes from BD patients also supports the autoinflammatory nature of the disease. The P2X7r is an ion channel promoting the release of

proinflammatory cytokines, especially IL-1 β , by means of a massive potassium efflux that in turn allows the assembling of the NLRP3 inflammasome (Castrichini et al, 2014*).

On the other side, BD shares with autoimmune diseases the association with a class I major histocompatibility complex (MHC) and is successfully treated with disease modifying anti-rheumatic drugs (DMARDs). In addition, the therapeutic benefit observed with interferon- α supports the hypothesis of a Th1-driven disease.

In any case, what drives the immune system and sustains the inflammation is not clear, but an infectious trigger linked to an innate immune abnormality (eg, a genetic mutation affecting an adhesion molecule, a proinflammatory cytokine or an intracellular signalling abnormality of a transcription factor) is an attractive hypothesis. The diminished mRNA expression and low protein production of the disease-associated IL-10 variant (the rs158111 A allele) in the whole-genome study mentioned above support this hypothesis since IL-10 production usually has an inhibitory role in inflammation. The inhibitory properties of IL-10 in eye disease have also been shown.

There is evidence that the clinical picture is not homogeneous and that there are various clusters of disease expression. A factor analysis has shown that superficial vein thrombosis, deep vein thrombosis, and dural sinus thrombi represent a disease cluster on one hand, while acne, arthritis, and enthesitis are another cluster on the other. Notably, acne and arthritis also cluster in families. The presence of such clusters may additionally suggest that different mechanisms are operating in the pathogenesis of the various subgroups of patients.

The aetiology of the thrombophlebitis deserves a special mention. Indeed, it has been the subject of controversy, as some claim that it is the result of procoagulant factors, whereas others suggest that it is caused by endothelial inflammation. To date, although increased levels of homocysteine have been observed in BD patients, none of the procoagulant factors are definitely associated with the thrombotic tendency of BD and no significant differences have been found in terms of coagulation parameters between patients with and without thrombosis. However, a procoagulant state has been observed in BD patients compared to healthy controls even when thrombosis is absent. This finding seems to be related to increased levels of fibrinogen and plasminogen activator inhibitor(PAI)-1 along with an increased generation of thrombin after unspecific stimuli (Fernández-Bello et al, 2013*). Overall, the procoagulant and antifibrinolytic state of BD seem to be related to endothelial activation/damage, which in turn may be owing to the increased oxidative condition associated with systemic inflammation.

1.14 Diagnosis and laboratory findings

The diagnosis of BD is clinical. A group of doctors involved in the care of large numbers of patients with BD formed the International Study Group (ISG) and in 1990 published the ISG criteria for diagnosis (table 3). Oral ulceration was the essential factor, as its presence was almost universal. However, one must be aware of the

fact that the utility of the criteria is dependent on the prevalence of the syndrome in the background population. There may also be atypical patients who do not fulfil the criteria. New international criteria for BD (ICBD) were published in 2014 taking into account vascular and neurological involvement (table 4). ICBD are based on a scoring system attributing 1 or 2 points to seven different BD signs/symptoms. Two points are attributed to oral aphthosis, genital aphthosis and ocular lesions, which represent the basilar triad of BD; the other signs and symptoms have a weight of 1 point. A scoring ≥ 4 classifies patients as having BD. Comparing the performance of the two set of criteria, ISG criteria have sensitivity and specificity of 85% and 96%, respectively; ICBD exhibit a sensitivity of 94.8% and a specificity of 90.5%.

Important considerations in the differential diagnosis are summarised in table 5.

Table 3 International Study Group criteria for the diagnosis of Behçet's disease. (Reproduced with permission from International Study Group for Behçet's disease, Lancet 1990;335:1078–80)

Manifestation	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous or herpetiform ulcers, observed by a physician or reported reliably by patient, recurring at least three times in one 12-month period
Plus any two of the following findings:	
Recurrent genital ulceration	Recurrent genital aphthous ulceration or scarring, observed by a physician or reported reliably by patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by qualified physician (ophthalmologist)
Skin lesions	Erythema nodosum-like lesions, observed by a physician or reported reliably by patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by a physician in post adolescent patients not receiving glucocorticoids
Positive pathergy test	Test interpreted as positive by a physician at 24–48 h, performed with oblique insertion of a 20 gauge or smaller needle under sterile conditions

Table 4 International Criteria for Behçet's disease. This set of criteria is based on a score system. Patients are classified as having BD for scores ≥ 4 . †Pathergy test is optional: in Countries where the test is performed, adding 1 point for pathergy test increases sensitivity from 95.5% to 98.5%, while specificity decreases from 92.1% to 91.6%.

BD manifestations	Score assigned
Ocular lesions	2
Oral aphthosis	2
Genital aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test†	1

Laboratory investigation is of little help in the diagnosis of BD, as no specific laboratory abnormality supports or excludes the diagnosis. A mild anaemia of chronic disease and neutrophilic leucocytosis are seen in 15% of patients, but they do not correlate with the clinical activity of the disease. The erythrocyte sedimentation rate and C-reactive protein may be moderately raised, especially with episodes of arthritis, erythema nodosum and acute thrombophlebitis. Young male patients with unexplained sustained acute phase response should be investigated for large vessel disease in the thorax or abdomen. The role of serum amyloid-A (SAA) has also been investigated in recent times. Higher levels of SAA could anticipate the occurrence of BD manifestations. A recent study found that SAA serum levels higher than 30, 50, and 150 mg/L were significantly associated with the occurrence of oral aphthosis, neurological impairment, and ocular disease, respectively. In addition, increased SAA levels might represent a mirror of thrombotic risk in patients with previous or concurrent vascular involvement (Vitale et al, 2014a*).

Rheumatoid factors and antinuclear antibodies are absent and tests for antineutrophil cytoplasmic antibodies are usually negative. Patients with BD who have gastrointestinal involvement seem to have high levels of anti-Saccharomyces cerevisiae antibodies, although larger numbers of patients are needed to confirm this. A soluble triggering receptor expressed on myeloid cells (sTREM-1) and anti- α -enolase antibody titres seem to correlate with clinical disease activity in gastrointestinal BD. Levels of IL-33 have showed to be significantly increased in BD patients with cutaneous and retinal vasculitis ; in addition, IL-33 exhibited a positive correlation with disease activity evaluated with BD Current activity Form (BDCAF) and was found between BDCAF score and IL-33 serum levels. However, the clinical usefulness of these tests is unknown. Low-titre anticardiolipin antibodies may occasionally be found in patients with thrombosis but are not of major concern.

HLA-B51 testing may be of help in patients who exhibit features of BD that cannot be explained otherwise and do not fulfil the ISG criteria. These are generally patients with uveitis or young men with an arterial aneurysm or venous thrombosis who do not have oral ulcers. The presence of HLA-B5/B51 has a constant effect on the disease among various ethnicities and the positivity ranges around 40–60% (Kirino et al, 2013a*). However, diagnoses other than BD should be considered in a suspected 'incomplete' BD case in a low-prevalence region before resorting to HLA testing.

Table 5 Highlights of the clinical manifestations of Behçet's disease and differential diagnosis

Area affected	Clinical features
Mouth ulcers	Majority similar to common aphthous ulcers in appearance, localisation and discomfort/pain; more frequent and often multiple; may scar
Genital ulcers	Most commonly scrotal or vulval, painful, recurrent and usually with scarring; urethral discharge and penile lesions very rare
Skin	Acneiform lesions similar to common acne in appearance and histology but also at uncommon sites such as the extremities; erythema nodosum-like lesions leaving pigmentation; not psoriasis
Eyes	Panuveitis and retinal vasculitis, usually bilateral, occurring within about 2 years of disease onset; conjunctivitis and sicca syndrome most unusual
Joints	Monoarthritis in 50%, otherwise oligoarticular or polyarticular involving relatively few joints; may be symmetrical; knees most often affected; intermittent and resolving in 2–4 weeks or chronic and continuous; not involving sacroiliac joints or spine; deformity and erosions rare, synovial fluid usually inflammatory with good mucin clot
Peripheral arterial and venous disease	Subclinical peripheral large vein disease uncommon, usually involves large segments with skip areas without embolisation; arteritis with pseudoaneurysms or less commonly occlusions; microaneurysms of the polyarteritic type very uncommon
Neurological involvement	Acute brainstem syndrome with pyramidal and cranial nerve signs; typical MRI of the brain shows contrast enhancing lesion extending from basal ganglia to brainstem; less commonly, myelitis with paraplegia and bladder dysfunction and sensory loss distal to cord lesion; convulsions, MS-like disease, optic neuritis and peripheral neuropathy uncommon
Pulmonary involvement	Haemoptysis associated with pulmonary arterial aneurysm; pulmonary artery occlusion; pleural involvement uncommon; interstitial involvement not expected
GI involvement	Severe abdominal pain; ulcerative lesions at any level but mainly in the ileocaecal region; mild GI symptoms should not be associated with BD
Cardiac disease	Pericarditis, valve lesions and coronary artery involvement uncommon; rarely intracardiac thrombi

BD, Behçet's disease; GI, gastrointestinal; MRI, magnetic resonance imaging; MS, multiple sclerosis.

1.15 Management

Therapeutic management of BD depends on the severity, clinical presentation and organs involved. Although colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and topical treatments with glucocorticoids are often sufficient for mucocutaneous and joint involvement, a more aggressive approach with immunosuppressive agents is warranted for severe manifestations such as posterior uveitis, retinal vasculitis, vascular, neurological and gastrointestinal involvement (Yazici et al, 2007*). After this, some patients will still have refractory disease, relapses, sight-threatening eye disease or irreversible organ damage. Recent improvements in understanding the pathogenic mechanisms have led to the identification of potential targets and future treatments for BD (Arida et al, 2011*; Comarmond et al, 2014*). In this context, biological treatments with tumour necrosis

factor(TNF) α inhibitors have proved to be a substantial role in the treatment of resistant cases or life- and/or sight-threatening conditions (Calvo-Río et al, 2014*; Vallet et al, 2015*; Vitale et al, 2017a*; Fabiani et al, 2017a*). Also IL-1 inhibitors may be taken into account in cases resistant to TNF α inhibition, as well as anti-IL-6 agents and interferon α (Fabiani et al 2017b*; Cantarini et al. 2015*; Emmi et al, 2016*). However, novel treatment options are emerging as possible therapies in patients with specific BD manifestations (Cantarini et al, 2016*; Vitale et al, 2016a*). In contrast to current non-specific immunosuppressive agents, the emergence of immunomodulatory drugs provides the possibility of interfering with specific pathogenic pathways. New targeted immunosuppressive therapies might be used in the future for BD.

Management of the systemic manifestations is summarised below.

1.15.1 Mucocutaneous manifestations

Studies aimed at assessing the treatment of BD oral aphthosis are currently lacking, as current management is based on evidences drawn from studies performed on recurrent aphthous stomatitis.

Initially, treatment of oral and genital aphthosis is topical with antimicrobial agents, sucralfate, topical glucocorticoids, amlexanox and lidocaine gel; however, in resistant and disabling cases systemic options should be taken into account. Wet dressings with aluminium acetate 3–5% may represent a useful topical treatment for erythema nodosum.

Although there is no solid evidence to show that it is beneficial for all mucocutaneous lesions, colchicine, combined or not with short-term systemic corticosteroids, has been widely used for oral and genital ulcers and for skin manifestations.

Azathioprine (AZA) or thalidomide has also been reported to be efficacious for treating patients with mucocutaneous lesions refractory to treatment with colchicine. However, teratogenicity, neurotoxicity and constipation restrict usage of thalidomide. In addition, erythema nodosum lesions may worsen during thalidomide treatment.

Pentoxifylline, which reduces the production of proinflammatory cytokines such as TNF, was effective in reducing the frequency and severity of oral and vaginal ulcers. In an open trial, dapsone was shown to improve severe skin lesions. TNF α blockers have increasingly been used in the treatment of BD. Almost all trials with anti-TNF α agents reported encouraging results for recalcitrant mucocutaneous lesions. A controlled, 4-week trial with etanercept among male patients showed that it was effective in controlling most of the mucocutaneous manifestations of BD but did not suppress the pathergy phenomenon. Among agents inhibiting other cytokines, based on case series the anti-IL-1 β canakinumab has induced a prompt and sustained clinical efficacy in oral and genital ulcers (Vitale et al, 2014b*). Conversely, in 9 patients treated with the IL-1 receptor antagonist anakinra mucocutaneous lesions appeared the most refractory despite the global response (Cantarini et al, 2015*). A

pilot open-label two-phase clinical trial conducted on 6 BD subjects with ongoing oral/genital ulcers found that two out of six patients reached remission defined as the absence of ulcers at two consecutive monthly visits performed between 3 and 6 months after the start of anakinra at the dose of 100 mg/day. Contrariwise, an improvement in the number and severity of ulcers was seen in 5/6 patients. Nevertheless, oral and genital ulcers were reported on 66% and 14% of the entire study time (16 months), respectively. Increasing the dosage to 200 mg/day significantly reduced the number of days with oral or genital aphthosis and allowed a milder severity of oral ulcers. Conversely, increasing anakinra to 300 mg/day did not result in further improvements (Grayson et al, 2017*).

The anti-CD20 monoclonal antibody rituximab has also demonstrated to be effective on mucocutaneous lesions, but current evidences are based on a single case report (Zhao et al, 2014*). On the contrary, the inhibition of IL-6 is not desirable in BD patients with predominant mucosal and skin involvement, as tocilizumab has proved a worsening of skin manifestations (Diamantopoulos et al, 2013*).

In a phase 2, multicentre, placebo-controlled study in which 111 patients with Behçet's syndrome who had two or more oral ulcers were randomly assigned to receive 30 mg of Apremilast twice daily or placebo for 12 weeks, the mean (\pm SD) number of oral ulcers per patient at week 12 was significantly lower in the Apremilast group than in the placebo group (0.5 ± 1.0 vs. 2.1 ± 2.6) ($P < 0.001$). The mean decline in pain from oral ulcers from baseline to week 12 was greater with Apremilast than with placebo (-44.7 ± 24.3 mm vs. -16.0 ± 32.5 mm) ($P < 0.001$) (Hatemi et al, 2015*).

1.15.2 Joint involvement

In two double-blind trials, colchicine was efficient in controlling arthralgias and reducing the occurrence of arthritis. For refractory exacerbations, agents such as NSAIDs, methotrexate, AZA or, in the most refractory cases, anti-TNF α , should be tried.

1.15.3 Ocular involvement

Uveitis and retinal vasculitis are sight-threatening manifestations of BD, with limited treatment options. Despite early treatment with glucocorticoids and immunosuppressant agents, up to 20% of patients become blind. Any patient with BD and inflammatory eye disease affecting the posterior segment should be following a treatment regimen including AZA and systemic glucocorticoids. If the patient has severe eye disease, defined as loss of visual acuity (>2 lines in the Snellen Eye Chart—a test to measure a person's distance visual acuity) and/or retinal disease (retinal vasculitis or macular involvement), it is recommended that either cyclosporine A (CsA) or infliximab (IFX) be used in combination with AZA and glucocorticoids.

According to an expert panel for the use of anti-TNF biologic agents in patients with ocular disorders (Levy-Clarke et al, 2014*) the use of IFX and adalimumab (ADA) is recommended as first-line therapy for the treatment of

ocular BD manifestations. Regarding IFX, an open-label study on 50 patients with refractory posterior uveitis (36 of which diagnosed with BD) pointed out a complete response in 68% of patients and a partial response in 22% after IFX treatment at the end of a mean follow-up of 36.8 months. Moreover, a significant improvement was observed in the mean visual acuity and a significant reduction of both ocular attacks and patients with cystoid macular oedema were observed, with no differences between subjects with BD and those with idiopathic posterior uveitis (Cantini et al, 2012*). Similarly, a study on 48 Japanese patients found an improvement of uveoretinitis in 44 after 1 year of IFX therapy (Okada et al, 2012*) and a study on 124 patients with refractory BD-associated uveitis showed that treatment with IFX or ADA had allowed remission of uveitis in 67.7% of cases at 1 year follow-up (Calvo-Río et al, 2014*). In this regard, Vallet et al (Vallet et al, 2015*) even reported a response to IFX or ADA in 96.3% of 80 patients with severe and refractory BD-related uveitis (Vallet et al, 2016*). A literature review on the use of anti-TNF α agents in 369 BD patients showed a sustained response in 89% of patients with uveitis treated with IFX and in all the few patients treated with ADA (Arida et al, 2011*). In a recent multicentre observational study on 160 patients with uveitis that had been refractory to other therapies, including 36% of BD, the overall response rate at 6 and 12 months was 87% (26% with complete response) and 93% (28% with complete response), respectively. The median time to complete response was 2 months. In multivariate analysis, BD and occurrence of >5 uveitis flares before anti-TNF initiation were associated with complete response to anti-TNF. BD was associated with increased odds of response. IFX and ADA appeared to be equivalent in terms of efficacy (Vallet et al, 2016*).

More recently, a retrospective observational study on 40 BD patients (66 eyes involved) receiving ADA found that the number of ocular flares significantly decreased from 200 flares/100 patients/year during the 12 months preceding ADA to 8.5 flares/100 patients/year during the 12 months following the start of therapy. Moreover, central macular thickness significantly improved at 12 month follow-up compared to baseline, while the number of patients with retinal vasculitis significantly decreased. The best corrected visual acuity also improved during the study period (Fabiani et al, 2017a*).

Also IL-1 inhibition with canakinumab and anakinra have recently proved to be possible therapeutic choices in patients showing a lack of response to other therapies. A recent multicentre retrospective observational study conducted on 19 consecutive BD patients (31 affected eyes) found a significant decrease of intra ocular flares during a 12-month follow-up period compared to the 12 preceding months. Similarly, the frequency of retinal vasculitis decreased both at 3- and 12-month follow-up evaluation. A significant steroid sparing effect was highlighted and no differences were identified between patients previously administered with other biologics and those undergoing IL-1 inhibition as first biologic approach (Fabiani et al, 2017b*). In addition to this study, a long series of case reports and case series had underlined the efficacy and safety of anakinra and canakinumab in ocular BD manifestations (Vitale et al, 2016b*). In this regard, also the anti-IL-1 β gevokizumab has proved to induced good results with a single intravenous infusion at the dosage of 0.3 mg/kg with rapid and complete

resolution of ocular inflammation within 21 days. Moreover, 5 patients re-treated with a second dosage maintained their response for several months (Gül et al, 2012*). A phase 2 trial on 21 BD patients suffering from posterior uveitis confirmed previous results by using gevokizumab at a dose of 30 or 60 mg every 4 weeks (Tugal-Tutkun et al, 2017*). However, although a preserved visual acuity and a less severe ocular inflammation were reported in patients undergoing gevokizumab, this biologic agent failed to meet the primary endpoint represented by the time to the first acute ocular exacerbation in a recent phase 3 randomised placebo controlled trial.

Alternatively, interferon α could be used instead (Kotter et al, 2004*). The efficacy of CsA versus IFX has been compared in the early phase of treatments in refractory uveitis in BD. In a retrospective study, 17 patients receiving monotherapy with IFX were compared with 20 patients treated with CsA (also without other concomitant immunosuppressive drugs). During the 6 months after starting the treatments, the number of episodes for each patient was 0.4 ± 1.0 in the infliximab group and 1.2 ± 1.2 in the CsA group ($p < 0.05$). Additionally, 82% of patients remained relapse-free in the group treated with IFX during the 6-month treatment period, compared with 45% of patients in the group treated with CsA (Yamada et al, 2010*).

IL-6 inhibition along with rituximab and the humanized monoclonal antibody against CD52 alemtuzumab represent further possible therapies for ocular BD, but to date this is mostly a field for clinical research (Lopalco et al, 2017*; Pelegrin et al, 2014*; Mohammad et al, 2015*).

1.15.4 Major vessel disease

There is no firm evidence to guide us in the management of major vessel disease in BD. For the management of acute large deep vein thrombosis in BD, glucocorticoids and immunosuppressive agents like AZA, cyclophosphamide (CYC) or CsA are recommended. For the management of arterial aneurysms and/or occlusion, according to EULAR recommendations, CYC and glucocorticoids are recommended (Hatemi et al, 2008*). For patients with BD and major vessel thrombosis, there is no consensus about giving anticoagulation, antiplatelet, or antifibrinolytic agents, or about the duration of anticoagulation. There are no controlled data or evidence of benefit of anticoagulants in the management of deep vein thrombosis of BD. Some authors recommend anticoagulants, whereas others suggest they should be avoided owing to the increased risk of fatal bleeding from coexisting pulmonary arterial aneurysm and an estimated low risk of pulmonary embolism in BD. According to a study on a large cohort of BD patients with vascular involvement, almost all patients with BD with deep vein thrombosis received anticoagulation therapy despite a high number ($n = 44$, 14.9%) of associated arterial aneurysms, of whom eight had pulmonary arterial aneurysms. The tolerance was satisfactory, with 2% of haemorrhagic complications. In addition, a previous study claimed that immunosuppressive agents significantly reduce venous thrombosis relapse in BD (Desbois et al, 2012*).

According to a recent open-label, single-arm phase 3 study involving 4 BD patients with active vascular lesions and poor response or intolerance to conventional therapy, IFX allowed clinical and laboratory improvement after 2 weeks of therapy, while imaging findings showed reversal of inflammatory changes in 3 out of 4 patients, thus supporting IFX as a new therapeutic option for patients with vascular BD (Hibi et al, 2016*). Similarly, in another study TNF α inhibition with IFX or ADA proved to improve cardiovascular manifestations in 4 out of 6 cases with diverse BD-related vascular features.

1.15.5 Neurological involvement

No controlled data guide the management of CNS involvement in BD. For patients with parenchymal neuro-Behçet's disease without any poor prognostic factor, AZA and glucocorticoids are usually prescribed as first-line treatment. For patients with more severe disease, intravenous CYC and glucocorticoids are recommended. If these regimens fail, TNF α -blocking drugs, such as IFX, should be added. For dural sinus thrombosis, glucocorticoids and anticoagulation are recommended. In a multicentre study including 17 BD patients with symptomatic parenchymal NBD, refractory to previous immunosuppressant and treated with anti-TNF α (infliximab 5 mg/kg [n=13] or adalimumab [n=4]), overall improvement following anti-TNF was evidenced in 16/17 (94.1%) patients including 6 (35.3%) complete response and 10 (58.8%) partial response. The median time to achieve remission was 3 months (Desbois et al, 2016*). Vallet et al evaluated IFX and ADA in 13 patients with NBD and meningo-encephalitis or rhombencephalitis, highlighting an overall improvement in 12 cases with TNF α inhibition (Vallet et al, 2015*).

IL-6 inhibition represents a promising therapeutic option for NBD. Indeed, IL-6 levels in cerebrospinal fluid have been found higher in patients with active NBD compared to unaffected controls. In addition, IL-6 levels are more elevated in cerebrospinal fluid of patients with acute NBD than in subjects with chronic neurological involvement, thus suggesting a direct involvement of IL-6 in neurological BD activity. In this context, tocilizumab infusions at 8 mg/kg every 4 weeks induced a prompt and sustained response with significant steroid tapering in 3 patients with parenchymal BD involvement. Although a loss of efficacy occurred after 18 months in one patient, the shortening of the interval between the infusions allowed a recovery of benefits (Addimanda et al, 2015*).

A recent case series claimed intravenous immunoglobulin treatment as a useful possibility in NBD unresponsive to conventional treatment or when clinical data do not allow a well-defined differential diagnosis with multiple sclerosis (Cantarini et al, 2016*).

1.15.6 Gastrointestinal disease

No evidence-based treatment can be recommended for the management of gastrointestinal involvement in BD. Sulfasalazine and 5-aminosalicylate are used empirically but might maintain remission in entero-BD. In a

retrospective study this treatment was found to maintain remission in 143 Korean patients with entero-BD (Jung et al, 2012*). An observational study has suggested 5-aminosalicylate as a valuable treatment for preventing postoperative recurrences (Hatemi et al, 2016*). Agents such as glucocorticoids, AZA and/or TNF antagonists should be tried first before surgery, except in an emergency (perforation).

Among TNF inhibitors, IFX is adopted from the regimen employed for Crohn disease (5 mg/kg intravenous at weeks 0, 2, and 6). A recent open-label single-arm phase 3 study conducted on 18 BD patients including 11 with gastrointestinal manifestations claimed that IFX is able to induce clinical improvement and decrease of inflammatory markers at 2-week follow-up (Kinoshita et al, 2013*). According to a Korean multicentre retrospective study on 28 patients treated with IFX, clinical response was obtained in 64.3% of patients and clinical remission in 28.6% at 4 week evaluation after IFX infusion (Lee et al, 2013*). Another retrospective study on 15 patients with refractory gastrointestinal involvement treated with IFX administered every eight weeks at the dosage of 5 mg/kg observed a good response to in 80% of cases and remission in 53% after 10 weeks. The percentage of patients maintaining the response at 12 and 24 months was 64% and 50%, respectively (Habit et al, 2016*).

Although current data on ADA efficacy in gastrointestinal BD are few, an increasing number of studies are proving the usefulness of ADA on gastrointestinal involvement. In particular, a phase 3, multicentre, open-label uncontrolled study on 20 Japanese patients with active and resistant intestinal BD showed that ADA administered at induction schedule of 160 mg at baseline, 80 mg at week 2 followed by 40 mg every other week induced an improvement of symptoms and endoscopic findings in 60% of patients at 52-week follow-up, while 20% of patients reached a complete remission (Tanida et al, 2015*). These data are supported also by retrospective studies (Vallet et al, 2015*).

Less experience has been gained on the use of etanercept for the management of gastrointestinal BD; however, current evidences suggest a better effect of etanercept compared to conventional therapies (Ma et al, 2014*).

Regarding the use of IL-1 inhibition on gastrointestinal involvement, although encouraging, current data are limited to case reports.

1.15.7 Comments on current management

A multidisciplinary expert committee has published the EULAR recommendations for the management of BD (Hatemi et al, 2009*). Recommendations related to eye and skin/mucosal disease and arthritis were mainly evidence based, whereas recommendations related to vascular disease and neurological and gastrointestinal involvement were based on expert opinion and on uncontrolled evidence from open trials and observational studies. Nine recommendations were developed and are presented in table 4.

Table 6 EULAR recommendations for the management of Behçet's disease. (Reproduced from Hatemi et al, *Ann Rheum Dis* 2009;68:1528–34*)

No.	Recommendation
1	Any patient with BD and inflammatory eye disease affecting the posterior segment should be following a treatment regimen that includes azathioprine and systemic glucocorticoids
2	If the patient has severe eye disease defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease (retinal vasculitis or macular involvement), it is recommended that either cyclosporine A or infliximab be used in combination with azathioprine and glucocorticoids; alternatively, IFN α with glucocorticoids may be used
3	There is no firm evidence to guide the management of major vessel disease in BD. For the management of acute deep vein thrombosis in BD, immunosuppressive agents such as glucocorticoids, azathioprine, CYC or cyclosporine A are recommended. For the management of pulmonary and peripheral arterial aneurysms, CYC and glucocorticoids are recommended
4	Similarly, there are no controlled data on, or evidence of, benefit from uncontrolled treatment with anticoagulants or antiplatelet or fibrinolytic agents in the management of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD
5	No evidence-based treatment can be recommended for the management of gastrointestinal involvement of BD. Agents such as sulfasalazine, glucocorticoids, azathioprine, TNF α antagonists and thalidomide should be tried first before surgery, except in emergencies
6	In most patients with BD, arthritis can be managed with colchicine
7	There are no controlled data to guide the management of CNS involvement in BD. For parenchymal involvement, glucocorticoids, IFN α , azathioprine, CYC, methotrexate and TNF α antagonists may be tried. For dural sinus thrombosis glucocorticoids are recommended
8	Cyclosporine A should not be used in patients with BD with CNS involvement unless necessary for intraocular inflammation
9	The decision to treat skin and mucosa involvement will depend on the perceived severity by the doctor and the patient. Mucocutaneous involvement should be treated according to the dominant or co-dominant lesions present
	Topical measures (i.e., local glucocorticoids) should be the first line of treatment for isolated oral and genital ulcers
	Acne-like lesions are usually of cosmetic concern only. Thus, topical measures as used in acne vulgaris are sufficient
	Colchicine should be preferred when the dominant lesion is erythema nodosum
	Leg ulcers in BD might have different causes. Treatment should be planned accordingly
	Azathioprine, IFN α and TNF α antagonists may be considered in resistant cases

BD, Behçet's disease; CNS, central nervous system; CYC, cyclophosphamide; IFN, interferon; TNF, tumour necrosis factor.

During recent decades, therapeutic strategy in BD has become more intensive with the use of immunosuppressive agents. Although new immunomodulatory therapies seem to be highly effective in uncontrolled studies and seem to have a rapid onset of action in different clinical situations, no consensus exists about their use in BD. Refractory manifestations that may warrant immunomodulatory treatment include severe ocular disease, CNS, and vascular involvement and some severe or refractory gastrointestinal, joint and mucocutaneous involvement.

However, TNF inhibition has got ahead as useful treatment for the protean clinical spectrum of BD. In addition to IFX and ADA, also other anti-TNF agents are taking up a space. In this regard, a recent retrospective observational study found golimumab as a useful therapeutic choice in multisystem resistant BD. In particular, golimumab was capable of controlling disease manifestations found at the start of therapy and reducing global disease activity (Vitale et al, 2017b).

Also other agents have been indicated as potential useful therapeutic choices, including the inhibitors of IL-1, IL-6, CD52, intravenous immunoglobulins and apremilast. Nevertheless, clinical research is required in order to establish which subgroup of patients should be firstly treated with these agents, what are the optimal dosages and intervals of administration.

1.16 Prognosis and impact on quality of life

Mortality and morbidity are high in young male patients with BD. Women have less severe disease than men. The main causes of death are major vessel disease and, particularly, pulmonary artery aneurysms and neurological involvement (Kural-Seyahi et al, 2003*). The disease typically abates after 40 years of age, but CNS involvement and major vessel disease may have a late onset (5–10 years after diagnosis). The death rate, quite different from that seen in systemic lupus erythematosus and rheumatoid arthritis, decreases in BD along the disease course. This might be related to (a) self-abating disease activity and (b) an absence of accelerated atherosclerosis, which is well known to be associated with the increased late death rates in classic autoimmune diseases. Both these points seem to be true for BD. Many patients from an initial cohort with BD would not fulfil any of the diagnostic criteria when surveyed 20 years later and preliminary evidence does not indicate accelerated atherosclerosis in BD.

A study of pulmonary arterial aneurysms has shown that the death rate has decreased from 50% to around 20% in the past decade owing to earlier recognition or better use of immunosuppressive agents.

Eye inflammation and greatest eye damage occur during the first 2 years. Loss of useful vision ensues in about 20% of patients despite treatment.

A retrospective study reporting the 10-year visual outcome of 39 patients with uveitis showed progressive eye disease and a visual acuity of <0.1 in 39% of affected eyes in spite of the multitude of available treatments. However, drug use during this period suggested that these patients might have been undertreated, as colchicine, CsA and glucocorticoids were the most frequently used agents and seven patients used only one drug (colchicine n = 5, CsA n = 2).

Regarding the impact on patient's life, BD is capable of significantly decreasing quality of life. Interestingly, although BD is usually more severe among men patients, the impact of BD seems to be higher among women. This evidence probably reflects social and physiological differences between males and females as well as a

different aptitude to BD acceptance. The impact of BD on quality of life is closely related to the overall disease activity; however, single organ involvements may also affect quality of life in an independent fashion, especially in relation to mucosal, NBD, musculoskeletal, and ocular manifestations. Concerning ocular involvement, quality of life is impaired especially in patients with panuveitis compared to other BD-related ocular manifestations and is inversely correlated with the best corrected visual acuity (Fabiani et al, 2017*).

SUMMARY POINTS - Behçet's disease

- ➔ **Behçet's disease (BD) is an inflammatory disease that runs a relapsing and remitting course.**
- ➔ **BD has a geographical predilection and is seen more frequently in the Mediterranean basin and the Far East.**
- ➔ **Mucocutaneous manifestations, uveitis and articular manifestations are more common than peripheral arterial disease, venous thromboses, and neurological and gastrointestinal involvement.**
- ➔ **Young males have more severe disease.**
- ➔ **The use of immunosuppressive agents has undoubtedly provided an improvement in the management of severe BD**
- ➔ **Tumour Necrosis Factor inhibition has improved the management of sight- and life-threatening BD manifestations**
- ➔ **Inhibition of interleukin(IL)-1 and IL-6 represent promising therapeutic options in BD patients**

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2 Relapsing polychondritis

Relapsing polychondritis (RP) is a rare autoimmune condition characterised by recurrent episodes of inflammation of cartilage, especially of the ears, nose and tracheobronchial tree. It has a variety of organ system involvement, including the joints, heart and kidney. It may occur alone (primary) or can be associated with a long list of conditions (secondary) (table 1). It has also been proposed that it “is not a primary disease, but a syndrome associated with multiple precipitating factors that appear in a genetically susceptible subject”. RP may have a rather benign course or, alternatively, a very severe course ending in death.

Table 1 Systemic diseases associated with relapsing polychondritis

Systemic vasculitides	Connective tissue diseases	Blood dyscrasias	Autoimmune and other conditions
Behçet's disease	Rheumatoid arthritis	Myelodysplastic syndrome	Vitiligo
Wegener's granulomatosis	Systemic lupus erythematosus	Haematological malignancies	Autoimmune thyroid disease
Polyarteritis nodosa	Sjögren's syndrome	Cryoglobulinaemia	Myasthenia gravis
Takayasu's arteritis	Juvenile chronic arthritis	Pernicious anaemia	Primary biliary cirrhosis
Leucocytoclastic vasculitis	Antiphospholipid syndrome	Thymoma	Dermatitis herpetiformis
Cogan's syndrome			Atopic dermatitis
Henoch–Schönlein purpura			
Thromboangiitis obliterans			Lichen planus
			Psoriasis
			Glomerulonephritis
			Inflammatory bowel disease
			Diabetes mellitus
			FMF
			Panniculitis
			Retroperitoneal fibrosis
			Spondylarthritides
			Sweet's syndrome

FMF, *familial Mediterranean fever*.

2.1 Epidemiology and genetics

RP is distinctly rare, with an estimated incidence of 3.5 cases per million/year; male and female subjects are equally affected. The peak incidence is in the fifth decade, but it can also occur in children and in older adults. The association with other autoimmune disorders, myelodysplasia and/or systemic inflammatory conditions is found in 25–30% of adult patients with RP (Kent et al, 2004*). No ethnic or familial clustering has been noted. However, there is an increased frequency of HLA-DR4 among patients.

2.2 Clinical findings

The usual onset is abrupt and relapses occur in the course of the disease. In the secondary forms the associated condition has usually been present for some time before RP onset.

Table 2 summarises the various clinical findings, with their approximate frequency at presentation or during the disease course. It is to be noted that almost all organs can be affected by either the primary or the secondary form.

Table 2 Clinical manifestations of relapsing polychondritis. (Adapted from Kent et al, *Curr Opin Rheumatol* 2004;16:56–61*)

Feature	Frequency (%)	
	At presentation	During course
Auricular chondritis	45	90
Arthritis	30	70
Nasal chondritis	20	60
Ocular disease	20	60
Laryngotracheal involvement	20	55
Reduced hearing and/or vestibular dysfunction	5	40
Skin–mucosa	5	30
Kidney disease	5	25
Heart disease	0	10
Vasculitis	2	15

The most common presenting symptom of RP (~50%) is inflammation of the external ear, which can be unilateral or bilateral. In a patient with inflammation in one ear, this is usually not attributed to a systemic disease, especially in the primary form where there is no associated disease to alert the patient or the physician. Often the inflammation is ascribed to infection and antibiotics are prescribed. However, one should search for recent local infection if the involvement is unilateral. Also frostbite or burns—including ultraviolet—can cause such inflammation in the external ear, even weeks after the original trauma.

The auricular portion of the external ear is inflamed in RP but the earlobes, which do not have cartilage, are spared. With continuing inflammation, the auricular portions become flabby (figure 1) as the cartilage matrix is destroyed.

Disease can also occur in the ear and related structures. The Eustachian tubes may close, leading to hearing loss and otitis. Associated arteritis of the internal auditory artery can sometimes cause tinnitus and vertigo due to impaired cochlear blood supply.

Figure 1 Earlobe destruction in relapsing polychondritis. (Image courtesy of Professor Ina Kötter, Tübingen, Germany)



The presence of additional sites of inflammation helps diagnosis. Nasal cartilage is the most common second site, involved in up to 54% of patients. There is pain, local tenderness and, if it progresses, a saddle nose deformity may result, especially in patients aged less than 50 years and in females. The nose feels stuffy and the patient may complain of frequent nose bleeds or serosanguinous exudation.

A laryngotracheobronchial disease appears in nearly half of RP patients and can be life-threatening as represents the main cause of death. The initial symptoms are hoarseness, non-productive cough, stridor and wheezing together with tenderness over the larynx and trachea. Upper airway obstruction necessitates emergency tracheostomy. Diseased cartilaginous structures of the lower airways can cause repeated bouts of pneumonia by interfering with normal drainage in the lungs. However, pulmonary infiltrates may also be related to an underlying vasculitis accompanying RP.

RP does not usually involve articular cartilage (see section 2.6) apart from the fibrocartilaginous costochondral joints, mimicking Tietze syndrome, a common and benign condition, causing local sternal pain. In rare instances the sternal disease may be more severe with involvement of the sternomanubrial and sternoclavicular joints with structural changes leading to pectus excavatus.

Even though articular cartilage is spared, arthritis is common in RP and can precede its onset by weeks or months. Indeed, it may be the presenting symptom in 33% of patients. It is a non-deforming, episodic oligoarthritis involving both large and small peripheral joints. Although the affected joints are warm and swollen, the synovial fluid is non-inflammatory.

Eye disease in RP can take many forms and affects over half of patients during the entire course of the disease. The most common lesions are episcleritis, scleritis and conjunctivitis. However, keratitis, corneal melt, uveitis, retinal vasculitis, and even periadnexal disease leading to proptosis, can be seen. Proptosis, lid oedema, iridocyclitis, retinopathy, optic neuritis and hypopyon uveitis, a feature typical for Behçet's disease (BD), are other possible manifestations as well as a vasculitis involving the extraocular muscles. MALT (mucosa-associated lymphoid tissue) lymphomas around the eye have also been described. Retinal disease can lead to visual loss.

Heart involvement is an integral part of the clinical picture in RP. It is seen in around 10% of patients with RP and its insidious and potentially sinister course necessitates due attention as represents the second most common cause of death in these patients. Cardiac involvement in RP can be due to valvular disease—notably, aortic with associated aortitis, coronary vasculitis (sometimes leading to myocardial infarction), problems with the conduction system and myocarditis or pericarditis (rare). In particular, aortic root involvement may develop years after the initial diagnosis and can progress despite immunosuppressive treatment administered for disease involvement at other sites and despite apparent RP remission. Also, aortic aneurysms occur frequently in RP in all parts of the aorta, possibly resulting in fatal rupture even in asymptomatic patients. Thus, it is important that patients with RP are followed up for developing murmurs, especially if congestive heart failure is present. Also a chest radiograph, an electrocardiogram and an echocardiogram should be part of the initial evaluation of a patient with RP, even in the absence of cardiovascular symptoms.

Arteries and veins of all sizes can also be affected. The aortic arch and the abdominal aorta can be diseased, with a clinical picture similar to Takayasu's arteritis; as with many other disease associations of RP, it is unclear whether cartilage inflammation in such patients is due to primary Takayasu's arteritis with secondary cartilage involvement or vice versa. Thrombosis of the large and small veins—as in BD—can also be seen. Aortic involvement is rare in RP, being encountered in 4–9% of the patients. It may lead to life-threatening complications, such as severe aortic insufficiency, active aortitis and aortic aneurysm (McAdam et al, 1976*).

Both the central nervous system (CNS) and the peripheral nerves can be involved by vasculitis resulting in heterogeneous manifestations such as headache, seizures, cortical lesions with pyramidal signs, aseptic

meningitis, meningoencephalitis, cerebral aneurysms and loss of cognitive function. The cranial nerves are the most commonly affected nerves of the CNS. Optic atrophy leading to visual loss and abducens paralysis resulting in loss of lateral gaze are the most frequent complications, followed by lesions in the seventh and eighth nerves. The CNS and peripheral neuropathy in RP has been ascribed to the generalised vasculitis seen in the primary and secondary forms, although this is seldom demonstrated.

Skin–mucosa involvement in RP can present in many forms. The most common lesions are recurrent oral ulcers, nodules on the limbs and purpura, while the most common histological finding is a leucocytoclastic vasculitis. A lot of other skin manifestations have been related to RP including urticarial-like lesions, erythema multiforme, erythema annulare centrifugum, erythema elevatum diutinum, skin panniculitis, actinic granulomas, and Sweet's syndrome (Cantarini et al, 2014*). About 90% of a subgroup of patients with RP characterised by the association of myelodysplastic syndrome, have skin disease. These patients are, on average, a decade or two older than other patients with RP, and some can present with fever of unknown origin. Notably, most patients with concomitant RP and Sweet syndrome show an association with malignancies, especially myelodysplastic syndromes (Diebold et al, 1995*).

Kidney involvement can be caused by primary renal parenchymal lesions, an underlying vasculitis (ranging from mesangial disease and IgA nephropathy to crescentic glomerulonephritis), or an associated autoimmune disorder. Although renal disease is quite rare, raised creatinine levels are reported in 10%, and abnormalities in urine analysis in 26%. However, renal disease indicated a worse prognosis, with a 10-year survival of 30% (Chang-Miller et al, 1987*).

The so-called MAGIC syndrome (mouth and genital ulcers with inflamed cartilage) is probably similar to that in BD with secondary RP.

2.3 Laboratory findings

No laboratory findings are specific for RP, and patients with secondary forms can show the more specific findings, if any, of the associated diseases. An augmented acute phase response is seen in most patients. Most patients show normocytic normochromic anemia, leukocytosis, thrombocytosis, and polyclonal hypergammaglobulinemia. Antibodies to native collagen II, present in about 50% of patients, are only used in research and are not sufficiently specific to be diagnostically useful. Up to 66% of patients show the presence of antinuclear antibodies (ANA), usually in a low titer and with a speckled pattern. This finding suggests the presence of a concomitant associated autoimmune disorder. Also anti-neutrophil cytoplasmic antibodies (ANCA) may be found, especially during the active phase of the disease.

2.4 Imaging

Radiographs may highlight calcific deposits in auricular, nasal or tracheal cartilage in patients with long-lasting disease. Computed tomography (CT) is useful in detecting early involvement of the upper airways as well as bronchial cartilage damage up to lobar and segmental bronchi. Morphological changes including wall thickness with or without calcifications and fixed narrowed airway along with increased airway wall attenuation and smooth diffuse thickening represent the most frequently encountered findings. Enlarged mediastinal lymph nodes can also be found. Magnetic resonance imaging (MRI) plays a major role in identifying inflammation of perichondrium and chondroepiphysis. MRI is also used to demonstrate the blood-endolymph barrier breakdown in cases with inner ear involvement. Positron emission tomography (PET)/CT may identify multi-systemic cartilaginous abnormalities and is also considered a useful tool for assessing disease activity and response to treatment. In addition Moreover, PET/CT provides advantages for an adequate targeted biotic procedure (Cantarini et al, 2014*).

End bronchial ultrasound allows the identification of airway chondritis and echocardiography is used to assess cardiac valves and aortic root in cases of cardiovascular involvement. Careful attention should be paid to bronchoscopy, which may exacerbate airway inflammation and is difficult in patients with small glottis due to cartilage destruction.

2.5 Diagnosis and differential diagnosis

Over the years, several sets of criteria have been proposed for diagnosis, all based on combinations of the spread of involvement of cartilaginous sites and the common clinical findings of the associated diseases. To date, diagnosis is based on criteria suggested by McAdams et al. in 1976 (McAdams et al, 1976*), later refined and improved by Damiani et al. (Damiani et al, 1979*) and Michet et al. (Michet et al, 1986*) Table 3 illustrates the diagnostic criteria proposed for RP. Anyway, as is true for all rare diseases, formulating 'diagnostic' criteria that are useful in an individual patient is probably also unrealistic in RP. The very low pre-test probability makes the likelihood of false positives unacceptably high even with criteria that have very high specificity and sensitivity. In the clinical setting, symmetrical cartilage involvement in the ears with an additional site of cartilage disease is usually adequate for diagnosis. Only in doubtful cases should one resort to histological diagnosis.

Table 3 shows diagnostic criteria currently employed for diagnosing relapsing polychondritis. The table has been adapted from Vitale et al, 2016.

Criteria	Items	Requirements for diagnosis
McAdam et al	<ul style="list-style-type: none"> - Bilateral auricular chondritis - Nasal chondritis - Respiratory tract chondritis - Non-erosive seronegative polyarthrititis - Ocular inflammation - Audiovestibular damage 	At least three items fulfilled
Damiani et al	<ul style="list-style-type: none"> - McAdam items - Histologic confirmation - Positive response to corticosteroids or dapsone 	At least three McAdam items fulfilled Or One McAdam criteria in addition to histologic confirmation Or Two McAdam items fulfilled in addition to effectiveness of corticosteroids or dapsone
Michet et al	Items A <ul style="list-style-type: none"> - Auricular cartilage inflammation - Nasal cartilage inflammation - Laryngotracheal cartilage inflammation Items B <ul style="list-style-type: none"> - Ocular inflammation - Hearing loss - Vestibular dysfunction - Sero-negative arthritis 	At least two items "A" Or At least one item "A" plus at least two items "B"

2.5.1 Ear problems

The foremost consideration in ear problems is bacterial or fungal infection, especially when the involvement is unilateral. Sparing of the ear lobes in RP and the presence of enlarged lymph nodes in infection are helpful.

Insect bites, chemical and physical trauma such as frostbite and sunburn are other considerations and it should be borne in mind that it might sometimes take weeks after the initial trauma before the ear inflammation begins.

2.5.2 Nasal findings

Indolent infections with mycobacteria (both tuberculosis and leprosy), leishmaniosis, syphilis and fungi, in particular, can cause damage to the nasal cartilage. Systemic lupus Erythematosus, Wegener's granulomatosis,

sarcoidosis and lymphomatous involvement in midline granuloma are other considerations. Sparing of the mucosa and the relative paucity of surrounding inflammation in RP might be helpful in diagnosis. Nasal deformation can occur after trauma and long-term cocaine inhalation.

2.5.3 Eye involvement

Episcleritis, scleritis, keratitis and uveitis can be seen both in primary RP and as part of the clinical spectrum of the long list of associated conditions. Important points to consider here are (a) scleritis and keratitis are unusual in BD, while episcleritis and hypopyon can be seen; (b) uveitis is not part of rheumatoid arthritis; (c) Wegener's granulomatosis can cause all the ophthalmic findings of RP and in addition proptosis, which can be seen in both Wegener's disease and RP. Interstitial keratitis is an integral part of Cogan's syndrome, which, with its vestibular neuritis, can be difficult to tell apart from RP.

2.5.4 Laryngotracheal involvement

Tracheal involvement is a very useful finding in differential diagnosis because, apart from direct trauma (eg, as a complication of intubation) and Wegener's disease (granulomatosis with polyangiitis), no other diseases cause a similar problem. However, also amyloidosis and sarcoidosis should be taken in mind in case of subglottic stenosis.

2.5.5 Articular involvement

When articular involvement is the presenting symptom, a mistaken diagnosis with rheumatoid arthritis may be possible. RP may be also misdiagnosis with spondyloarthritis when articular and ocular symptoms coexist. However, unlike rheumatoid arthritis, joint involvement is generally non-deforming, non-erosive, and synovial liquid analysis shows a not-so-clear inflammatory picture. In addition, spondyloarthritis is generally associated with anterior uveitis.

2.5.5 Aortic involvement

Enlargement of the aortic root can also be seen in ankylosing spondylitis, Marfan or Ehlers–Danlos syndrome. Also Takayasu's arteritis and polyarteritis nodosa may present with aortic aneurysms, but they are not primarily characterized by cartilage involvement.

2.6 Evaluation of disease activity

No laboratory markers exist to evaluate the entity of cartilage damage and disease activity in clinical practice and current proposals are mainly confined to laboratory research. Conversely, based on clinical evaluation, an international collaboration involving 27 experts proposed the Relapsing Polychondritis Disease Activity Index (RPDAI), a clinometric tool based on 27 items with individual weights ranging from 1 to 24 and a maximum

theoretical score of 265. The RPDAI should be filled taking into account the 28 days preceding the medical examination (Arnaud et al, 2012*).

2.7 Pathology

No biopsy findings are pathognomonic for the diagnosis of RP and biopsies of the nose, ear or other involved cartilages provide useful information only in a minority of cases. However, histopathological examination may be taken into account when the diagnosis is puzzling.

The early and active lesions in the cartilage show infiltration with lymphocytes (mainly CD4) together with neutrophils, mononuclear and plasma cells in variable proportions. C3 and immunoglobulin deposition may also be found. This is followed in time by more immunoglobulin and complement deposition with increasing amounts of cartilage destruction. The chondrocytes initially phagocytose the degraded material and later they themselves degenerate. A loss of basophilic staining of the cartilage matrix and capillary endothelial cell proliferation are also observed on biopsies. The final stages show fibrosis with focal areas of calcification, gelatinous cysts and new bone formation.

Chronic synovitis is seen only at the diarthrodial joints on the hand. Aortitis is characterised by mononuclear cell infiltration with destruction of the collagen and elastic fibres. The inflammation can involve the whole arterial wall and lead to aneurysm formation.

Kidney involvement can range from mild mesangial disease to IgA nephropathy or segmental crescentic glomerulonephritis, mostly representing the pathological landmarks of the associated diseases.

2.8 Pathogenesis

The exact pathogenesis of RP is not known but an autoimmune mechanism is strongly implicated. The evidence for this is several fold:

- The histology of the involved tissue as discussed above.
- A frequent association with other autoimmune disorders.
- Matrilin 1 is a cartilage matrix protein prominent in tracheal, auricular and nasal cartilages. Injection of this protein into mice causes a clinical picture quite similar to RP and antibodies to the same have been described in human disease.
- About half of patients with RP develop antibodies to native collagen type II, found in abundance in cartilage and sclera. Furthermore, immunising DQ8 and HLA-DQ6 double transgenic mice with collagen type II can induce chondritis in these animals.
- Humoral and cellular reactivity against collagen type IX and XI have also been observed.

- The frequency of HLA-DR4—an allele associated with several autoimmune diseases, including rheumatoid arthritis—is increased among patients with RP.
- Finally, cartilage is considered to be an immunologically privileged site like the eye, so there is no immunological tolerance to its structural proteins in the healthy organism. This, in turn, makes the cartilage prone to an autoimmune insult after different noxae including trauma, toxins or infectious diseases. Thus, the cartilage damage seen in RP associated with many autoimmune/autoinflammatory diseases may be similar to the uveal disease seen in some of these conditions as well.

Hormonal factors have also been postulated, as RP can be triggered during pregnancy.

2.9 Management

Owing to the rarity of the condition and perhaps to the association with many other diseases, there are no evidence-based treatment options for managing RP. Treatment is mainly based on published expert opinion which, in turn, is based on uncontrolled observations.

However, management is tailored to disease extent and severity. If involvement is limited to the external ear and the cartilage of the nose, with no apparent destructive changes or arthritis, treatment with non-steroidal anti-inflammatory drugs may be all that is required. A second choice would be dapsone (50–200 mg/day). Still others prefer small doses of steroids (10–20 mg prednisone/day) in this setting.

More destructive changes in the cartilage or laryngotracheal, vestibuloneural, lung, eye, heart or kidney involvement or systemic vasculitis require higher doses of steroids (prednisone at ~60 mg/day). Long-term steroid therapy represents the mainstay option in order to decrease the severity and frequency of disease bouts. Disease modifying anti-rheumatic drugs (DMARDs) are useful in resistant cases and as corticosteroid-sparing agents. In particular, cyclophosphamide at 1–2 mg/kg/day is usually added in more severe, life-threatening lung, heart or kidney disease. Azathioprine, methotrexate or cyclosporine A (with due attention to kidney function) can also be used either as remission-inducing or steroid-sparing additional treatment. Patients resistant to other treatment may respond to biologic agents. To date, TNF α inhibitors represent the most commonly described agents for the treatment of RP and are regarded the ideal treatment in case of nonresponsive central nervous system involvement. Current experience with TNF α inhibitors mainly deal with infliximab, adalimumab and etanercept (Vitale et al, 2015*). In particular, according to a case series reporting on 9 patients treated with twenty-two biologic courses, anti-TNF α -agents used led to partial or complete disease control in 6 out of 7 cases treated with TNF α inhibition. However, a loss of efficacy was recorded in 5 cases, obligating to switch to a second TNF α inhibitor or to another biologic agent. In this context, the cytotoxic T lymphocyte antigen 4-immunoglobulin abatacept and the anti-IL-6 agent tocilizumab proved to be effective as second-line biologics, while the anti-interleukin(IL)-1 receptor antagonist anakinra brought about poor results (Moulis et al, 2013*).

Anyway, cases unresponsive to anti-TNF α drugs are widely described as well as patients reporting severe adverse events soon after the start of treatment, including infections, a fulminant necrotizing eosinophilic myocarditis and the occurrence of Sweet syndrome (Adamson et al, 2013*; Moore et al, 2014*). Of note, a case report claimed that RP may also develop as a paradoxical effect of anti-TNF therapy (Hernández et al, 2011*).

Regarding abatacept, data currently available are quite conflicting and support the use of this agent especially in patients with joint involvement and ear, nose and throat chondritis. Notably, the intravenous formulation seems better than the subcutaneous administration (Peng et al, 2013*). Similarly, contrasting results are published on the IL-6 receptor antagonist tocilizumab, whose use could be limited to RP patients with elevated serum IL-6 levels (Wendling et al, 2013*). However, tocilizumab has been reported to be effective in patients with refractory RP-related aortitis (Loricera et al, 2014*; Stael et al, 2015*).

Also the IL-1 receptor antagonist anakinra and the anti-CD20 agent rituximab have proved to induce clinical remission in some cases and no clinical results in others (Vitale et al, 2015*).

Non-pharmacological treatment of RP is primarily focused on the management of airway lesions. A laryngotracheobronchial involvement appears in nearly half of patients and is complicated by local obstructions, which may be life threatening. Consequently, involvement of the cartilaginous structures of the airways may require physical measures, which include continuous positive airway pressure, especially at night, and surgical procedures including tracheostomy, stenting, airway dilatation, laser extirpation and laryngotracheal reconstruction.

As discussed, cardiac valvular involvement may be insidious and resistant to treatment. In patients undergoing aortic valve replacement, it is also advisable to insert a synthetic graft in the ascending aorta to minimise postoperative aneurysm formation and valvular leaks.

Plastic surgery on auricular and nasal structures may have a role for aesthetic reasons in order to solve cartilage deformities.

2.10 Prognosis

Two decades ago, the reported 10-year survival was 55% in a case series, while a more recent figure puts this close to 95%. Increased general awareness, with recognition of milder cases, probably plays an important role in this improved survival. Prognosis depends on specific organ involvement and response to treatment. The prognosis is poor for patients displaying respiratory tract involvement. In Michet's series, infection (mainly pneumonia, but also cellulitis, bacteraemia, abscess), airway collapse or obstruction and cardiovascular complications were the major causes of death. In patients aged ≤ 50 years, anaemia, saddle nose deformity, vasculitis, arthritis, laryngotracheal stenosis and microhaematuria at the time of diagnosis were associated with an increased risk of death. In patients aged > 50 years, anaemia was the only prognostic factor associated with a

higher mortality. Patients who have both RP and systemic vasculitis have been reported to have a 5-year survival rate of 45%, and usually die from vasculitis rather than from other complications of RP.

SUMMARY POINTS - Relapsing polychondritis

- ➔ Relapsing polychondritis (RP) is an acute-onset, relapsing inflammation of the cartilage, but a multiorgan damage is possible.
- ➔ RP may occur together with a primary disease but may also be a primary disease itself.
- ➔ Major sites of involvement are the auricular and nasal cartilages and eyes.
- ➔ Arthritis is also common.
- ➔ Relapsing polychondritis is generally not life threatening unless it involves laryngotracheal cartilage or major artery roots.
- ➔ Immunosuppression to prevent relapses is the mainstay of treatment.

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3 Eye symptoms in rheumatic diseases

Autoimmune disorders can have severe systemic and ocular effects, so an early diagnosis is key to successful treatment and better prognosis.

Ocular symptoms may include dry or red eyes, pruritus, photophobia, pain, foreign body sensation, visual changes and even complete loss of vision. Because a number of these conditions may initially present with non-specific ocular manifestations, physicians should keep in mind that they might be the presenting symptom of active, potentially fatal systemic disease, despite their vague character (Harper and Foster, 1998*).

Therefore, in any patient with a rheumatic disease who has ocular symptoms, a thorough ophthalmic examination, including ocular motility, pupillary reaction, visual acuity, visual field testing, external inspection with the slit lamp, corneal staining with fluorescein and direct or indirect ophthalmoscopy, should be sought. In dry eye syndrome, simple tools such as Schirmer's test or the break-up time of the tear film can be useful in diagnosis.

3.1 Ophthalmological manifestations

3.1.1 Keratoconjunctivitis sicca

Keratoconjunctivitis sicca (KCS), also known as dry eye disease, is a multifactorial affection of the tears and ocular surface resulting in tear film instability, ocular discomfort, visual disturbance and potential damage of ocular surface. Patients with dry eye syndrome mostly complain of dryness, foreign body sensation, burning, grittiness, blurred vision and blepharospasm. The symptoms are more prominent in the morning, owing to incomplete lid closure during the night, and during the latter part of the day because of evaporation of the tear film. Of note, discordance between patients' symptomatology and the severity of ocular surface clinical signs is frequent.

Triggering factors for (KCS) include older age, female sex, local environment, use of video display, smoking, contact lens wear and exposure to specific treatments such as antidepressants, antihistamines, antipsychotics, and diuretics. Hormonal condition play an important role in dry eye disease as peri- and postmenopausal females are especially affected. In addition, hormones influence aqueous tear secretion, meibomian gland function, and conjunctival goblet cell density. However, despite aetiology, surface inflammatory events and tear hyperosmolarity are universally accepted as the turning point of pathogenesis in inducing qualitative and quantitative changes in tears.

Currently, two subgroups of dry eye disease are recognized: aqueous deficient and evaporative. The former subgroup refers chiefly to a failure of lacrimal secretion due to lacrimal acinar destruction or dysfunction, which in turn causes hyperosmolarity as a stimulus for inflammatory pathways. Conversely, the evaporative dry eye is related to an excessive water loss from the exposed ocular surface in subjects with normal lacrimal secretory function.

Sjögren's syndrome, which represents the prototype of autoimmune induced dry eye in the rheumatologic context, is a large part of the aqueous tear-deficient subtype. Sjögren's syndrome may be a primary autoimmune disorders or secondary to rheumatoid arthritis or other connective tissue diseases. In both cases, the infiltration of lacrimal and salivary glands by activated T-cells causes acinar and ductular cell death and subsequent expression of autoantigens at the surface of epithelial cells. However, lacrimal gland infiltration may be also caused by other immune driven disorders including sarcoidosis, lymphoma, graft vs host disease and human immunodeficiency virus (HIV) infection, which should be taken into account during the diagnostic process.

Simple tests for the diagnosis of KCS are Schirmer's test without local anaesthesia (Schirmer I, for measuring the basal secretion rate of the lachrymal gland), calculation of the tear break-up time and slit lamp examination after fluorescein and/or Rose Bengal staining. In addition, corneal examination with the slit lamp may show punctate keratopathy (figure 2) or even filaments.

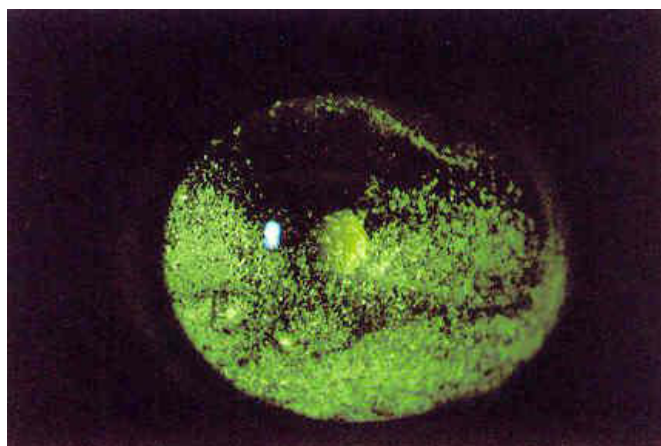
Schirmer test requires a <10 mm wetting of the paper after 5 minutes for the diagnosis of dry eye. As illustrated in figure 1, paper strips have to be placed in the lower eyelid pouch. The break-up time measures the time the tears break up in the eye by instilling fluorescein into the patient's tear film. The time elapsed between the last blink and the appearance of the first dry spot in the tear film should not be under 10 seconds. The fluorescein and/or Rose Bengal staining detect damages of conjunctival epithelium and cornea.

As regards the diagnosis of Sjögren syndrome, clinical classification criteria have been developed over time. Recently, European–American consensus criteria have been recently developed for the classification of primary Sjögren's syndrome (Shiboski et al, 2017*).

Figure 1 Schirmer's test. Patient consent obtained.



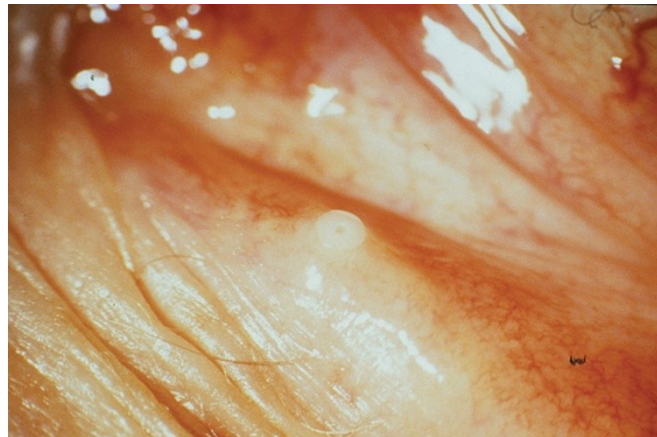
Figure 2 Punctate erosive keratopathy (yellow coloured spots stained with fluorescein).



Treatments for dry eyes consist of topical lubricants, which represent the first line topic approach, and immunomodulating agents, such as cyclosporine A eye drops. As preservatives in eye drops can be toxic to the cornea, the artificial tear substitutes should be preservative free. Omega-3 essential fatty acids have shown anti-inflammatory properties and also improve the quality and quantity of ocular film. Secretagogues can also be taken into account in severe cases, while systemic disease-modifying anti-rheumatic drugs (DMARDs) are reserved for patients with Sjögren syndrome ad extraglandular involvement. Another treatment option is the use of permanent lachrymal plugs (figure 3), which should be inserted intracanalicularly with the aim of stopping

tear fluid drainage. Patients should also be told about simple therapeutic measures, such as using sunglasses and room humidifiers, quitting smoking, and avoiding dry environments.

Figure 3 Intracanalicular implant with a lachrymal plug.



It is known that lachrymal gland functions return to normal in patients with secondary Sjögren's syndrome when the disease remits, so systemic application of immunosuppressive drugs should be considered.

3.1.2 Keratopathy

Corneal disease can be an isolated complication, but it is most commonly associated with KCS or scleritis and may include keratitis, sclerosing keratitis and paracentral or peripheral ulcerative keratitis (figure 4). The origin of this sterile keratitis is an immune complex-mediated vasculitis of the limbal area and it is marked by an inflammatory corneal cell infiltrate that may result in corneal scarring, ulceration, perforation or melting. Patients with keratitis mostly complain of red eye, pain, tearing and blurred vision. The diagnosis is made by slit lamp examination.

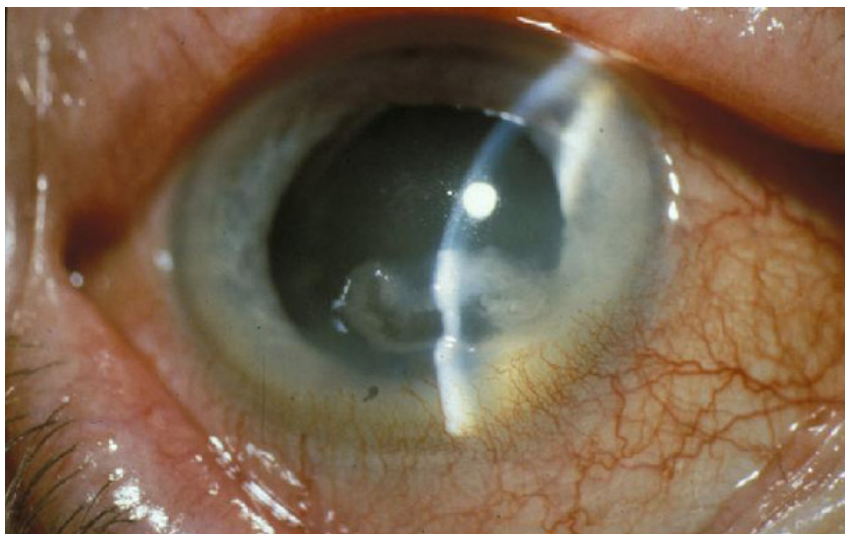
In the context of dry eye disease, filamentary keratitis owing to the accumulation of tear film debris or mucus clumping causes eye pain and foreign body sensation. Stromal or sclerosing keratitis are possible complications of anterior scleritis, while interstitial keratitis, involving the corneal stroma without epithelial damage, is associated with Cogan syndrome after having ruled out syphilis, Lyme disease and Epstein Barr virus infection.

Peripheral ulcerative keratitis in patients with rheumatoid arthritis is a rare but classical finding in the rheumatologic context. It is characterised by a progressive thinning of the peripheral cornea due to immune complex deposition and complement activation, followed by activation of collagenases and proteases which in turn leads to keratolysis. This condition may be clinically quiescent with gradual reduction of vision or rarely present with painful eye, severe inflammation up to corneal perforation. Ulcerative keratitis is often independent of systemic disease activity. Because ulcerative keratitis is a sign of active systemic vasculitis and a higher death rate, immunosuppressive therapy will be required to preserve life and vision. In particular, the management is based on topical glucocorticoids; however, in case of perforation, intravenous glucocorticoids

followed by high dose oral glucocorticoids should be administered. In addition to steroids, DMARDs have to be employed as antiproliferative and steroid-sparing agents, while pulsed intravenous cyclophosphamide should be considered in patients with severely active necrotizing forms. More recently, biological therapies have been used, but randomised controlled trials are lacking. In any case, corticosteroids and immunosuppressive drugs should be introduced only after having ruled out an underlying infective cause of corneal ulceration and any secondary infection.

Despite the above-mentioned aggressive medical treatment, surgical intervention will often be required. Surgical options mostly include penetrating keratoplasty or the application of tissue adhesives.

Figure 4 *Peripheral corneal ulceration in rheumatoid arthritis.*



For other than ulcerative keratitis, treatment options consist of local treatments, especially topical lubricants and cyclosporine A eye drops. Because of their antiproliferative character, care must be taken when steroids are used locally. More specific treatments can be taken into account in relation to the systemic disease causing corneal involvement.

3.1.3 Episcleritis and Scleritis

Inflammation of the sclera is a common eye manifestation of the various rheumatic disorders (especially systemic lupus erythematosus (SLE), systemic scleroderma, Wegener's granulomatosis, Behçet's disease and panarteritis nodosa, sarcoidosis, relapsing polychondritis, inflammatory bowel diseases, rheumatoid arthritis and more rarely, the spondyloarthropathies) and includes a spectrum that ranges from harmless simple episcleritis to painful, sight-threatening, destructive necrotising scleritis.

Episcleritis (figure 5A) is a relatively common condition, found especially among young women and often characterized by a self-limiting course. Although episcleritis can be seen in patients with rheumatoid arthritis

and other rheumatologic entities, it is generally a benign recurrent inflammation of the tissue that lies between the conjunctiva and the sclera.

In scleritis the inflammatory process can affect the anterior and/or the posterior part of the sclera, it can be confused with severe conjunctivitis because of the bright red appearance of the eye due to engorged scleral vessels (figure 5B) and may spread to the adjacent tissues, causing ocular complications such as uveitis, keratitis, glaucoma, cataract, optic neuritis, macular oedema, serous retinal detachment or perforation of the globe.

The importance of correctly diagnosing and distinguishing between scleritis and episcleritis is based on the potential ocular and systemic complications associated with scleritis. Indeed, as well as extremely painful, it is a potentially blinding condition associated with autoimmune conditions in around 40% of cases. According to the location of inflammation, scleritis can be divided into anterior, the most frequent, and posterior.

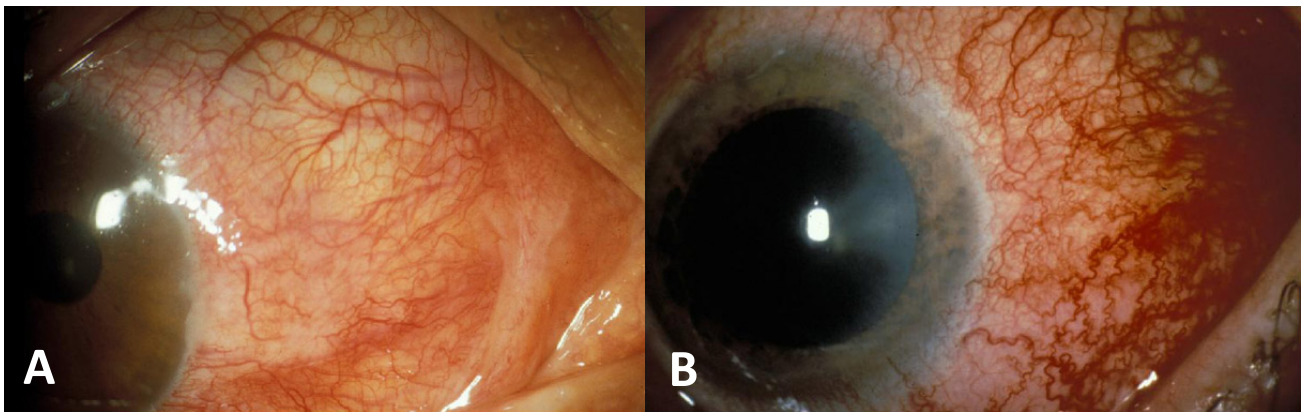
Anterior scleritis may be diffuse when scleral oedema occupies one or more quadrants of the anterior sclera and nodular when one or more raised areas (nodules) of tender scleral thickening are observed. Then, scleritis is distinguished in non-necrotising and necrotising, the latter being the most severe type. Noteworthy, it is particularly important to recognise necrotising scleritis, since it is often associated with ocular complications and a poor prognosis. From a clinical point of view, the eye is extremely painful with radiation to the forehead and temporal region, the ocular globe is tender, while visual loss, discharge and photophobia are generally lacking. The eye is almost always red, but seldom appears white. During inactive phases a bluish/black hue of the sclera can be observed as the result of a scleral thinning owing to previous active scleritis. Acute scleritis can complicate with anterior uveitis, stromal or sclerosing keratitis, globe perforation, glaucoma and even astigmatism as a consequence of the scleral thinning that causes a change in the shape of the eye globe.

Posterior scleritis is less common, but equally sight-threatening. It is associated with systemic autoimmune conditions, especially rheumatoid arthritis and vasculitides, in about 1 out of 3 patients. Also in this case symptoms are characterized by mild-to-severe eye pain, possibly referred to brow or jaw ; in addition, a visual loss and a hypermetropic shift are often recorded as well as lid oedema, proptosis, lid retraction, diplopia. At ophthalmologic examination shallow anterior chamber, choroidal folds, annular choroidal detachment, exudative retinal detachments, macular oedema and optic disc oedema may be observed. The measurement of scleral thickening with B-scan ultrasonography may assist the diagnosis (Murray et al, 2016*).

Taking into account the different nature and prognosis of scleritis and episcleritis, distinguishing between the two ocular entities is essential. Apart from the pain, that is much less severe in episcleritis, the instillation of topical phenylephrine 2.5% brings about blanching of the more superficial vessels of episcleritis, but not of the deeper scleral vessels of scleritis, thus allowing an easy and practical differential diagnosis.

In patients with associated vasculitic systemic disease, the appearance of scleritis indicates a generalisation of the vasculitis, which may have potentially fatal systemic complications. Therefore, only early diagnosis and adequate aggressive treatment can preserve ocular functions and the patient's life.

Figure 5 (A) Episcleritis with engorged episcleral vessels in systemic lupus erythematosus. (B) Scleritis in a patient with rheumatoid arthritis; the inflamed vessels give the eye a bright red appearance.



When required, the initial treatment of episcleritis should be focused on administering ocular lubricants and non-steroidal anti-inflammatory drugs (NSAIDs), at first topically and, then, systemically. In patients who do not respond to these drugs, glucocorticoids or even immunosuppressant agents should be given.

In patients with scleritis, routine treatment with topical non-steroidal or steroidal anti-inflammatory drugs alone is insufficient. However, in many cases systemic NSAIDs are efficacious, in particular flurbiprofen (Agrawal et al, 2016*); if not, short-term treatment with systemic glucocorticoids is recommended. When treatment fails or if only high-dose systemic steroidal anti-inflammatory drugs are efficacious in controlling the scleral disease, immunosuppressive drugs should be added or substituted. In particular, methotrexate, mycophenolate mofetil or azathioprine should be employed. If this is not sufficient to achieve remission, an anti-TNF α biologic agent or the anti-CD20 rituximab may be administered as well. In particular, according to the expert panel recommendations for the use of anti-TNF agents in patients with ocular inflammatory involvement, infliximab may be considered as second-line corticosteroid-sparing therapy in subjects with chronic and severe scleritis (Levy-Clarke et al, 2014*). In patients with scleritis related to granulomatosis with polyangiitis, infliximab may induce different degree of response and rituximab has showed to be noninferior to cyclophosphamide. Conversely, etanercept seems to be not effective in scleritis and cases of paradoxical anterior scleritis have even been reported after the start of etanercept.

In the specific context of patients with posterior or necrotising scleritis, intravenous corticosteroids should be urgently started as rescue therapy, followed by oral corticosteroid in addition to a DMARD or a biological agent.

3.1.4 Uveitis

Uveitis, an inflammation of iris and ciliary body anteriorly and the choroid posteriorly, is subdefined as anterior, intermediate or posterior based upon the location of inflammation relative to the equator of the eye. However, adjacent structures are often involved including the cornea, sclera, retina and the optic nerve.

Then, uveitis may be described as *sudden* or *insidious* according to how ocular inflammation starts; in addition, uveitis may be *limited* when lasts for up to 3 months or *persistent* when lasts for more than 3 months. On this basis, uveitis is *acute* when characterized by a sudden onset and a limited duration. Conversely, the term *chronic* should be limited to persistent uveitis characterized by a relapse within 3 months after the discontinuation of therapy, while the term *recurrent* indicates uveitis characterized by episodes separated by periods of inactivity in patients with no treatment for uveitis (Jabs et al, 2005*).

Overall 30%-40% of uveitis is associated with a systemic disease. In particular, two types of uveitis are commonly found in rheumatic disorders: uveitis anterior and uveitis posterior. The course of inflammation is mostly a chronic relapsing one with an acute onset.

3.1.4.1 Anterior segment changes

Anterior uveitis is an inflammation which is limited to the anterior chamber and can involve the iris and the ciliary body (iritis, iridocyclitis, anterior cyclitis). Anterior uveitis comprises more than 90% of cases. In differential diagnosis physicians should rule out infectious agents including cytomegalovirus, herpes simplex virus, varicella zoster virus, Treponema pallidum, Mycobacterium tuberculosis, Borrelia burgdorferi (Lyme disease). Among non-infectious diseases, anterior uveitis may be caused by local or systemic disorders. The former include trauma and Fuchs's uveitis, an idiopathic condition characterized by modification of the iris colouring, predisposition to cataract and glaucoma, and keratic precipitates on the posterior surface of the cornea. Among systemic diseases the most frequent conditions causing anterior uveitis are: HLA-B27 associated spondyloarthritis, juvenile idiopathic arthritis, multiple sclerosis, Behçet's disease, sarcoidosis, and tubulointerstitial nephritis. Of note, up to one-third of patients with anterior uveitis have ankylosing spondylitis and 50% of patients with anterior uveitis are likely to be HLA-B27 positive in the Western world (Murray et al, 2016*).

Patients with anterior uveitis often have redness, periorbital pain, photophobia and blurred vision. Slit lamp examination shows conjunctival injection, ciliary flush in the perilimbal area, cells and flare in the anterior chamber and fine keratic precipitates (figure 6), which confirm the diagnosis. Keratic precipitates cells (Figure 6) and flare in the anterior chamber and posterior synechiae are characteristic signs of anterior uveitis. Keratic precipitates are inflammatory cellular deposits on the inner corneal endothelium, varying in shape and distribution according to the specific type.

The number of cells in the anterior chamber at the slit lamp correlate with inflammation and this can be graded using a validated scoring system that describes inflammation ranging from 0 (less than 1 cell in 1 mm slit beam) to 4+ (more than 50 cells). Cells may precipitate to the bottom of the anterior chamber forming a white sediment defined hypopyon, more frequent in HLA-B27 associated uveitis and in Behçet's disease. Albumin passed into the aqueous humour organice in the so-called flares, which create opalescence. The severity of inflammation also correlate with flares and are graded according to the intensity of opalescence from 0 to 4+, as detailed in table 1.

Table 1 shows the gradings describing the intensity of inflammation in anterior uveitis as identified according to the density of cells visible in 1 mm slit beam (A) and to the opalescence induced by flares (B). The table is adapted from the Standardization of Uveitis Working Group (Jabs et al, 2005*)

A – Grading for Anterior Chamber Cells	
Grade	Number of Cells in 1 mm slit beam
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50
B – Grading for Anterior Chamber Flare	
Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Figure 6 Acute anterior uveitis; note the keratic precipitates.

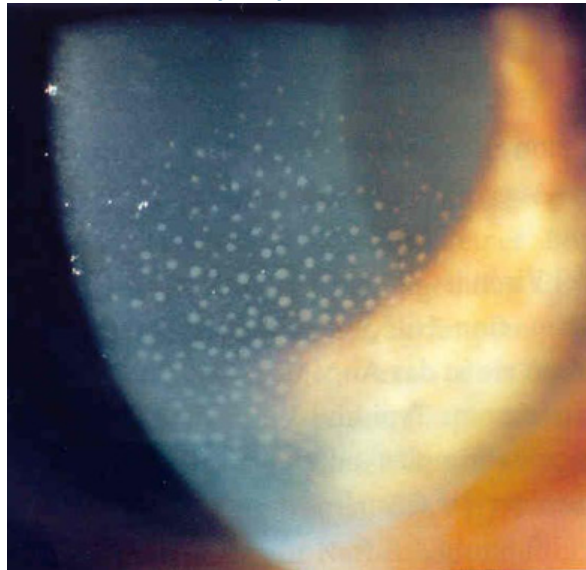
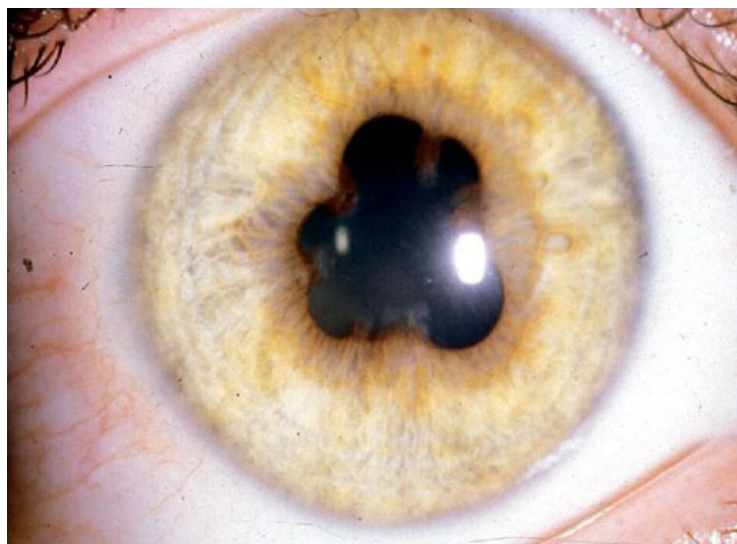


Figure 7 Posterior synechia.



Common complications due to intraocular inflammation include posterior synechiae (Figure 8) secondary glaucoma, secondary cataract formation and development of macular oedema (figure 7).

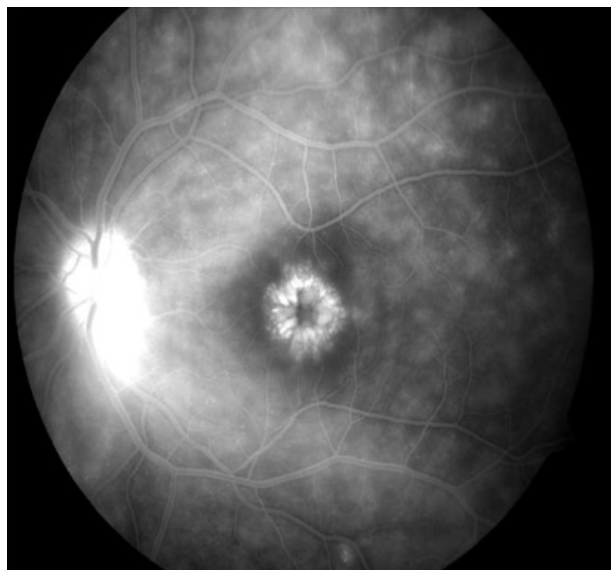
Posterior synechiae are pathologic adhesions between iris and anterior lens capsule capable of changing the pupil into shape irregular forms.

Intraocular pressure may rise for many reasons, especially as a result of corticosteroid treatment and because of the presence of synechiae inducing a complete adhesion of iris on anterior lens capsule, in turn resulting in a decreased flow of aqueous humour through the pupil. Of note, the standardization of uveitis nomenclature working group distinguishes between elevated intraocular pressure, defined as an increase of pressure above

the normal range, and glaucoma, term reserved to those situation in which a visual field loss or a disk damage are observed (Jabs et al, 2005*).

Cystoid macular oedema (CMO) is one of the major causes of vision impairment related to uveitis. Although CMO complicates more frequently intermediate, pan- and posterior uveitis, it is also a relatively uncommon complication of anterior uveitis. The visual acuity is reduced by the accumulation of fluid in the macular area of the retina, which is responsible for central vision. CMO is assessed with fluorescein angiography or optical coherence tomography (OCT) and is generally treated with intraocular injections of the corticosteroids (Fabiani et al, 2017a*).

Figure 8 Cystoid macular oedema in fluorescein angiography.



During an acute inflammatory attack, local treatment should consist of eye drops or ointments containing glucocorticoids. Application frequency depends on the severity of the inflammation. For severe anterior uveitis—for example, if a fibrinous reaction is present, subconjunctival steroid injections may be helpful. In contrast, topical steroids are not effective for macular oedema. For this condition steroids and acetazolamide given systemically are useful. In addition it is necessary to apply sympathomimetics or parasympatholytics locally both to prevent posterior synechiae (figure 8) and to relieve ocular pain.

If local treatment is insufficient, systemic treatment with first-line glucocorticoids and second-line immunosuppressant agents should be discussed. A small number of patients fail to respond to all these treatments and anti-TNF α biologics infliximab or adalimumab should be taken into account (Levy-Clarke et al, 2014*).

3.1.4.2 Intermediate uveitis and pars planitis

The term intermediate uveitis should be used when the vitreous is the site of inflammation; the presence of peripheral vascular sheathing and CMO should not change the classification. The term pars planitis should be used for the subset of idiopathic intermediate uveitis where there is snowbank or snowball formation occurring in the absence infectious or systemic diseases. Consequently, in the rheumatologic context the term pars planitis does not play a part. Conversely, an intermediate uveitis may be found as an expression of sarcoidosis and multiple sclerosis or in the context of syphilis or Lyme disease, but an isolated vitreous inflammation is not characteristic of rheumatic disease.

3.1.4.3 Posterior segment changes

Involvement of the posterior part of the eye, so-called posterior uveitis, includes the retina and the choroid as primary sites of inflammation, while the posterior vitreous humour, optic nerve head and retinal vessels may be secondarily affected (Jabs et al, 2005*). If the inflammation starts in the choroid and then affects the retina, it is called chorioretinitis. If the inflammation begins in the retina and secondarily affects the choroid, it is called retinochoroiditis. Both these manifestations lead to retinal, optic nerve and macular oedema. Posterior uveitis accounts for 15% to 22% of all uveitides and is responsible for about 10% of blindness in western world mostly due to CMO. Although it can affect all age groups, the highest prevalence is observed within the fourth and the fifth decades of life (Rothova et al, 1996*).

Posterior uveitis may be supported by infectious agents such as in toxoplasmosis, cytomegalovirus infections, syphilis, Bartonella (cat-scratch disease) and tuberculosis but also by systemic immune disorders including connective tissue diseases, Behçet's disease, Vogt-Koyanagi-Harada disease and sarcoidosis. However, several ocular-specific affections should be taken in mind as the white dot syndrome, multifocal choroiditis, and birdshot choroidopathy. Diagnosis is based on a careful evaluation of medical history, travel history, slit lamp examination, and ophthalmoscopy. Patients usually do not complain at the beginning of posterior segment inflammation or if the involvement is located in the peripheral retinal areas. Later they may see 'floaters' due to vitreous involvement and, especially when the inflammation is located on the posterior pole, may experience blurred vision up to severe visual loss. In addition to decreased sight, symptoms include deep pain, hyperaemia, photophobia, metamorphopsia, and scotomas. Among instrumental tools, fluorescein angiography, indocyanine green angiography, and ultrasonography may be useful for diagnosis. In addition, OCT may be helpful in detecting and monitoring CMO, epiretinal membranes, choroidal membranes, and macular holes. Fluorescein angiography may confirm the inflammatory activity and identifies neovascularization, capillary non-perfusion areas, and vascular staining in cases of retinal vasculitis. Ultrasonography is a very useful tool, especially when the media is hazy and in cases with cataract or vitreous haemorrhage.

Complications include secondary cataract formation, secondary glaucoma and, as mentioned above, retinal detachment, phthisis of the eye, optic disc atrophy and visual loss that may lead to blindness.

Another severe inflammatory condition of the posterior segment is retinal vasculitis. Typical for this condition are dilatation and engorgement of retinal vessels, cotton wool spots (ischaemic infarcts of the retinal ganglion cell layer) (figure 9), perivascular sheathing with inflammatory whitish yellow exudates and retinal haemorrhages (figures 10–12). Especially in the beginning, at ophthalmoscopy these conditions look like an early hypertensive retinopathy. In cases of occlusive retinal vasculitis, the funduscopy may show occluded, so-called 'silver wired', vessels (figure 13), chorioretinal scars, alterations of retinal pigment epithelium, and retinal and also optic nerve atrophy. In addition, occlusive retinal vasculitis causes tissue hypoxia, which stimulates the growth of new vessels at the optic disc or elsewhere in the retinal layer (Zierhut et al, 2005*). These neovascularisations (figure 14) can rupture and bleed, leading to organisation with membrane formation, causing retinal holes and subsequent retinal detachment.

Figure 9 Multiple cotton wool spots in systemic lupus erythematosus retinopathy.



Figure 10 Inflammatory whitish yellow exudates, and retinal haemorrhages.



Figure 11 Perivascular sheathing.



Figure 12 Staining of the vessel walls during fluorescein angiography.

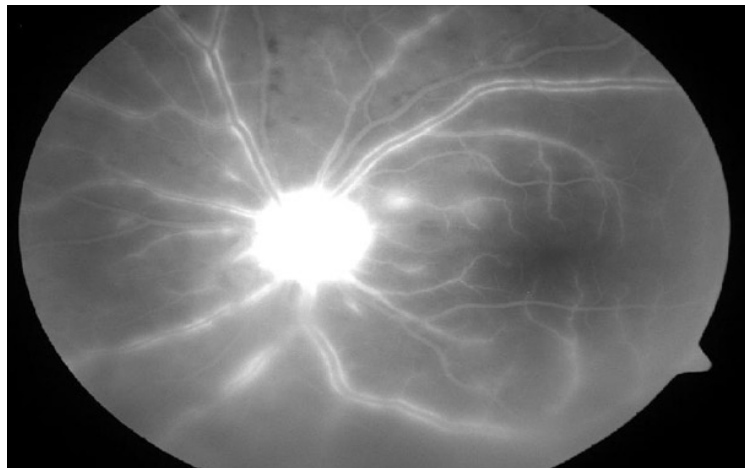


Figure 13 Silver wired (=already occluded) vessels in a patient with Behçet's disease.

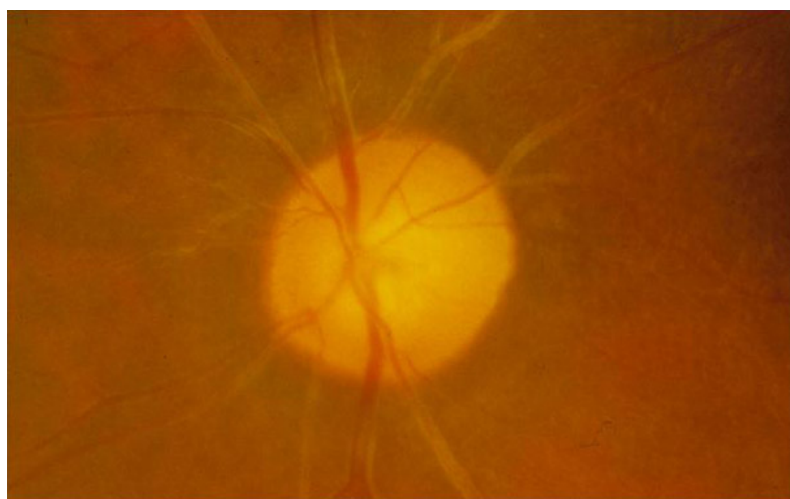
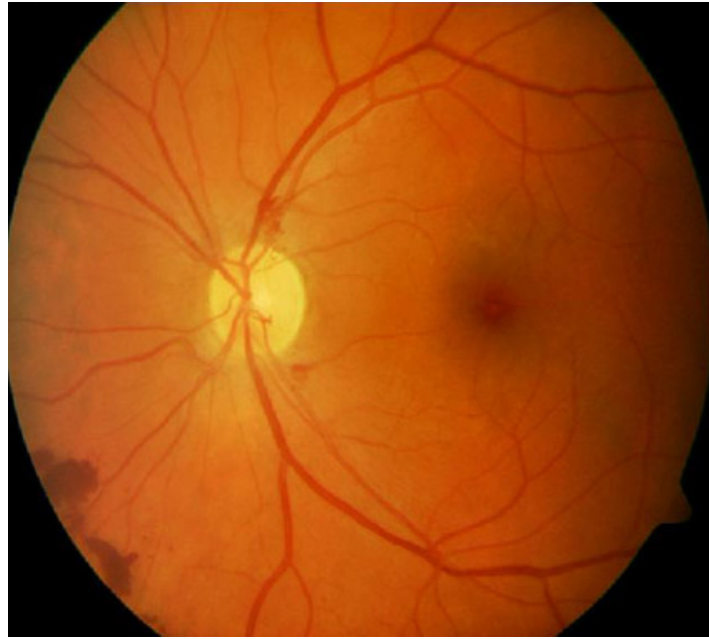


Figure 14 Retinal and optic disc neovascularisations.

As retinal vasculitis indicates systemic activity of the underlying disease and, as a consequence, a bad prognosis, treatment should be started urgently. Since local treatment is ineffective for retinal involvement, systemic application of glucocorticoids or immunosuppressant agents is required (Perez et al, 2004*). Recent evidences strongly suggest TNF α inhibition as effective therapy for retinal vasculitis, especially in patients with Behçet's disease (Calvo-Río et al, 2014*; Sharma et al, 2015*). In this regard, the American Uveitis Society recommendations claim that infliximab and adalimumab can be considered as first-line immunomodulatory agents in patients with Behçet's disease eye manifestations (Levy-Clarke et al, 2014*). According to data from a Spanish registry enrolling 124 patients with Behçet's disease, the number of patients with retinal vasculitis significantly decreased from 89 (143 eyes) to 8 (13 eyes) at 1-year follow-up after the start of infliximab or adalimumab (Calvo-Río et al, 2014*). Similarly, Vallet et al found an improvement of retinal vasculitis in 46/49 (93.9%) patients with Behçet's disease even though retinal vasculitis was negatively associated with complete response in both univariate and multivariate analysis (Vallet et al, 2015*). Adalimumab administered to 40 Behçet's disease patients with ocular involvement proved to induce a significant reduction of retinal vasculitis already at 3-month follow-up and a further significant decrease at 12-month evaluation. Notably, the concomitant use of DMARDs did not affect the overall response of retinal vasculitis; similarly, no differences existed between patients undergoing adalimumab as first line biologic agent and those previously administered with other biologics (Fabiani et al, 2017b*).

The anti-CD20 rituximab has also been described as a therapeutic opportunity in patients with resistant retinal vasculitis associated to Behçet's disease, systemic lupus erythematosus and granulomatosis with polyangiitis (Hickman et al, 2010*; Najem et al, 2015*; Davatchi et al, 2010*).

Based on retrospective studies, also IL-1 inhibition has revealed good clinical results on retinal vasculitis in terms of prompt and sustained response (Gül et al, 2012*; Fabiani et al, 2017c*).

A very recent work has also highlighted the possibility to use intraocular dexamethasone implants to control recalcitrant retinal vasculitis (Fabiani et al, 2017a*).

3.1.4.4 Panuveitis

The term panuveitis should be reserved for those situations in which inflammation has no predominant, but the inflammatory process is localized in the anterior chamber, vitreous, and retina and/or choroid (Jabs et al, 2005*). As for other subtypes of uveitis, panuveitis may be induced by infectious agents or systemic inflammatory diseases, especially Behçet's disease, Vogt-Koyanagi-Harada disease and sarcoidosis. Clinical manifestations overlap with those described for posterior, intermediate and anterior uveitis and diagnosis is equally based on clinical history, slit lamp examination, ophthalmoscopy, evaluation of intraocular pressure to early identify intraocular hypertension or glaucoma. OCT can help in the early identification of CMO and cystoid macular oedema and fluorescein angiography may find retinal vasculitis, neovascularization, and capillary non-perfusion areas.

3.1.4 Systemic treatment for uveitis

Patients with anterior acute uveitis often respond well to topical corticosteroids and cycloplegic and/or mydriatic agents. Patients with anterior chronic uveitis, intermediate uveitis, posterior uveitis, or panuveitis, often require a more aggressive therapy with tapering high-dose systemic steroids (40 to 80 mg daily of prednisone or equivalent). In severe cases, parenteral steroids should be taken into account. DMARDs, especially azathioprine, methotrexate, mycophenolate, and cyclosporine, should be added in resistant cases or as steroid-sparing agents. However, multiresistant patients are not rare. In these cases biologic agents should be added to improve patients' quality of life and avoid sight-threatening complications. Among biologic agents, TNF α inhibitors take advantage of the wider scientific literature reporting retrospective and prospective trials. According to the recommendations of the American Uveitis Society (Levy-Clarke et al, 2013*), infliximab or adalimumab represent the second-line agents after methotrexate to treat uveitis in patients with juvenile idiopathic arthritis. For patients with Behçet's disease, infliximab or adalimumab were recommended as first- or second-line corticosteroid-sparing agents with high- and moderate-quality evidence, respectively. In the context of spondyloarthritis, infliximab or adalimumab were strongly recommended as corticosteroid-sparing agents, but were only discretionary recommended as adjunctive therapy for sight-threatening uveitis. Discretionary recommendations were made also for the use of infliximab or adalimumab for uveitis in the context of sarcoidosis.

Looking at literature data, infliximab has shown good clinical results in patients with Behçet's Disease, juvenile idiopathic arthritis, sarcoidosis, spondyloarthritis, and Crohn's disease when used at a dose ranging from 3 mg/kg every 8 weeks to 10 mg/kg every 4 weeks. A prospective study on 63 Japanese patients with Behçet's disease (the analysis of efficacy was performed on 50 patients) claimed that at 1-year follow-up infliximab induced an improvement of uveoretinitis in 69% of cases, a slight improvement in 23%, while 8% of patients unchanged (Okada et al, 2012*). In another study on 23 patients with uveitis due to different non-infectious aetiologies, infliximab brought about clinical response in 78% of cases already at 10-week evaluation (Suhler et al, 2009*).

Regarding adalimumab, a prospective study on 31 patients with multiple underlying systemic conditions, response was recorded in 68% of patients at 10-week visit and in 39% at 50-week evaluation (Suhler et al, 2013*). In the VISUAL I randomized placebo-controlled study on 217 patients with non-infectious uveitis, the risk of treatment failure was significantly reduced in the adalimumab arm than patients undergoing placebo, as the median time to treatment failure was 24 weeks for patients undergoing adalimumab and 13 weeks in the placebo group (Jaffe et al, 2016*). In the Visual II study on 229 patients with inactive disease owing to prednisone treatment, patients were randomized to adalimumab or placebo with a mandatory prednisone taper from week 2. Treatment failure was identified in 55% of patients in the placebo group and 39% of patients in the adalimumab group. Time to treatment failure was significantly higher among patients undergoing adalimumab compared with the placebo group (Nguyen et al, 2016*). Adalimumab has been recently tested in 40 patients with Behçet's disease suffering from multirefractory uveitis. The study highlighted a significant decrease in the number of ocular flares during a 12-months study period compared to the 12 months preceding the start of adalimumab, along with a significant improvement of CMO at OCT and of best corrected visual acuity (Fabiani et al, 2017b*).

Among other TNF α inhibitors, golimumab has proved effectiveness in retrospective studies on patients with ankylosing spondylitis, juvenile idiopathic arthritis, Behçet's disease (Yazgan et al, 2016*; Calvo-Río et al, 2016*; Miserocchi et al, 2014*; Vitale et al, 2017*). Conversely, the use of etanercept in patients with uveitis is controversial, as it seems associated with paradoxical uveitis after TNF α inhibition much more than other TNF antagonists (Lim et al, 2007*).

As for other cytokine blockers, current research efforts are directed toward interleukine(IL)-6 and IL-1 inhibition. The monoclonal IL-6 receptor antibody tocilizumab given at the dosage of 8 mg/Kg every 4 weeks has proved to be a successful therapeutic option in patients with uveitis due to various illnesses and previously unresponding to conventional therapy and anti-TNF α agents (Deuter et al, 2017*; Calvo-Río et al, 2017*; Mesquida et al, 2017*). A recent study on 12 patients with various diseases, tocilizumab allowed a significant improvement of central macular thickness and visual acuity at 12- and 24-month follow-up. Tocilizumab was withdrawn in 5 patients because of persistent uveitis remission, but macular oedema relapsed in all cases within 3 months.

Rechallenge of tocilizumab induced a recovery of efficacy (Mesquida et al, 2017*). Another study on 25 patients with juvenile idiopathic arthritis proved the rapid improvement to tocilizumab, with reduction in anterior chamber cell number in 79.2% of patients at 6-month visit and 88.2% at 1-year follow-up. In addition, central macular thickness and visual acuity showed significant improvement at 6-month examination (Calvo-Río et al, 2017*). Of note, 4 patients with juvenile idiopathic arthritis have been recently described as showing a good clinical response to tocilizumab administered intravenously, but experiencing uveitic relapses soon after switching to subcutaneous tocilizumab. On this basis, the Authors speculated that ocular disease may be more readily controlled with intravenous injections owing to the higher blood levels achieved (Quesada-Masachs et al, 2017*).

Gevokizumab has been the first IL-1 antagonist to demonstrate efficacy in severe resistant uveitis in an open-labelled pilot study (Gül A et al, 2012*). The results were later confirmed by an exploratory phase 2 open-label randomized multicentre study (Tugal-Tutkun et al, 2017*). However, although a preserved visual acuity and a less severe ocular inflammation were reported in patients undergoing gevokizumab, gevokizumab has failed to meet the primary endpoint represented by the time to the first acute ocular exacerbation in a recent phase 3 randomised placebo controlled trial. IL-1 inhibition with anakinra and canakinumab for the treatment of uveitis in patients with Behçet's disease has been described in numerous case report and case series over the last decade (Vitale et al, 2016*). A recent retrospective study on 19 patients with Behçet's disease and inflammatory ocular involvement treated with anakinra at the dosage of 100 mg/day or canakinumab at different dosages described a significant reduction of ocular flares from 200 episodes/100 patients/year during the 12 months preceding the start of IL-1 inhibition to 48.87 episodes/100 patients/year during the first 12 months of treatment. In addition, a significant steroid sparing effect and a reduction in retinal vasculitis at fluorescein angiography were observed. Corticosteroid use and the line of biologic treatment did not condition the response (Fabiani et al, 2017c).

Among other biologic agents, abatacept and rituximab have shown a therapeutic role in uveitis, especially among patients with juvenile idiopathic arthritis (Birolo et al, 2016*; Miserocchi et al, 2016*), while IL-17 inhibitors have failed to reach primary efficacy endpoints in three different studies. An interdisciplinary panel consensus on the management of uveitis in juvenile idiopathic arthritis have recently proposed different levels of treatment as a stepwise therapeutic algorithm starting from the use of topical corticosteroids (level I), followed by methotrexate (level 2), adalimumab (level III), infliximab (level IV) and other rescue treatments represented by abatacept, tocilizumab, golimumab or rituximab (level V) (Bou et al, 2015*).

As recommended by a recent expert committee (Wakefield et al, 2017*), before starting any long-term systemic immunosuppressive or biologic therapy, patients should be evaluated to prevent or minimize therapy and disease-related complications. In particular liver or sexually transmitted infections, dental diseases, human papilloma virus infection, and a history of or exposure to tuberculosis should be ruled out. Moreover, bleeding

disorders and thrombosis should be investigated as well as neoplastic diseases and renal, liver, and endocrine disorders. A baseline bone density and fracture risk assessment should be reserved to patients undergoing high-dose and prolonged systemic corticosteroids, looking at adequate treatment when required. Immunization status (HBV, Varicella Zoster Virus, pneumococcus) should also be considered and special attention should be given to children in terms of drug dosages, immunization and long-term effects. Young women should be informed about the need for planning pregnancy and lactation, while elders should be carefully evaluated for co-morbidities, poly-pharmacy and drug interactions.

Finally, it is necessary to keep in mind that ocular surgery—for example, laser coagulation, vitrectomy, cataract extraction, should be carried out only if anti-inflammatory therapy has already been started because of the otherwise high risk of relapse. For retinal hypoperfusion and secondary neovascularisations, laser coagulation may be helpful. Laser coagulation should be performed only if the patient is receiving anti-inflammatory therapy.

3.1.5 Side effects of drugs used to treat rheumatic diseases

The most significant side effects of the drugs used to treat rheumatic diseases are the maculopathy associated with antimalarial agents, and cataracts and glaucoma associated with glucocorticoid use.

3.1.5.1 Antimalarial drugs

The incidence of hydroxychloroquine retinopathy is low. A review of more than 1200 hydroxychloroquine prescriptions filled in a Kaiser Permanente Medical Care Program found only one case of definitive retinopathy (0.08%) and a few cases of indeterminate but probable toxicity (0.4%). The condition is closely related to the daily drug dose and duration of treatment. Risk factors for developing retinopathy include doses of chloroquine >3 mg/kg daily and doses of hydroxychloroquine >6.5 mg/kg daily, doses of hydroxychloroquine >400 mg/day and cumulative doses >500 g.

In 2000, the American Academy of Ophthalmology issued recommendations on screening for chloroquine and hydroxychloroquine toxicity. They suggested that all patients starting either chloroquine or hydroxychloroquine treatment should have a full dilated eye baseline examination within the first year and should then receive an annual follow-up, especially patients at high risk (Marmor et al, 2002*).

3.1.5.2 Tumour necrosis factor α antagonists

Treatment with TNF α blockers will often be started in inflammatory diseases resistant to conventional immunosuppressive agents; however, paradoxically ocular inflammation is a reported adverse event following the use of etanercept. To date, many cases of inflammatory eye disease (uveitis, scleritis, orbital myositis) have been associated with TNF inhibitors, especially etanercept (Lim et al, 2007*).

3.2 Autoimmune diseases (Patel and Lundy, 2002*)

3.2.1 Arthritides

3.2.1.1 Rheumatoid arthritis

Ocular involvement in rheumatoid arthritis is common—found in about 25–30% of patients. KCS can be detected in 15–25% of patients with rheumatoid arthritis, making it the most common manifestation in this disease. Interestingly, the severity of dry eye is independent of rheumatoid arthritis activity.

Scleritis or episcleritis occurs with a frequency of 4–10% and in scleritis, rheumatoid arthritis is the most common cause of this manifestation, accounting for about 18–33% of cases. Corneal disease in patients with rheumatoid arthritis can be an isolated complication but is most commonly associated with KCS or a form of anterior scleritis. Other rare manifestations are choroiditis, retinal vasculitis, idiopathic retinal haemorrhage, retinal detachment and macular oedema. Special attention should be given to peripheral ulcerative keratitis, as it is both a sight-threatening complication and a sign of active systemic vasculitis requiring resolute treatment.

3.2.1.2 Spondyloarthropathies

Among the seronegative spondyloarthropathies, the most frequent ocular manifestation is acute anterior, unilateral, relapsing, uveitis. It may occasionally be bilateral. Often anterior uveitis is the first symptom of a previously undiagnosed HLA-B27 associated disease, especially among female subjects. The prognosis of uveitis is usually excellent with topical treatment, and only those with posterior pole involvement with a tendency to chronicity might benefit from systemic anti-inflammatory treatment. Other rare ocular involvement includes KCS, keratitis, scleritis and posterior uveitis (Lyons and Rosenbaum, 1997*).

Ankylosing spondylitis. During the course of their disease, about 25–40% of patients with ankylosing spondylitis develop anterior uveitis, which occurs relatively more often in HLA-B27-positive than in HLA-B27-negative patients. There is a minor correlation between the activity of ankylosing spondylitis and the development of anterior uveitis. In ankylosing spondylitis, in particular, but also in other HLA-B27 associated inflammatory diseases, sulfasalazine is a possible treatment for preventing recurrences and reducing the severity of anterior uveitis.

Reactive arthritis. Conjunctivitis is the most common ocular symptom in reactive arthritis and usually appears within a few weeks of the onset of arthritis or urethritis in about 58% of patients. The second most common ocular symptom is anterior uveitis, occurring in up to 12% of patients. Anterior uveitis is more frequent in patients who are HLA-B27 positive and in those patients who have sacroiliitis. In addition, episcleritis, scleritis, keratitis, retinal oedema and retinal vasculitis have all been reported.

Psoriatic arthritis. Eye involvement in patients with psoriatic arthritis occurs in up to 10% and is described mainly in patients with associated arthritis. In the literature, scaling of the eyelids, conjunctivitis, dry eye syndrome and anterior uveitis have been noted, interestingly twice as often in men as in women.

Enteropathic arthritis. The eye is involved in 4–10% of patients with enteropathic arthritis. Acute anterior uveitis but also episcleritis and marginal keratitis have been most frequently reported. In 1991, Salmon and co-workers reported that patients with additional arthritis or arthralgia had a higher incidence of ocular inflammation than patients without joint involvement.

3.2.2 Connective tissue disease

3.2.2.1 Systemic lupus Erythematosus (SLE)

Ocular manifestations of SLE most often reflect systemic disease and occur in 20% of patients, but independent studies also show the possibility of ocular inflammatory problems preceding diagnosable SLE by more than 5 years. KCS is the most common and is present in 10–25% of cases. Episcleritis and scleritis can be found in about 10% of patients and necrotising scleritis occurs in 23% of inflamed eyes. Other ocular changes of the anterior eye segment include uveitis, interstitial keratitis and a discoid lupus rash over the eyelids, which is often confused with blepharitis.

In the posterior eye segment, the retina and the choroid are frequently involved, second only to KCS, and in 88% of these affected patients active SLE is present. Cotton wool spots (figure 9) and haemorrhages are the most commonly reported retinal findings, but retinal and macular oedema, microaneurysms and occlusive retinal vasculitis have also been noted.

Several reports indicate a role of antiphospholipid antibodies in retinal and choroidal vasculopathy, although their precise role in this process is uncertain. In addition, neuro-ophthalmological manifestations like optic neuritis, ischaemic optic neuropathy, and chiasmal and retrochiasmal problems such as internuclear ophthalmoplegia, have been seen. The possibility of a false diagnosis of multiple sclerosis due to the presence of internuclear ophthalmoplegia and optic neuritis should be kept in mind.

If retinal involvement is present, aggressive treatment is required owing to high morbidity (Soo et al, 2000*).

3.2.2.2 Systemic sclerosis

The main ocular feature in this disease entity is KCS and is seen in about 40–70% of patients with systemic sclerosis. In addition to the inflammatory changes of the lachrymal gland, patients will have fibrotic changes of the eyelids, the conjunctiva and the lachrymal ducts. Episcleritis is present in 5% of patients. Retinal involvement occurs in about 50% of patients and is manifested most often as a mild retinopathy with cotton wool spots and intraretinal haemorrhages.

3.2.2.3 Primary Sjögren's syndrome

Primary Sjögren's syndrome is characterised by an active inflammatory stage followed by a chronic stage. The KCS is probably due to residual lachrymal gland damage from the initial active process. Corneal ulceration and perforation due to KCS is described in patients with Sjögren's syndrome.

In addition to the treatment noted above, oral pilocarpine may improve the symptoms of dry eyes and dry mouth.

3.2.2.4 Dermatomyositis

The hallmark of ocular involvement is the heliotrope rash affecting the eyelids. In addition, episcleritis, scleritis, keratitis, anterior uveitis and retinal vasculitis rarely occur.

3.2.3 Vasculitides

3.2.3.1 Large vessel vasculitis

Giant cell (temporal) arteritis. It is important to note that ocular involvement is not uncommon in the absence of systemic signs and symptoms. Hayreh and co-workers reported that about 50% of their patients had both ocular and extraocular symptoms, while 21.2% presented with ocular involvement only (Hayreh et al, 1998*).

Patients may complain of pain, visual loss, diplopia and amaurosis fugax. The most severe ocular involvement of giant cell (temporal) arteritis is sudden loss of vision from ischaemic optic neuropathy (in 81–94% of these patients) or central retinal artery occlusion. Both manifestations may be irreversible and bilateral. The reported prevalence of vision loss ranges from 15% to 50%.

Diagnosis is confirmed with biopsy of the temporal artery and raised titres of erythrocyte sedimentation rate and C-reactive protein. Biopsy will remain positive for up to 2 weeks after starting glucocorticoid treatment. Immediate treatment with intravenous glucocorticoids is quickly effective and prevents permanent visual loss.

Takayasu's arteritis. Up to 40% of patients with Takayasu's arteritis have microaneurysms and arteriovenous anastomoses due to underlying retinal vasculitis identified by fluorescein angiography. Neovascularisations and consequent vitreous haemorrhage can occur secondary to retinal ischaemia.

3.2.3.2 Medium vessel vasculitis

Polyarteritis nodosa. An ocular manifestation is present in 10–20% of patients with polyarteritis nodosa and includes episcleritis, scleritis (diffuse, nodular or necrotising), peripheral ulcerative keratitis (which may be the initial presenting symptom) and inflammation of the orbital vessels. The last of these may lead to bilateral orbital pseudotumour, resulting in exophthalmos.

Manifestation in the posterior eye segment is frequent in polyarteritis nodosa and choroidal involvement is the most common. Also, direct involvement of the retinal vasculature (arteries) can cause occlusive retinal vasculitis, cotton wool spots and central retinal artery occlusion, whereas vasculitis of the optic nerve vasculature can lead to papilloedema, papillitis and optic nerve atrophy. The described retinal findings may also occur secondary to systemic hypertension or renal disease. In addition, neuro-ophthalmological manifestations can occur and include extraocular muscle palsies, amaurosis fugax, homonymous hemianopia and nystagmus.

When the eye is involved, immediate treatment with systemic glucocorticoids and/or immunosuppressant agents is required.

Kawasaki's disease. Anterior uveitis occurs in up to 66% of patients, mostly in the first week of disease manifestation. Other ocular involvement includes conjunctival hyperaemia, keratitis, papilloedema and rarely, retinal vasculitis.

3.2.3.3 Small vessel vasculitis

Churg–Strauss syndrome. Involvement of the anterior eye segment may present as granulomatous nodules of the conjunctiva and the eyelids, episcleritis and marginal corneal ulcer. Panuveitis, retinal vasculitis with branch retinal artery occlusion and optic disc vasculitis have been described as manifestations in the posterior eye segment. Neuro-ophthalmological involvement may be present as ischaemic optic neuropathy, amaurosis fugax and cranial nerve palsies. In most cases, the intraocular inflammation resolves after systemic glucocorticoid therapy.

Cutaneous leucocytoclastic vasculitis. Ocular involvement is rare. In the literature only a few cases with anterior uveitis, panuveitis, multifocal chorioretinitis and vasculitis have been reported. Treatment with systemic glucocorticoids is sufficient to control the ocular disease in most cases.

Essential cryoglobulinaemic vasculitis. Slit lamp examination may reveal corneal deposits of cryoglobulin. Therapeutic options include superficial keratectomy and excimer laser phototherapeutic keratectomy. In addition, a Purtscher-like retinopathy (retinopathy of the central retina after thoracic trauma with cotton wool spots, exudates, haemorrhages and engorgement of retinal veins), retinal vasculitis and serous retinal detachment have been reported.

Henoch–Schönlein purpura. Manifestations in the eye are rare. Only a few cases have been reported, and they include episcleritis, keratitis and anterior uveitis.

Microscopic polyangiitis. Ocular involvement is rare, but in patients with microscopic polyangiitis eye inflammation may be the first presenting symptom and prompts the patient to seek an appointment with the

ophthalmologist. Most often these presenting symptoms are nodules of the eyelids and of the conjunctiva with central ulceration or peripheral ulcerative keratitis.

Wegener's granulomatosis. Ocular manifestations are seen in 29–52% of patients, 15% of whom have already presented with ocular disease. In principle, Wegener's granulomatosis can affect any ocular or periocular structure, but orbital involvement is most common (50%). As a consequence, secondary changes such as compressive optic neuropathy, exophthalmos and exposure keratopathy may be seen. Other complications, which occur in about 25% of patients, are dacryoadenitis, dacryocystitis and occlusion of the nasolachrymal duct. Owing to inflammation of the lachrymal gland, dry eye syndrome is present in about 50% of patients and episcleritis, scleritis and marginal corneal ulceration may be present in an additional 25%. Patients with scleritis, in particular, demonstrate the necrotising or posterior type, which both have a bad prognosis and require immunosuppressive therapy. Occlusive retinal vasculitis, retinitis, choroiditis and ischaemic optic neuritis have also been described. Neuro-ophthalmological involvement may result in Horner's syndrome, cranial nerve palsy and cavernous sinus thrombosis.

3.3 Autoimmune diseases with secondary vasculitis

3.3.1 Relapsing polychondritis

Ocular manifestations occur in up to 59% of patients with RP, the most common being scleral involvement, which has a frequency of 41%. In these patients all types of scleral inflammation (recurrent episcleritis, necrotising and posterior scleritis) may be seen; anterior diffuse scleritis has most often been reported. Other eye manifestations include anterior uveitis (25%), keratitis (10–15%) and ischaemic fundus changes, such as cotton wool spots, intraretinal haemorrhages, branch or central retinal vein occlusions and ischaemic optic neuropathy (Rucker and Ferguson, 1965*).

3.3.2 Cogan's syndrome

The typical ocular manifestation consists of bilateral non-syphilitic interstitial keratitis with patchy vascularisation of the middle and deep corneal stroma. Other reported manifestations are eyelid oedema, conjunctival injection, scleritis and mild iritis.

3.3.3 Sarcoidosis

Eye involvement occurs in 25–30% of patients with sarcoidosis. In 50% of these patients inflammatory changes of the lachrymal glands are present. Anterior uveitis can be seen in 20–70% of patients with a possible occurrence of iris granulomas. Changes in the posterior eye segment (14–43%) include retinal vasculitis with typical 'candle wax' phenomena of the retinal vessels and often a multifocal choroiditis (white (inflammatory)

spots on the retina) will occur. In about 10–17% of patients with sarcoidosis, intermediate uveitis has been reported in combination with retinal periphlebitis (especially venous sheathing).

3.4 Pseudovasculitides

3.4.1 Angioid streaks

Angioid streaks are a generalized disorder of the Bruch membrane, appearing as bilateral, narrow, irregular lines deep to the retina configured in a radiating fashion from the optic disc. They are mainly seen in Pseudoxanthma elasticum, Paget's disease and Ehlers–Danlos syndrome. However, no systemic disease will be diagnosed in 50% of these patients.

The ruptures in the Bruch membrane results in angioid streaks resembling choriocapillaries. The development of subretinal membranes, with a pronounced impairment of visual function, is possible when the defects reach the macular region. Treatment with photocoagulation is in most cases unsatisfactory.

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SUMMARY POINTS - Eye involvement

- Patients with rheumatic disease often have keratoconjunctivitis sicca, keratopathy, episcleritis/scleritis, uveitis anterior or posterior and retinal vasculitis.
- The most severe manifestations affecting visual acuity are uveitis and retinal vasculitis.
- Eye involvement may be the first symptom of rheumatic disease and requires intensive diagnostic and often systemic therapy.
- Biologic agents have really improved the outcome of ocular manifestations in rheumatologic diseases

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module

EULAR on-line course on Rheumatic Diseases

Behçet's disease, relapsing polychondritis, and eye involvement in rheumatic disease

David Saadoun, Cloé Comarmond, Nicole Stübiger

A previous version was co-authored by Hasan Yazici, Izzet Fresko, Nicole Stübiger

IN-DEPTH DISCUSSION I

Cardiovascular involvement in Behçet's disease

Vascular involvement is a common complication of Behçet's disease (BD) and affects up to 40% of BD patients. These complications worsen the prognosis of BD. The concept of vasculo-Behçet has been adopted for cases in which vascular complications dominate the clinical features. Vascular manifestations affect particularly young men, during the first years following onset of the disease. Venous involvement outnumbers arterial disease (approximately 85% vs 15%) (1, 2, 3). Treatment is based on corticosteroids and immunosuppressive drugs. The use of anticoagulation in venous thrombosis is still controversial.

Venous involvement

Venous complications are the most frequent vascular complications, affecting 14 to 40% of BD patients. Superficial and deep lower limb thrombosis is the most frequent venous complications but one third of venous thrombosis concern large vessels (such as cerebral venous thrombosis, pulmonary embolism, and inferior or superior vena cava).

Deep vein thrombosis (DVT) of the legs makes up 70 % of all vascular manifestations and is observed as an acute or subacute swelling of the involved extremity (4). Pain usually accompanies swelling while, as a novel observation venous claudication, manifested as difficulty in walking due to venous stasis, can also be seen (5). It is bilateral in 60% of the patients. Popliteal and superficial femoral veins, tributary veins of the calves, common femoral, external iliac and common iliac veins are diseased in decreasing order (6). A post-thrombotic syndrome characterized by stasis dermatitis and leg ulcerations is not unusual in the long term.

Less common forms of venous involvement are superior and inferior vena caval disease, Budd-Chiari syndrome and cerebral venous thrombosis (7). Superior vena caval disease leads to cyanosis and swelling of the face and upper extremities whereas inferior vena caval involvement causes venous collaterals in the abdomen, leg swelling and leg ulcers. The former has a more favourable prognosis. The Budd-Chiari syndrome is rare (1.5-3.2%). It is, however, the most lethal pathology of the venous spectrum causing a one year mortality of approximately 50% (8). Cerebral venous thrombosis accounts for 17-30% of central nervous system involvement and is usually manifested as headache and papilloedema; findings of intracranial hypertension (9, 10). It responds well to pulses of methylprednisolone.

Like all serious manifestations of BS, males have a higher risk of having venous disease compared to women (40% vs 5%) (1, 2, 3, 11). The vascular events usually occur within 5 years of disease onset although venous disease as the initial manifestation of BS is also a possibility (1, 3). Recurrence is common (23% after 2 years and 38% after 5 years in a retrospective study) and coexistence with arterial involvement is frequent (4).

The management of venous disease is controversial. Some groups use routine anticoagulation whereas others utilize immunosuppressives. A combination of the two approaches is also occasionally advised (12) The absence of embolisation, the lack of a consistent coagulation abnormality (13,14) coupled with a tightly

adherent thrombi to the vessel wall suggesting an inflammatory pathology (15) favours the use of immunosuppressives but controlled data are lacking.

Arterial involvement

Although not very frequent (15% of all vascular involvement in BS, range 5-18%) (16), arterial involvement is responsible for most of the serious morbidity and mortality in BS. It is mostly associated with aneurysms and less frequently with occlusions of the major arteries although combinations are also possible (6, 17). Recurrences are observed (18).

One of the main patterns of arterial involvement is aneurysms of the peripheral arteries. They are seen in decreasing order of frequency in the abdominal aorta, pulmonary, femoral, popliteal and carotid arteries (1, 16, and 19).

Fever, fatigue and an increased acute phase response characterize the early stages of these aneurysms. With the exception of those in the abdominal aorta, they usually present as a painful, pulsatile hyperaemic mass. Abdominal aortic aneurysms, on the other hand, cause non-specific findings such as back or flank pain or constipation necessitating a high degree of suspicion (20).

Peripheral arterial aneurysms should be managed surgically since they do not regress spontaneously. Ligation is the preferred approach if the circulation is adequate and graft replacement with synthetic grafts if it is not sufficient (21). Immunosuppressive therapy should be given before surgery especially in cases in which the disease is active (22).

The second important pattern of arterial involvement is the pulmonary arterial aneurysms (PAA). They are observed in around 5% of the patients, are usually seen at an earlier stage than other types of arterial involvement (mean age 31 years compared to 39 years) and are the leading cause of mortality in BS (3, 4). A literature review has shown that 89% of the patients with PAA are males (23). The aneurysms, usually bilateral, develop preferentially in the large and medium sized pulmonary arteries (24). Thrombi within the aneurysms are also common.

PAA usually present with haemoptysis, accompanied by chest pain, cough and dyspnoea in varying degrees. Fever and fatigue may also be seen. Coexisting venous thrombosis is present in 81% of the patients with PAA (25) and intracardiac thrombus formation and arterial disease in other sites may additionally complicate the clinical picture (26).

A plain chest radiograph usually shows round hilar or peripheral opacities (27). Spiral CT scan of the lungs shows the aneurysms and the accompanying thromboses in most of the cases and may also be used in monitoring therapy (28). Parenchymal areas of consolidation probably due to ischemic areas caused by

thrombi in the minor pulmonary arteries may accompany or precede the aneurysms (29). Multi slice CT and MR angiography are other imaging alternatives (30). Technetium-99m-hexamethylpropylene amine oxime lung scintigraphy has also been proposed as a tool (31). Pulmonary angiography should not be performed since it has the risk of causing new aneurysms and thromboses at the puncture site.

The presence of haemoptysis may lead to the misdiagnosis of tuberculosis, a condition endemic in BS prevalent geographies. The abundance of the haemoptysis in pulmonary arterial aneurysms and its characteristic radiological findings differentiate the two conditions. The frequent association with deep venous thrombosis of the legs also causes confusion with thrombo-embolic disease; sometimes leading to unnecessary and dangerous anti-coagulation. The occasional presence of perfusion defects in ventilation perfusion scintigraphies of the lungs adds to the dilemma. The presence of aneurysms in imaging studies and the other manifestations of the syndrome aid in the differential diagnosis (23, 32).

The medical treatment of pulmonary arterial aneurysms is empirical. Three pulses of 1 gr of methylprednisolone followed by 1 mg/kg/day of oral prednisolone and monthly boluses of 1gr of intravenous cyclophosphamide is what we usually prefer. The steroid dose is tapered according to the clinical response and is discontinued in 1 year. The cyclophosphamide intervals are switched to every second month after one year and all therapy is discontinued at the end of 2 years. The whole cycle is repeated in case of a relapse. Anecdotal reports of successful therapy with infliximab have also been reported (33). Surgery is not satisfactory due to the multiple nature of the aneurysms (34).

The prognosis of pulmonary arterial aneurysms has improved in recent years. A one year mortality of 50% was reported 15 years ago (30) that decreased to 15% in 10 years, probably due to earlier diagnosis and treatment (25).

Cardiac involvement

Cardiac complications occur in up to 6% of BD patients. Cardiac abnormalities include pericarditis, endocardial lesions (aortic regurgitation and less often mitral insufficiency), myocardial lesions (myocardial infarction, myocarditis and endomyocardial fibrosis) and intracardiac thrombosis (right ventricle and atrium). Coronary lesions complicated to myocardial infarction are the most severe cardiac complications. The prognosis of cardiac involvement in BD is poor and improves with oral anticoagulation, immunosuppressive therapy, and colchicine (35).

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module

EULAR on-line course on Rheumatic Diseases

Behçet's disease, relapsing polychondritis, and eye involvement in rheumatic disease

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A previous version was co-authored by Hasan Yazici, Izzet Fresko, Nicole Stübiger

IN-DEPTH DISCUSSION II

Biotherapy in Behçet's disease

BD significantly increases morbidity and mortality. The leading cause of morbidity in BD is eye involvement with the potential threat of visual loss. Male sex, arterial involvement, and the number of flares are associated with mortality in BD (1).

Over the past year substantial advances have been done in the understanding of the genetic and immunology of BD. BD is at the crossroad between autoimmune and autoinflammatory syndromes. The pathogenesis of BD is still unknown, but major determinants of the genetic and immune system abnormalities have been reported recently. Triggering infectious factors are supposed to participate in the outbreak of BD in genetically predisposed patients. Two recent large genome-wide association study (GWAS) conducted in Turkey and Japan reported association between single nucleotide polymorphism (SNP) of interleukin (IL)-10 and IL-23R/IL-12RB2 genes and BD. New insights into the perturbations of T cell homeostasis of BD recently emerged. We have demonstrated the promotion of Th17 responses and the suppression of regulatory T cells (Tregs) that were driven by interleukin (IL)-21 production and that correlates with BD activity. Inflammatory cells within BD inflammatory lesions included mostly neutrophils, Th1 and Th17 cells, and cytotoxic CD8+ and $\gamma\delta$ T cells. Altogether, the recent progresses in the knowledge of BD pathogenesis pave the way for innovative therapy. Therapeutic management of BD depends on the clinical presentation and organ involved (2, 3). Although colchicine, nonsteroidal anti-inflammatory agents and topical treatments are often sufficient for mucocutaneous and joint involvement, more aggressive approach with immunosuppressive agents is warranted for severe manifestations such as posterior uveitis, retinal vasculitis, vascular, neurological and gastrointestinal involvement. However, some patients still have refractory disease, relapse, sight threatening eye disease, or irreversible organ damage. Recent improvements in the understanding of the pathogenic mechanisms have led to the identification of potential targets and future therapies for BD. In contrast to current non-specific immunosuppressive agents mainly used empirically, the emergence of biotherapies provides the possibility of interfering with specific pathogenic pathways. Novel targeted biotherapies might be used in the future for BD.

Biotherapies in BD: new therapeutic options

Proinflammatory cytokines, B- and T-cells play an important role in the pathogenesis of BD (4–7). Therefore, immunomodulatory approaches with biotherapies such as modulation of NF κ B expression, inhibition of TNF α , IL-1 or IL-6 signalling, B- or T-cells depletion has been proposed as therapeutic option for BD. In patients presenting with severe BD disease, more targeted therapies offer the potential advantage of faster delay of action as compared the generally slow response to conventional immunosuppressive drugs.

Interferon α

Since the first report of therapeutic effect in three cases of BD treated by IFN α in 1986, the efficacy of IFN α has been well established, especially in sight-threatening ocular manifestations (8–12). In 2004, Kötter and al

reported in a large literature review that 94% of patients with ocular BD exhibited partial or complete remission within 2 to 4 weeks after onset of IFN α (13). Intermediate to high IFN α dosages (18 to 126 x10⁶ UI/week) were more effective than low-dose regimens (5 to 9 x10⁶UI/week) and led to up to 56% long-term remissions after discontinuation of IFN α . IFN α has dramatically improved the long-term visual prognosis in patients with severe ocular BD (11, 12, and 14). In 53 patients followed during a median of 6 years (range 2–12.6 years), 89% were in remission after 2 years of IFN-alpha therapy and ocular BD was still in remission in 50% of the patients 46 months after cessation of the first IFN course (14). Compared with TNF alpha antagonists, IFN α offers the advantage that even after cessation of treatment a high percentage of patients remain in remission. Currently, the use of TNF α -antagonists is only recommended in patients who are intolerant or with ocular manifestations resistant to IFN α . Regarding the use of infliximab for ocular involvement resistant to IFN α , remission was observed in 18 of 20 patients (15–22). Interferon α is generally administered subcutaneously, with a dose between 3 and 9 million units, most often 3 times weekly. To avoid an antagonistic effect of IFN α which works via NF κ B, corticosteroids (which blocked NF κ B) need to be use at the lowest dose as possible when associated to IFN α (14). Furthermore, an open Turkish trial of AZA plus IFN α in 10 male BD patients with retinal involvement had to be stopped because of additive hematologic toxicities (23). Pain and duration of oral ulcers, number of pustular papules, as well as frequency of genital lesions, erythema nodosum-like lesions and thrombophlebitis are also significantly reduced in patients receiving IFN α compare to those receiving placebo (9). In an open trial including 50 patients treated by IFN α for refractory ocular BD (24), IFN α was effective on ocular manifestation with a response rate of 92%. This treatment was also beneficial for the extraocular manifestations of the disease, i.e. genital ulcerations, arthritis, and skin lesions, although less so for oral aphthous ulcers (24). A case series of 2 male adolescents reports that IFN α is also effective for refractory juvenile BD with CNS involvement (25). Thus, IFN α is not only an alternative treatment for uveitis but also for extra-ocular manifestations of BD. Adverse effects are common, especially the flu-like syndrome that occurs in almost all patients but it is easy to prevent with paracetamol. In addition, depression, asthenia, cytopenia and in a lesser extent, psoriasis and sarcoidosis can be induced or worsened. However, IFN α is the one of the only therapy that allows sustained ocular remission after discontinuation of the treatment.

Thalidomide

Thalidomide is also an immunomodulatory drug by suppressing TNF α -induced NF- κ B activation and ATP-induced IL-1 β secretion (26). Modulating the activity of NF- κ B, thalidomide can up-regulate the expression of downstream genes involved in the pathophysiology of BD. Thalidomide has reported efficacy in treating patients with mucocutaneous lesions refractory to treatment with colchicine. However, teratogenicity, neurotoxicity, and constipation restrict usage of this drug (27, 28).

Inhibition of cytokine signalling

Anti-TNF α

TNF α -antagonists are increasingly used for patients with BD, especially infliximab and in a lesser extent adalimumab (29–32). We find no report with certolizumab in BD but the first case of BD with refractory uveitis treated by golimumab has been recently reported (33). Nevertheless, only 1 randomized, double-blind, placebo-control trial assessed the effect of etanercept on mucocutaneous manifestations and arthritis (34). Among anti-tumor necrosis factor (anti-TNF) agents, infliximab has been used in more than 300 cases, mainly for refractory ocular BD and with 89% of improving patients who were resistant to conventional therapies (15, 19, 31, 35–41). The relapse rate of uveitis and daily corticosteroid doses were significantly lower during infliximab treatment (42) in patients with BD in whom uveitis was resistant to combination therapy with corticosteroids, azathioprine, and cyclosporine (38, 43). In 2004, Giasanti and al reported a case of retinal neovascularization caused by panuveitis in BD that completely regressed 8 months after the first anti-tumor necrosis factor treatment and with six infusions of infliximab (44). Complete remission were observed in 83% and 82% of patients with gastrointestinal and CNS involvement, respectively (18, 45). Rapid onset of action and steroid-sparing effect characterize the efficacy of TNF α -antagonists, mainly reported in patients resistant to conventional therapies (19, 36–38, 40, 46–49). The switching of anti-TNF- α agents after a failure of a first anti-TNF- α agent can be an alternative therapeutic option but the two monoclonal antibodies, infliximab and adalimumab, seem more effective than the soluble antibodies, etanercept notably for uveitis (50, 51). However, repeated long term infusions are warranted to sustain remission (usually at week 0, 2, 4, then at interval 6 to 8 weeks) as TNF α -antagonists are likely suspensive. Other important issue is the use of associated immunosuppressive drug (CsA, AZA or MTX) in association with TNF α -antagonists that could be not only prevent the production of TNF α antibodies but also could be more effective compared to monotherapy (31, 52).

Anti-IL1

IL-1 has been found elevated in sera of patients with BD (53). Anakinra is a recombinant, non-glycosylated human IL1 receptor antagonist and was shown effective in case report of BD patient refractory to conventional treatments (54). More recently, an open-label pilot study show that XOMA 052 (gevokizumab), a recombinant humanised anti-interleukin 1 β antibody, was well tolerated and resulted in a rapid onset and sustained reduction in intraocular inflammation in seven patients with resistant uveitis and retinal vasculitis. Complete regression of intraocular inflammation was achieved in 4-21 days (median 14 days). All patients except one were in remission after 28 days. Moreover, the beneficial effect was observed despite discontinuation of immunosuppressive agents and without the need to increase corticosteroid dosages (55). Canakinumab, a human monoclonal antibody targeted at interleukin-1 beta, has been used successfully in 2 patients with

resistant BD (56, 57). Similarly to switching of anti TNF- α agent, one of the patient with resistant ocular BD including failure of anakinra, responds after to canakinumab (56).

Anti-IL6

The level of IL6 is associated with disease activity according to several studies (58, 59). Tocilizumab, a humanized anti-interleukin 6 receptor antibody, is currently approved only for the treatment of moderately to severely active rheumatoid arthritis refractory to one or more anti-TNF drugs. It may constitute a therapeutic option for refractory Behçet's disease. Three resistant cases of BD with recurrent meningo-encephalitis or uveitis have been successfully treated with tocilizumab (60–62).

Lymphocytes-targeted therapies

Anti-CD20

Rituximab is an anti-CD20 antibody, which depletes B-lymphocytes. Rituximab, given in two 1000-mg courses (15-day interval), was found effective in severe ocular lesions including retinal vasculitis due to Behçet's disease, resistant to prednisolone, azathioprine and etanercept (63,64).

Anti-CD52

The predominant effect of anti-CD52 antibody therapy (alemtuzumab) is T-cell depletion. Alemtuzumab, given in one course of 134 mg, can induce sustained treatment-free remission in BD poorly controlled by conventional therapy (65, 66). Among 18 patients with orogenital ulcerations (100%), ocular involvement (66.7%) and/or neurological involvement (72%), 72% had entered remission and 33% could discontinue their treatment.

Anti-CD25

Daclizumab, a humanized monoclonal antibody against CD25, was not superior to placebo in a randomized, placebo-controlled, double-blind trial including 17 patients with severe ocular BD (67).

Biotherapies in the therapeutic strategy of BD

During last decades, therapeutic strategy in BD becomes more intensive in terms of immunosuppressive use. Although novel biotherapies currently available appear highly effective in uncontrolled studies and with rapid onset of action in different clinical situations, no consensus exists about their use in BD. Refractory manifestations that may warrant biotherapy include severe ocular, CNS, and vascular involvement and some severe or refractory gastrointestinal, joint, and mucocutaneous involvements. In clinical practice, colchicine is the most frequently and widely used drug for oral ulcers, genital ulcers, papulopustular lesions and arthralgias.

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Polymyalgia rheumatica and giant cell arteritis

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LEARNING OBJECTIVES

- Describe the epidemiology and the association between polymyalgia rheumatica (PMR) and giant cell arteritis (GCA)
- Describe the mechanisms involved in the pathogenesis of PMR and GCA
- Correctly diagnose PMR and GCA on the basis of their common and less common clinical manifestations. 2012 EULAR - ACR classification criteria, overlap between PMR, GCA and Inflammatory arthritis
- Define the role of laboratory investigations and imaging studies in the diagnosis of PMR and GCA and the role of histology in GCA
- Distinguish PMR from other inflammatory disorders that may present with clinical features mimicking PMR
- Treat patients with PMR and GCA, 2015 EULAR ACR treatment guidelines for PMR

Polymyalgia rheumatica (PMR) is an inflammatory disorder characterised by pain, aching and morning stiffness in the shoulder girdle and often in the pelvic girdle and neck. Giant cell arteritis (GCA), also known as Horton or temporal arteritis, is a vasculitis mainly involving the large and medium arteries, especially the branches of the proximal aorta, including extracranial branches of the external carotid artery such as the temporal arteries (Dejaco et al 2016; Salvarani et al, 2002; Weyand and Goronzy, 2003; Gonzalez-Gay et al, 2006; Salvarani et al, 2008b; Masson, 2012*; Kermani and Warrington, 2013; Weyand and Goronzy, 2014*). Epidemiological studies suggest that PMR and GCA occur together more often than expected by chance alone. Both disorders almost exclusively affect patients aged ≥ 50 years. A systemic inflammatory response and a marked response to glucocorticoid therapy are typical features of PMR and GCA, although in GCA higher doses of glucocorticoids are required. Classically, PMR and GCA generally require treatment for 18 – 24 months. However, over 50% of patients have a chronic relapsing course and may require glucocorticoids for several years.

Overall, neither disease causes excess mortality, but significant morbidity and even increased mortality in some sub groups (such as patients with irreversible sight loss) is seen, mainly resulting from glucocorticoid-related adverse reactions. Principal glucocorticoid side effects—for instance, diabetes, hypertension, hyperlipidaemia and osteoporosis, should be monitored and measures taken to prevent and manage them.

The mainstay of the treatment of GCA is glucocorticoid therapy.

However, three phenotypes should be distinguished: cranial GCA, large vessel GCA and isolated PMR.

Symptoms of cranial GCA may consist of isolated temporal headache without evidence of ischemia.

Complicated GCA is defined by the presence of ischemic lesions involving the optic nerve and disc or retina (ciliary arteries and central retinal artery), which carries a heavy burden of permanent blindness; or involving the aorta and branches of the aortic arch (aortitis, aneurysm, dissection, stenosis and occlusion), or other arteries such as the vertebral or upper-limb arteries. All patients with more than low probability of suspicion for GCA require glucocorticoid treatment and fast track specialist assessment and appropriate intervention should be started on the same day.

1 Classification criteria for PMR

One of the challenges in the diagnosis of PMR is the lack of any diagnostic tests that are specific for this condition. Additionally, several other conditions can mimic this diagnosis or present with polymyalgic symptoms.

Several diagnostic criteria for PMR have been proposed based on retrospective clinical series (Bird *et al.* 1979; Jones and Hazleman, 1981; Chuang *et al.* 1982; Healey, 1984). Most of these include an age cut off, presence of bilateral shoulder girdle and hip girdle pain, morning stiffness and elevated markers of inflammation. Due to lack of any specific diagnostic tests for PMR, clinicians often use a prompt response to GCs as a confirmation of

the diagnosis. However, PMR can be mimicked by many other conditions, many of which also respond initially to glucocorticoids. Additionally, only 55-60% of patients with PMR respond completely to low dose GCs even after 3–4 weeks of therapy. Therefore GC responsiveness is no longer regarded as a cardinal feature of PMR [Hutchings *et al.* 2007; Dasgupta *et al.* 2012a, 2012b].

Given the diagnostic difficulty recent Classification criteria have been proposed by the European League against Rheumatism and the American College of Rheumatology (EULAR/ACR) as a research tool to identify patients with PMR [Dasgupta B *et al* 2012].

Consensus derived candidate criteria were evaluated in a 6-month prospective inception cohort study using the single eligibility criterion of new onset bilateral shoulder pain. The study recruited 125 patients with new-onset PMR and 169 non-PMR comparison subjects with conditions mimicking PMR. Potential criteria were assessed for their ability to discriminate PMR from other conditions and a scoring algorithm was developed. New-onset bilateral shoulder pain in subjects aged 50 years or older and elevation of CRP and/or ESR are regarded as essential items for classification as PMR. (Dasgupta B *et al* 2012).

The EULAR/ACR criteria include three required and four additional criteria. A scoring algorithm was developed with four additional criteria items (see table 1).

A score of 4 or greater had 68% sensitivity and 78% specificity for discriminating all comparison subjects from PMR. The specificity was higher (88%) for discriminating shoulder conditions from PMR and lower (65%) for discriminating RA from PMR. The positive predictive value was 69% and the negative predictive value was 77%

Table 1. The EULAR/ACR criteria

Required Criteria = 3	Additional criteria
age ≥50 years	morning stiffness ≥45 minutes = 2 points
bilateral shoulder aching	Pain or limited range of motion at the hip= 1 point
abnormal CRP or ESR	Absence of RF or anti-CCP = 2 points
	Absence of peripheral joint pain = 1 point

One study compared the performance of the EULAR/ACR criteria with other previously published classification criteria in 136 patients with PMR and 149 controls with rheumatoid arthritis and other inflammatory arthritides [Macchioni P 2014].

The EULAR/ACR criteria were the most sensitive (93 percent), although they were not the most specific (82 percent). In addition to clinical features the inclusion of shoulder and hip ultrasound in the EULAR/ACR criteria increased specificity to 91 percent, see Table 2.

Table 2: 2012 EULAR ACR Classification criteria

Polymyalgia rheumatica classification criteria: scoring algorithm. Required criteria: age \geq 50 years, bilateral shoulder aching, and abnormal CRP and/or ESR^a

	Points without US 0–6	Points with US ^b 0–8
Morning stiffness >45 minutes	2	2
Hip pain or limited range of motion	1	1
Normal RF or ACPA	2	2
Absence of other joint involvement	1	1
At least 1 shoulder with sub deltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) AND at least 1 hip with synovitis and/or trochanteric bursitis	Not applicable	1
Both shoulders with sub deltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	Not applicable	1

^a A score of 4 or more is categorized as PMR in the algorithm without US and a score of 5 or more is categorized as PMR in the algorithm with US.

^b Optional ultrasound criteria.

Ultrasound was performed in 120 PMR subjects, 154 comparison subjects (46 with RA and 47 with shoulder conditions), and 21 additional controls who did not have shoulder conditions. Patients with PMR were more likely to have abnormal ultrasound findings in the shoulder (particularly sub deltoid bursitis and biceps tenosynovitis), and somewhat more likely to have abnormal findings in the hips than comparison subjects as a group. PMR could not be distinguished from RA based on ultrasound, but could be distinguished from non-RA shoulder conditions and subjects without shoulder conditions. Adding ultrasound criteria of either both shoulders and/or a shoulder and hip showing typical abnormalities, an algorithm score of 5 or more has 66% sensitivity and 81% specificity for discriminating all comparison subjects from PMR. Ultrasound abnormalities at presentation were also predictive of a good steroid response.

In the absence of alternative diagnoses, a score of 4 or greater (without ultrasound), or 5 or greater (with ultrasound) is indicative of PMR. Patients with a score of less than 4 (based on clinical plus laboratory criteria) cannot be considered to have PMR and need further diagnostic workup. Ultrasound improves the specificity of PMR diagnosis, and shows particularly good performance in differentiating PMR from non-inflammatory conditions and thus is a recommended investigation for PMR.

2 Classification criteria for GCA

Criteria for the classification of GCA were developed by the ACR in 1990, Table 3 (Hunder et al, 1990). They were designed to differentiate GCA from other vasculitides and are thus not useful for diagnosing GCA in individual cases in which GCA must also be differentiated from non-vasculitic diseases. The recent use of imaging has increased our understanding that GCA is a spectrum of overlapping phenotypes and it encompasses classical cranial arteritis and extra – cranial GCA, also referred to as large vessel GCA (GCA- LVV). Temporal artery biopsy (TAB) remains the ‘gold standard’ for the diagnosis of GCA, although about 10–20% of TABs in patients with GCA are negative. Imaging methods are increasingly used for the diagnosis of GCA (Dejaco C 2011). When possible, a TAB or ultrasound scan should be performed before starting treatment. However, TAB specimens may show arteritis after more than 2 weeks of glucocorticoid therapy.

Table 3: American College of Rheumatology classification criteria for giant cell arteritis

Original Criteria	Additional Suggested criteria
Age at disease onset ≥50 years: New headache: new onset or new type of localised pain in the head	Visual symptoms, sight loss, PMR, Constitutional symptoms, Jaw and or claudication
Temporal artery abnormality (temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis)	And or extra cranial arteries, decreased pulsation, bruits of extra – cranial arteries unrelated to arteriosclerosis
ESR ≥50 mm/hour	CRP > 10 mg/L
Abnormal artery biopsy: biopsy specimen with artery showing vasculitis characterised by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells	And or abnormal imaging (US, MRI and or FDG PET)
<i>GCA is diagnosed if at least three of these five criteria are present.</i>	

3 Epidemiology

GCA is the most common type of vasculitis in Europe and North America, especially in people aged >70 years (Salvarani et al, 1995a; Salvarani et al, 1995b; Gonzalez-Gay et al, 2009b*; Gonzalez-Gay et al, 2010a). It mainly affects white people and almost exclusively occurs in subjects aged >50 years. Incidence increases with age and peaks in the 70–79-year-old age group. Women are affected two to three times more commonly than are men. However, a lower ratio of women to men was seen in Israel and Southern Europe (Gonzalez-Gay et al, 2009a*). It is likely that the occurrence of GCA will increase due to an aging population. The projected world-wide disease burden of GCA by 2050 is more than 3 million, and about 500,000 people will become visually impaired if the treatment is not adapted (De Smit E 2015).

The incidence of GCA increases with latitude in the Northern hemisphere (Baldursson et al, 1994). The highest incidence rates are reported in Scandinavian countries and in North American populations of Scandinavian descent (Franzen et al, 1992; Gran et al, 1997; Haugeberg et al, 2000). In these regions, the annual incidence is generally $>17/100\ 000$ population aged ≥ 50 years. However, the incidence of GCA is $<12/100\ 000$ population aged ≥ 50 years in Southern European and Mediterranean countries (Bas-Lando et al, 2007). A lower incidence of GCA was reported in Afro-American individuals from Tennessee (Smith et al, 1983). A very low annual incidence of GCA was reported in Turkey ($1.13/100\ 000$ people aged ≥ 50 years) (Pamuk et al, 2009). GCA was also found to be very uncommon in an Asian population: a nationwide survey in 1997 showed an extremely low prevalence of GCA in Japan of $1.47/100\ 000$ population aged ≥ 50 years (Kobayashi et al, 2003). A very low incidence of biopsy-proven GCA among Alaska natives ($\sim 1/100\ 000$ in those aged ≥ 50 years) was described (Mader et al, 2009).

It is possible that higher physician awareness may account for the progressive increase in GCA reported in different parts of the world (Nesher et al, 1996). In this regard, a reappraisal of the incidence of biopsy-proven GCA in the Lugo region of north-western Spain over the period 1981–2005 showed a progressive increase in the incidence of GCA (Gonzalez-Gay et al, 2007b).

As reported for GCA, the incidence of PMR has been found to be higher in subjects of Scandinavian background. Thus, the annual incidence of PMR in Ribe County, Denmark, over the period 1982–1985 was $68.3/100\ 000$ population aged ≥ 50 years (Boesen and Sorensen, 1987). Similarly, the annual incidence of PMR in Göteborg, Sweden, between 1985 and 1987 was $50/100\ 000$ population aged ≥ 50 years. Also, in Olmsted County, Minnesota (USA), where the population has a strong Scandinavian background, the annual incidence of PMR between 1970 and 1991 was $52.5/100\ 000$ population aged ≥ 50 years (Machado et al, 1988; Salvarani et al, 2004). However, as described for GCA, the annual incidence of PMR is lower in Southern European countries. The annual incidence of PMR in Reggio Emilia, Italy, over the period 1980–1988 was $12.7/100\ 000$ population aged ≥ 50 years (Salvarani et al, 1991). Likewise, the annual incidence in Lugo, Spain, for those aged ≥ 50 years during the period 1987–1996 was $18.7/100\ 000$ for overall PMR (associated or not with GCA) and $13.5/100\ 000$ for subjects with isolated ‘pure’ PMR (Gonzalez-Gay et al, 1999c).

4 Aetiology and pathogenesis

The aetiology of GCA and PMR is unknown. However, evidence suggests that both genetic susceptibility and environmental risks factors may play a role in the development of the disease.

4.1 Influence of environmental factors and infectious agents

A possible influence of environmental factors and infectious agents in the pathogenesis of GCA and PMR has been proposed. Simultaneous fluctuations in the incidence of GCA and PMR in different regions of Denmark

support an association with *Mycoplasma pneumoniae*, parvovirus B19 and *Chlamydia pneumoniae* epidemics (Elling et al, 1996). Other environmental agents that have been reported bacterial strains such as *Chlamydia* and *Burkholderia* or viruses such as parvovirus B19 and varicella-zoster virus. Regular cyclical and seasonal variations of GCA have been reported from several studies worldwide (Bird HA 1979, Mowat AG 1984, Cimmino MA 1990)

4.2 Role of genetic factors

A genetic component has been reported, particularly in patients with biopsy-proven GCA. Several genes within the major histocompatibility complex may have independent effects on susceptibility to GCA and PMR (Salvarani et al, 1991; Salvarani et al, 2000; Gonzalez-Gay et al, 2001a; Gonzalez-Gay et al, 2003; Gonzalez-Gay et al, 2004a; Gonzalez-Gay et al, 2007c). Thus, association with HLA-DRB1*04, TNF microsatellite polymorphisms MICA and HLA-B genes with genetic susceptibility to GCA have been suggested. Other studies have also reported that different genetic variants influence the key components of immune and inflammatory pathways in GCA and PMR susceptibility (Dababneh et al, 1998). In addition, a functional variant of the vascular endothelial growth factor gene has been associated with severe ischaemic complications in patients with GCA. On the other hand, a polymorphism of the intercellular adhesion molecule-1 has been associated with PMR and GCA susceptibility and conferred an increased risk of relapse in Italian patients with PMR (Amoli et al, 2002). The presence of both HLA-DRB1*0401 and some gene polymorphisms in the intercellular adhesion molecule-1 codon was also associated with an increased risk of relapses in patients with isolated PMR from north-western Spain. The first large-scale GCA genetic study, using the ImmunoChip platform, was published in 2013, and confirmed HLA-DRB1*04, followed by PTPN22 rs2476601, as the strongest genetic risk factors for GCA (Carmona FD 2015). The study also identified other putative risk loci for GCA involved in Th1, Th17, and Treg cell function. Collaborative efforts for larger, genome-wide association studies, involving international consortia from Europe, North America, and Australasia, are currently underway. New risk alleles such as plasminogen and P4H42 in GCA are also identified (Carmona FD 2017)

4.3 Influence of traditional cardiovascular risk factors

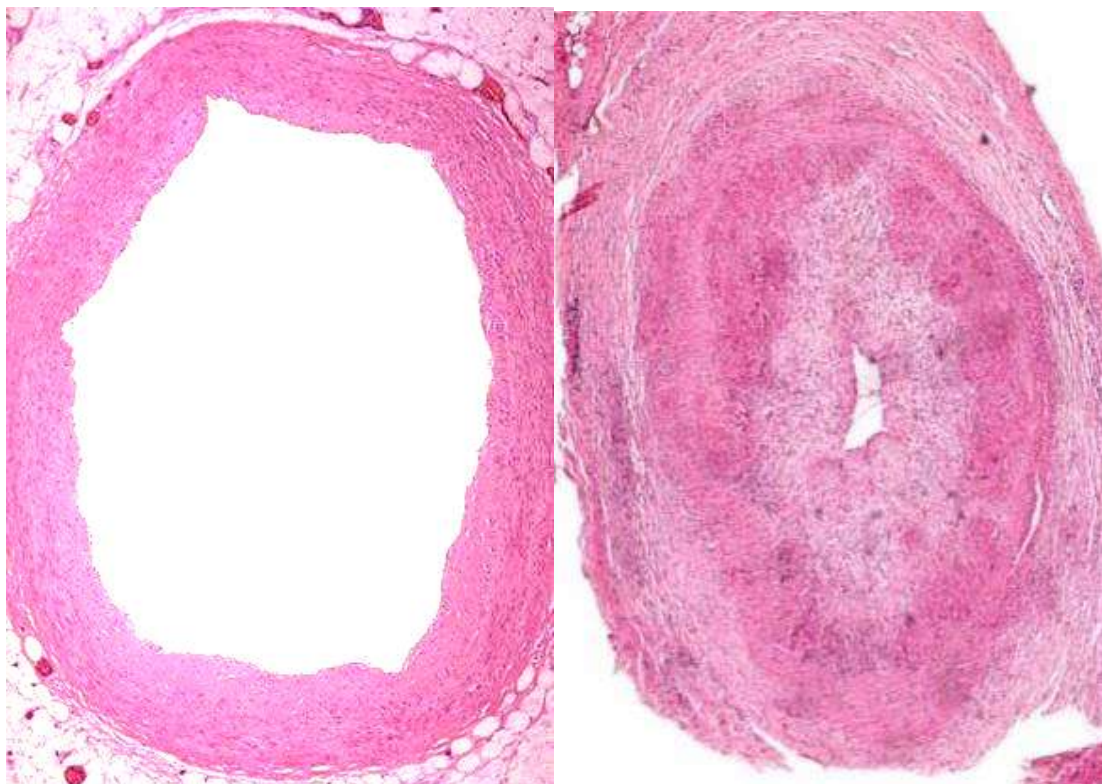
Some studies suggested an association between smoking and GCA. The presence of traditional risk factors for atherosclerosis before the diagnosis of the vasculitis—in particular, a history of hypertension, has also been found to increase the risk of developing severe ischaemic complications in GCA (Machado et al, 1989; Duhaut et al, 1998; Gonzalez-Gay et al, 2004f).

4.4 Pathogenesis

GCA is an antigen-driven disease with local T cell and macrophage activation in the vessel wall and proinflammatory cytokines playing an important role. Inflammation of the arterial wall and vessel occlusion

through rapid and concentric intimal hyperplasia (figure 1) lead to the severe ischaemic complications that may occur in patients with GCA. Dendritic cells localised at the adventitia–media border of normal large and medium arteries play a pivotal role in the initiation of the vasculitis process (Wagner et al, 2003; Weyand et al, 2005). These cells produce chemokines that recruit and locally activate T cells. Dendritic cells express a singular surface receptor profile, including a series of toll-like receptors (TLRs) (Ma-Krupa et al, 2005; Pryshchep et al, 2008). Ligands of TLR-4 promote activation and differentiation of adventitial dendritic cells into chemokine-producing effector cells with a high level of expression of both CD83 and CD86 and mediate T cell recruitment through release of pro-inflammatory cytokines. Activated T cells undergo clonal expansion and are stimulated to produce interferon gamma (IFN γ). This leads to the differentiation and migration of macrophages and the formation of giant cells. In the adventitia, macrophages produce proinflammatory cytokines such as IL-1 and IL-6, whereas in the media and intima they contribute to arterial injury by producing metalloproteinases and nitric oxide. This destructive mechanism of the arterial wall is associated with a repair mechanism that includes the secretion of growth and angiogenic factors (platelet-derived growth factor and vascular endothelial growth factor) through the infiltration of mononuclear cells and multinucleated giant cells (Rueda et al, 2005). These changes ultimately lead to the degradation of the internal elastic lamina and to occlusive luminal hyperplasia.

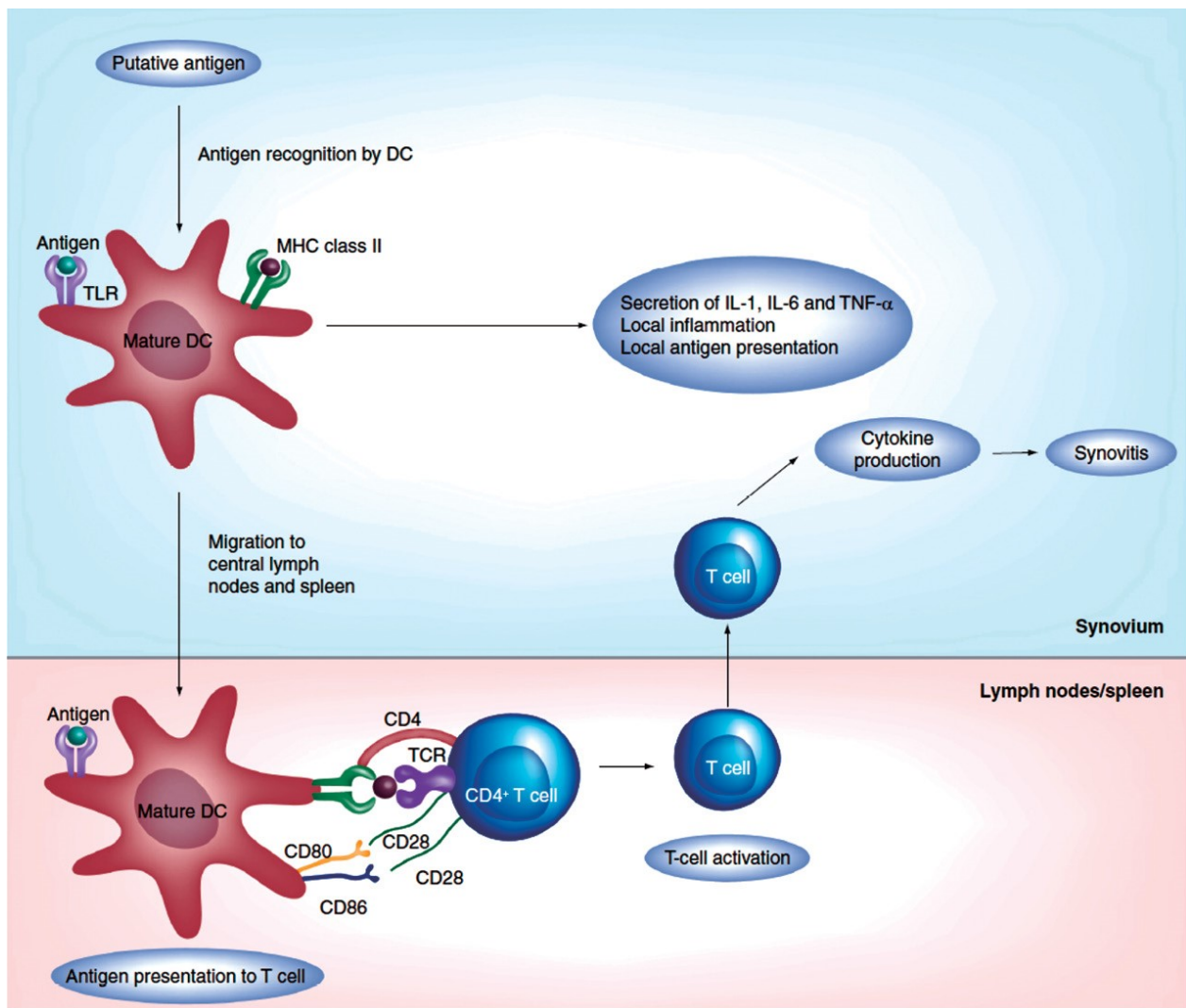
Figure 1 Normal temporal artery (left) and a temporal artery positive for giant cell arteritis (GCA) (right). Note the inflammatory infiltrate in the artery wall with intimal hyperplasia and luminal occlusion.



Although proinflammatory cytokines such as IL-1 and IL-6 are implicated in the pathogenesis of GCA and PMR, IFN γ specifically seems to play a key role in the pathogenesis of GCA and in the development of the severe ischaemic manifestations of this condition (Weyand et al, 1994; Weyand et al, 1997; Weyand and Goronzy, 1999; Weyand et al, 2004). High transcription of IFN γ mRNA was associated with the formation of giant cells and with evidence of cranial ischaemic symptoms in patients with GCA. Key cytokines involved in the pathogenesis of chronic inflammation, intimal hyperplasia and proliferation of vascular smooth muscle cells include interleukin-17 as well as PDGFA and B, VEGF, neurotrophins and endothelins which can increase sensitivity to vaso constriction.

In PMR, pathological findings are much less prominent than in GCA. The current concept is that GCA and PMR are the opposite ends of the same spectrum with the absence of vascular involvement in pure PMR. Bursitis, mainly involving the shoulders, is typical of PMR (Salvarani et al, 2002a; Salvarani et al, 2008a). Synovitis, bursitis, and tenosynovitis around the joints are all seen in PMR. Inflammation is initiated inside the tissue (synovium or bursa) with recognition of putative antigen by dendritic cells (DCs) or macrophages (Figure 1). Activated DCs or macrophages secrete inflammatory mediators, including IL-1, IL-6, and tumour necrosis factor alpha (TNF α), which are responsible for the systemic features of the disease. These cells migrate to central lymphoid organs where they present antigen to T cells, which then migrate to the synovium, enhance the adaptive immune response, and secrete further cytokines promoting local inflammation. Two different T-cell subsets, Th17 (steroid-sensitive acute lesions) and Th1 (steroid-insensitive chronic lesions) may relate to the persistence of disease in GCA and a similar mechanism for disease persistence may be relevant to PMR. Two different T-cell subsets, Th17 (steroid-sensitive acute lesions) and Th1 (steroid-insensitive chronic lesions) may relate to the persistence of disease in GCA (Deng J 2010). A similar mechanism for disease persistence may be relevant to PMR.

Figure 2: Pathogenesis of polymyalgia rheumatica. From Ghosh et al. *Expert Rev Clin Immunol* 2010;6(6):913–928.



5 Clinical manifestations

5.1 Clinical manifestations of PMR

The hallmark features of PMR are proximal bilateral pain and stiffness in the shoulder and pelvic girdle in patients over the age of 50. The onset is usually abrupt. Typically, early morning stiffness lasts 30 min or longer. The patients usually also describe stiffness after periods of rest. Shoulder pain is reported by 75–99% of patients, whereas the hip girdle and neck are less often involved (50–90% of cases). Pain usually radiates distally towards the elbows and knees. It can be initially unilateral, but soon becomes bilateral. It is inflammatory and hence particularly associated with early morning disability and patients have problems getting out of bed and dressing, hygiene, reaching or rising from a chair. On examination, painful restriction of active and often passive movements of the shoulders and hips is present with or without detectable joint swelling. There can also be muscle tenderness. Constitutional manifestations such as low-grade fever, sweats, fatigue, and anorexia and weight loss occur in up to 40% of patients. However, high spiking fever is uncommon.

in PMR in the absence of GCA. Muscle weakness is not a feature of the disease, although it can be difficult to assess in the presence of muscle pain.

Some reports have emphasised the presence of distal musculoskeletal manifestations in patients with PMR. In a series of 177 patients with PMR, carpal tunnel syndrome was diagnosed in 14% of patients and distal tenosynovitis in 3%, while peripheral arthritis predominantly involving the knees and wrists with an asymmetrical pattern was seen in 25% of patients (Salvarani et al, 1998). However, it is uncommon for feet and ankles to be affected. Moreover, PMR-associated arthritis is non-erosive and usually remits after glucocorticoid therapy or after increasing glucocorticoid dosage.

There may also be an overlap with inflammatory arthritis. Peripheral arthritis in patients can be associated with RS3PE (remitting seronegative symmetrical synovitis with pitting oedema), a condition mainly characterised by joint synovitis and flexor tendon synovitis of the hands and feet. Symptoms promptly respond to small doses of glucocorticoids.

Musculoskeletal ache and pain mimicking PMR may occur in some malignancies—in particular, in multiple myeloma and solid malignancies such as renal adenocarcinoma. However, musculoskeletal manifestations associated with neoplasm differ from those of PMR, with more diffuse pain, absent or minimal morning stiffness, little if any proximal joint restriction, no shoulder bursitis on ultrasonography (US) and a poor response to glucocorticoid treatment. There is no association between typical PMR and malignancies.

PMR should be diagnosed by a step-wise approach using core inclusion criterion of proximal pain and stiffness, thereafter excluding infection, cancer, GCA and other rheumatological conditions with clinical evaluation and pertinent blood tests. Low dose steroids should be used only after receiving results of preliminary blood tests. Meticulous follow up is necessary to exclude late emergence of an alternative condition.

5.2 Clinical manifestations of GCA

GCA is now recognized as a clinically heterogeneous disease with a wide spectrum of features. Clinical features of GCA are mainly due to involvement of the cranial arteries (Gonzalez-Gay et al, 1992; Gonzalez-Gay et al, 2005c). Headache is the most frequent expression of this vasculitic process. New onset of headache, or changes in the pattern of a pre-existing headache, is the most common symptom, occurring in over 60% of patients with GCA. The headache is characteristically of sudden onset, severe and predominantly temporal. However, it may affect any part of the head, such as occipital, frontal and parietal regions. Scalp tenderness occurs in around a third to a half of patients and is usually noticed while brushing or combing the hair. The new onset of headache in a patient aged ≥ 50 years should alert the clinician to the possibility of GCA. Physical examination in GCA may reveal tenderness, thickening, nodules and occasionally redness of the superficial

temporal arteries (figure 2). Temporal artery pulses may be decreased or absent; extra-cranial arterial pulses should be examined including a search for bruits, particularly in the supra-aortic branches.

Some 40–50% of patients report jaw claudication (pain on chewing that improves after stopping mastication) due to ischemia of the masseter muscles, and about 7% of patients describe trismus. Ischemic jaw and tongue pain claudication is highly specific for GCA. Occasionally, intermittent claudication can affect the tongue or the muscles involved in swallowing, leading to tongue necrosis or dysphagia, respectively. Unilateral scalp necrosis due to involvement of the branches of the scalp arteries is occasionally seen.

Constitutional symptoms, such as fever, day and night sweats, anorexia, weight loss and fatigue, are present and often quite prominent (Calamia and Hunder, 1981; Gonzalez-Gay et al, 2004b; Gonzalez-Gay et al, 2004c) in the sub group of cases we now call large vessel GCA. This group often presents with polymyalgia and persistent high inflammatory markers. In some cases, they may be the only clinical manifestations of GCA. Fever is usually low grade, but it may exceed 38°C in about 10% of patients. Large vessel GCA may present as fever of unknown origin (FUO), and may account for up to 16% of cases of FUO in the elderly (Knockaert DC 1993)

Figure 3 Patient with giant cell arteritis. On physical examination, a segment of the right temporal artery is thickened and nodular and the temporal artery is tender on palpation. Patient consent obtained.



GCA is a major cause of irreversible visual loss. The incidence of ocular complications ranges from 14% to 70% in different series. Hayreh et al (1998) reported ocular manifestations in 50% of 170 patients with GCA. A lower incidence of ocular manifestations of 20–30%, often at disease onset, is reported in patients with GCA initially seen by a rheumatologist. In unselected patients with biopsy-proven GCA from north-western Spain, visual complications were found in 25% of cases, and irreversible visual loss in 15% of patients (Gonzalez-Gay et al, 1998a; Gonzalez-Gay et al, 2000a). Partial or total visual loss was found in 19% of patients with GCA from Reggio Emilia (Italy) (Salvarani et al, 2005a). Permanent irreversible sight loss usually occurs in the very elderly and in patients with co-morbidities.

The most common ophthalmic manifestation of GCA is anterior ischaemic optic neuropathy (AION) and it occurs almost always prior to glucocorticoid therapy. This is caused by interruption of blood flow in the posterior ciliary arteries to the optic nerve head. Patients usually have preceding jaw and/or tongue pain, visual symptoms such as diplopia, blurred vision or amaurosis fugax. Visual loss may present as a mist in the entire field or part of the visual field and evolve within 24–48 h to total blindness. One eye is affected first, but involvement of the other eye in untreated patients may occur 1–10 days after the initial event. In the acute phase of AION, the optic disc is pale and swollen but the retina is almost normal. Afterward, atrophy of the optic nerve associated with optic disc cupping is seen. Fundoscopy and fluorescein angiography usually demonstrates extensive choroidal hypoperfusion. More rarely, visual loss is caused by central retinal artery occlusion, ischaemic retro bulbar neuropathy or occipital infarction in association with a stroke involving the vertebrobasilar territory. When the arteritic process involves the central retinal artery leading to retinal stroke, the retina is primarily damaged and appears greyish and swollen, while a contrasting red zone can be seen in the macula—the so-called ‘cherry red spot’. In the extremely rare cases of blindness in GCA due to cortical ischemia, the optic disc appears unaffected on fundoscopy. The extent of sight loss can be significantly reduced by fast track GCA pathways and immediate start of high dose glucocorticoids.

In assessing a series of 84 consecutive patients with GCA, visual loss was due to AION in 91% of cases: central retinal occlusion was found in 10.5%, cilio retinal artery occlusion in 10% and/or posterior ischaemic optic neuropathy in 4%, either alone or in different combinations (Hayreh et al, 1998). AION was reported by Salvarani et al to be the cause of partial or permanent visual loss in 24 of 26 patients who had this complication (Salvarani et al, 2005a).

Amaurosis fugax has been reported to occur in 2–30% of patients with GCA. It is generally unilateral and it often precedes the development of visual loss. Amaurosis fugax was reported to precede the development of permanent visual loss in 12 of 24 cases from north-western Spain. It is the best clinical predictor of permanent visual loss. Diplopia is another ocular manifestation due to ischemia of the oculomotor nerves or the extra ocular muscles. In a series by Hayreh et al (1998), diplopia was observed in 5.9% of cases and was transient in all of them. In north-western Spain, diplopia was reported in 5.6% of patients.

About a third of all patients with GCA have evidence of large vessel vasculitis, which can be complicated by vascular stenosis, aortitis dissections and aneurysms (Martínez-Valle et al, 2010; Bossert et al, 2011; Garcia-Martinez et al, 2013). In a retrospective study from Olmsted County, Minnesota (USA), thoracic aorta aneurysms, abdominal aorta aneurysms and large vessel stenoses (predominantly affecting the upper limbs) were found in 11%, 10% and 13% of unselected patients with GCA, respectively (Nuenninghoff et al, 2003). These complications occurred on average 5, 6.3 and 1.1 years, respectively, after the onset of GCA. The incidences of aneurysmal disease per 1000 person-years in populations followed up in Olmsted County and north-western Spain were remarkably similar (18.7 in Olmsted County and 18.9 in north-western Spain) (Gonzalez-Gay et al, 2004d). Thoracic aortic aneurysmal disease was slightly more common in north-western Spain. In contrast, abdominal aortic aneurysmal disease was more common in Olmsted County.

Data obtained from prospective studies designed specifically to detect vascular stenoses and aneurysms in patients with GCA, show an even higher incidence of these complications. However, although stenoses and aneurysms occur relatively late in the course of GCA, large vessel inflammation has been demonstrated early on using sensitive imaging techniques. In a study of 35 newly diagnosed, untreated patients with GCA, 18F-fluorodeoxyglucose positron emission tomography (FDG/PET) showed large vessel vasculitis in 83% of cases (Blockmans et al, 2006). Another prospective study showed large artery disease in 29-83% with newly diagnosed GCA. (Muratore F 2015). In a recent prospective study of 54 GCA patients who underwent CT scan and ultrasound aortic structural damage affects up to 33.3% with maximal incidence within the first 5 years (Garcia – Martinez A 2014)

Several studies showed differences in clinical aspects when GCA patients with large vessel disease are compared with cranial involvement. They are likely to be younger, less likely to present with headaches and positive TAB. They have more constitutional symptoms, polymyalgia, persistent raised inflammatory markers and they generally require higher dose of GCs and frequently relapse (Muratore F 2015).

Other investigations such as colour Doppler ultrasonography (CDUS), CT and MRI can also record early large vessel vasculitis. Axillary artery intimal medial thickness on ultrasound is currently being investigated as a marker for large vessel involvement. Aortic murmurs and vascular bruits in the arms, as well as upper extremity claudication, are signs suspicious for large vessel involvement, while hypertension, hyperlipidaemia, PMR and coronary artery disease have been considered to be risk factors for the subsequent development of large vessel complications. Patients with active large vessel vasculitis should be treated with glucocorticoids, even in the absence of cranial vessel involvement, to prevent future complications.

Transient ischaemic attacks and strokes caused by severe obstruction or occlusion of the internal carotid artery or especially the vertebral arteries have been reported in around 3% of patients (Gonzalez-Gay et al,

2009b*). Inflammation of intracranial or intradural arteries is considered rare although recent studies with 3T and 7T MRI have shown involvement (Christina Goll 2016).

Visual manifestations, jaw claudication and cerebrovascular accident seem to be less common in patients with GCA with negative TAB than in patients with biopsy-proven GCA (Duhaut et al, 1999b).

Facial pain (González-Gay et al, 1998b) and swelling (Liozon et al, 2006) is another uncommon feature of GCA. Other facial manifestations include odontogenic pain, chin numbness, glossitis, submandibular swelling and necrosis of the scalp (Gonzalez-Gay et al, 2009a*; Gonzalez-Gay et al, 2009b*), tongue and lips. Some patients have carotidynia (pain felt over the carotid arteries) (Gonzalez-Gay et al, 1998c).

Finally, pericardial and pleural effusions (Valstar et al, 2003), myocardial infarction (Lie et al, 1986), female genital tract and breast involvement (Bajocchi et al, 2007), inappropriate antidiuretic secretion syndrome (Luzar et al, 1982) and dysarthria (Lee et al, 1999) have been occasionally reported as presenting features.

5.3 Association between PMR and GCA and LVV

Both PMR and GCA are characterised by onset at over 50 years of age, with progressively increasing incidence with older age, a higher prevalence in women, a systemic inflammatory response and generally good response to glucocorticoid therapy (Rodriguez-Valverde et al, 1997; González-Gay et al, 1998a; Gonzalez-Gay et al, 2004e). The incidence of both conditions peaks in patients above 70 years of age. Patients with GCA often present clinical manifestations of PMR. In biopsy-proven GCA, PMR manifestations are found in up to 50% of cases. PMR may be the presenting feature in patients who later develop the typical cranial manifestations of GCA (Narvaez et al, 2015). Also, PMR and GCA may appear simultaneously or PMR may develop after clinical manifestations of GCA are evident. Different population-based studies have shown the presence of biopsy-proven GCA in 16–21% of patients with PMR. In a part of Italy, during the period 1996–2000, 12/76 (16%) patients with PMR from Prato, had histological evidence of GCA. However, only one (1.3%) of these 76 patients with PMR had a positive TAB without any clinical feature of GCA. In the remaining 11 patients with PMR, cranial manifestations of GCA were present at the time of biopsy. In northwestern Spain, 9% of patients presenting with isolated ‘pure’ PMR had a positive TAB. A population-based study conducted to establish differences between isolated PMR and PMR in the setting of biopsy-proven GCA, disclosed that the patients in the former group were significantly younger than those with PMR associated with biopsy-proven GCA. Patients with isolated PMR had a lower frequency of asthenia, anorexia and weight loss, and seemed to have a milder inflammatory disease as shown by significantly less abnormality in the majority of laboratory findings (Gonzalez-Gay et al, 1998e). Clinically silent arteritis has been observed in patients initially diagnosed as having isolated PMR (Gonzalez-Gay et al, 2004c). Abnormal vascular uptake was observed using PET in 31% of patients with PMR without clinico-histological evidence of GCA, although the uptake seen in PMR was less intense than that seen in GCA (Blockmans et al, 2007).

LV-GCA occurs in up to 83% of patients with GCA and with unknown frequency in PMR. The possibility

Of coexistent GCA arises in PMR patients with incomplete GC response, constitutional symptoms and markedly elevated acute phase reactants (Blockmans D 2006, Prieto-Gonzalez S. *et al* 2012).

LV-GCA may be present at diagnosis, and may occur at any point during the disease course, and is detected with increasing frequency in GCA patients after 4 to 5 years of disease (Kermani T 2013). The definition of LV GCA is still imprecise, which hampers the performance of proper epidemiological studies. A biopsy of larger Arteries is not feasible in routine practice, and LV-GCA diagnosis is thus based on imaging methods such as axillary ultrasound, ¹⁸F-fluorodeoxy-glucose positron emission tomography (¹⁸F-FDG–PET), computed tomography angiography (CTA) or magnetic resonance imaging (MRI) to assess mural inflammation and changes in the lumen.

The new understanding of GCA as a disease complex that is not limited to cranial arteries, along with advanced imaging techniques and international efforts to better define the disease will facilitate future studies on the epidemiology of GCA, permitting better understanding of its incidence, prevalence and disease course.

Table 4: Clinical spectrum of GCA /PMR and Large Vessels Vasculitis (LVV)

Clinical features	Cranial GCA	LV-GCA	PMR
Headache	Present	Absent	Absent
Scalp tenderness, artery thickening	Present	Present	Absent
Jaw claudication	Present	Absent	Absent
Visual symptoms	Present	Absent	Absent
Constitutional symptoms	mild	Mod - severe	Mod-severe
Arm claudication	Present	Prominent feature	Not a feature
polymyalgic	mild	Mod- severe	severe
Acute phase reactants	Present	Present	Present
Peripheral arthritis/RS3PE	May occur	May occur	Mostly associated

Some studies showed that patients with coexisting GCA and PMR may need longer glucocorticoid treatment than those with GCA or PMR alone.

6 Laboratory investigations

For years, a high erythrocyte sedimentation rate (ESR) has been considered a hallmark for the diagnosis of GCA or PMR. Raised inflammatory indices such as ESR and C-reactive protein (CRP) support the diagnosis of PMR

and GCA and can also be used to monitor disease activity over time (Andersson et al, 1986; Kyle et al, 1993; Cantini et al, 2000; Gonzalez-Gay et al, 2005a). CRP may be a more sensitive indicator of disease activity than ESR in PMR and GCA. However, it is not clear whether CRP or ESR is better in clinical practice for the diagnosis of PMR and GCA. An ESR <40 mm/1st h is very uncommon in PMR and in GCA. In a population-based study of a series of patients with biopsy-proven GCA, only one of the 240 patients had an ESR <40 mm/1st h and the median ESR value were 93 mm/1st h (Salvarani and Hunder, 2001). In this same series, 97% of patients had a CRP >5 mg/L at the time of diagnosis and the median CRP was 83 mg/L. Therefore, normal ESR and CRP values make a diagnosis of GCA very unlikely. In a population-based study of 273 patients with biopsy-proven GCA, only 10 (3.6%) had an ESR <50 mm/1st h. But a normal ESR and a normal CRP does not rule out GCA. A biopsy-proven ocular complicated case of GCA with a normal ESR and CRP has recently been reported (McAlinden et al, 2014*). Patients with isolated PMR and low ESR have also been described (Gonzalez-Gay et al, 1997b).

Significant differences in the frequency of visual ischaemic complications were observed according to different ESR levels (Cid et al, 1998; Hernández-Rodríguez et al, 2002). In one study (Lopez-Diaz et al, 2008b); there was an increased frequency of visual ischaemic events in the subgroup of patients with biopsy-proven GCA with an ESR between 70 and 100/1st h at the time of diagnosis. Twenty-five (21%) of 120 subjects with ESR values between 70 and 100 mm/h experienced permanent visual loss compared with only 10 (7%) of the remaining 153 patients (10 with an initial ESR <50 mm/1st h, 28 with an ESR between 50 and 69 mm/1st h, 115 with an ESR >100 mm/1st h). In this study an ESR between 70 and 100 mm/1st h was the best predictor of visual ischaemic complications and irreversible visual loss. But in another population-based study of 180 patients with biopsy-proven GCA, ESR and CRP values at diagnosis were significantly lower in patients with cranial ischaemic events, including permanent visual loss. Other studies have emphasised the protective role of a strong inflammatory response (constitutional symptoms, fever and very high inflammatory markers) against the development of ischaemic complications, including loss of vision in GCA. Cid et al (1998) also found that the mean ESR was significantly reduced in patients with irreversible cranial ischaemic complications compared with the other patients with biopsy-proven GCA.

Normochromic-normocytic inflammatory anaemia is common and may be the presenting manifestation of GCA. Haemoglobin values <12 g/dL may be found in about 50% of patients at the time of diagnosis. High platelet counts have also been widely described in patients with GCA, but their frequency varies from one series to another. In north-western Spain, thrombocytosis (>400 000 platelets/mm³) was seen in 117 (48.8%) of 240 patients with biopsy-proven GCA. Leucocytosis, generally not severe, has also been described in almost one-third of patients with GCA.

Abnormal liver function tests—in particular, raised alkaline phosphatase, have also been described in these patients. Approximately one-quarter of patients with active GCA have a raised alkaline phosphatase, which normalises with glucocorticoid therapy.

Patients with GCA have positive tests for anticardiolipin antibodies more often than age- and gender-matched controls, but without an increased risk of thrombosis. Such anticardiolipin antibodies correlate, at least to some extent, with GCA activity and disappear after treatment onset (Manna et al, 1998; Liozon et al, 2000). A contribution of antiferritin antibodies to the diagnosis of GCA has been recently described but has not been widely confirmed and deserves further study (Baerlecken et al, 2012; Regent et al, 2013). IL-6 and BAFF cytokines have also been found to correlate with GCA disease activity (Van der Geest KS- 2015).⁷ Diagnosis of GCA and PMR.

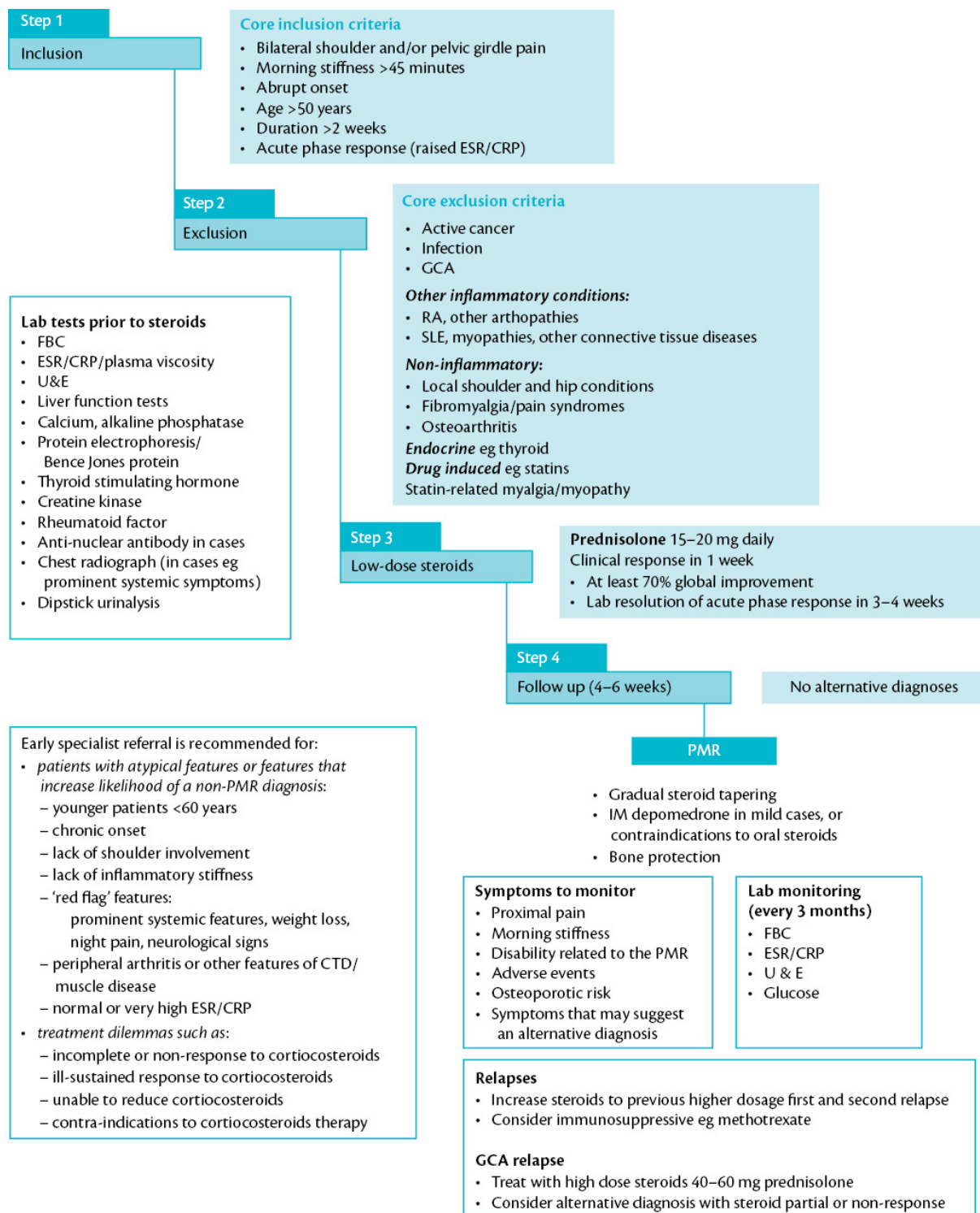
There are no definite diagnostic tests for PMR and even for GCA. The diagnosis is based on clinical presentation, exclusion of mimics, systemic inflammation and imaging. A stepwise approach for the diagnosis of PMR is recommended.

7.1 Temporal artery biopsy

TAB remains the ‘gold standard’ for diagnosis of GCA (Gonzalez-Gay et al, 2005b; Marí et al, 2009). A TAB is considered to be positive if there is interruption of the internal elastic laminae with infiltration of mononuclear cells into the arterial wall (figure 3). Intimal hyperplasia is a characteristic feature and its severity is associated with presence/absence of ischemic complications. Multinucleated giant cells are often seen (40–60% of cases), but their presence is not required for diagnosis. In some cases the inflammation is restricted to the vasa vasorum or to periadventitial small vessels, or both. The frequency of cranial ischaemic events of these groups of patients is similar to that of patients with classic GCA. Therefore, the clinician must also value this histological TAB pattern as proof of GCA and plan adequate treatment.

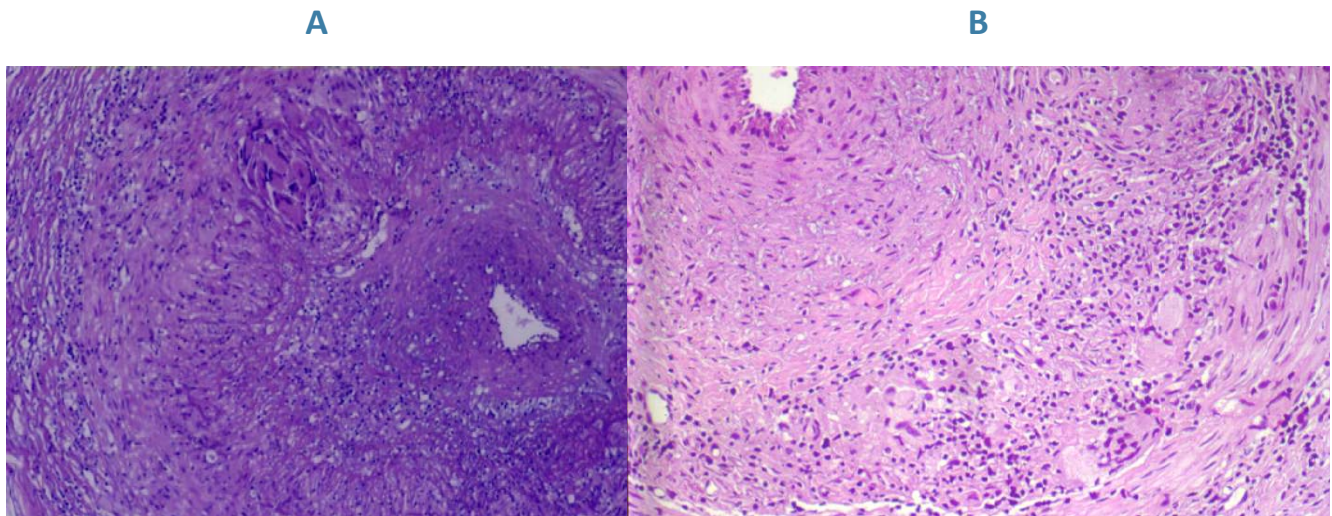
GCA affects vessels focally and segmentally, yielding areas of inflammatory vasculitic lesions juxtaposed with areas of normal artery. Because of skip inflammatory lesions, histological signs of inflammation may be missed in temporal artery biopsies performed in arteritis-free segments. As a consequence, in most series, 10–20% of temporal artery biopsies are reported to be negative in patients with GCA, although the rate may be as high as 40%. TAB findings have been reported as being negative in 42% of patients with large vessel involvement.

The best set of clinical features to predict a positive TAB in a community hospital is the association of headache, jaw claudication and abnormal temporal artery on palpation, with a significantly increased frequency of severe visual ischaemic complications (transient or permanent visual loss or diplopia) in patients with biopsy-proven GCA compared with patients with GCA with a negative TAB (Gonzalez-Gay et al, 2001b).



*Step approach flow chart is Reproduced with permission from clinical medicine, 2010; 10(3): 270-4. In the Lab investigations we now recommend adding ACPA. Drug induced PMR should include effects of immune checkpoints inhibitors.

Figure 4. (A) Disruption of the internal elastic lamina by inflammatory cells and (B) presence of multinucleated giant cells. GCA, giant cell arteritis.



A threshold length of 1.0 cm of post-formalin fixed arterial segment on biopsy was associated with increased diagnostic yield indicating GCA (Taylor-Gjevre et al, 2005). These authors recommended collecting a minimum TAB length of at least 1.5 cm to allow for an estimated 10% tissue shrinkage during fixation. A post-formalin fixed TAB length of at least 0.5 cm could be sufficient to make a histological diagnosis of GCA (Mahr et al, 2006). A review of 305 TAB reports for 173 patients showed that the TAB segments in the biopsy-positive patients were significantly longer than in biopsy-negative cases (Breuer et al, 2009b). These authors suggested that increasing post-fixation TAB length beyond 20 mm might further increase the rate of positive biopsies.

TAB should be performed on the most symptomatic site. Colour duplex sonography-guided TAB did not improve the sensitivity of TAB for diagnosing GCA (Germano et al, 2014*). A contralateral biopsy is not required unless the original biopsy was sub-optimal.

BSR and EULAR recommendations emphasise that a TAB should be performed soon after the onset of treatment whenever a diagnosis of GCA is suspected. However studies suggest that 2 – 4 weeks of prior glucocorticoid treatment does not affect the likelihood of a positive result (Narvaez J 2007)

7.2 Imaging studies in PMR

US, MRI and PET have been used in PMR to detect synovitis in proximal joints and periarticular structures and may help with diagnosis. Bilateral subacromial/sub deltoid bursitis and trochanteric bursitis are the most common lesions in most patients with PMR who have pain in the shoulder or pelvic girdle, respectively (Cantini et al, 2001b; Pipitone et al, 2008a; Pipitone et al, 2008b; Macchioni et al, 2009, Dasgupta et al 2012). See Figures 5, 6, 7, and 8. US and MRI are equally effective in confirming the presence of these lesions with a sensitivity and specificity of >90% (Cantini et al, 2004). US evidence of bilateral shoulder bursitis may support

the diagnosis of PMR in patients with normal or subnormal ESR. Shoulder US inflammatory findings are associated with better response to glucocorticoid therapy; milder US signs may persist even in those patients who achieve clinical response to treatment. Although shoulder bursitis is highly suggestive of PMR, it is not specific. In a study comparing patients with PMR with those with rheumatoid arthritis (RA) and psoriatic arthritis, bilateral subacromial/sub deltoid bursitis was found in all patients with PMR, but also in 20% of patients with RA, while glenohumeral synovitis was present in all patients. Bursitis has also been shown to be associated with neck or lumbar pain in PMR. In a study of 12 patients with new-onset, untreated PMR, interspinous cervical bursitis was found using MRI in all (Salvarani et al, 2008a). A subset of patients with rheumatologist-diagnosed PMR seem to have a characteristic, extra capsular pattern of MRI inflammation, especially around the hips, associated with elevated IL-6/CRP and with complete patient-reported glucocorticoid responsiveness (Mackie et al, 2016).

FDG/PET may be useful for detecting large vessel vasculitis in some patients presenting with PMR features (Blockmans et al, 2007): (a) patients with PMR for whom glucocorticoids do not produce an adequate response; (b) patients with PMR and persistently raised inflammatory markers and (c) patients with PMR and severe constitutional symptoms.

Plain X-ray examinations are not useful for diagnosing PMR, but the presence of erosions, chondrolysis or chondrocalcinosis in peripheral joints shifts the diagnosis away from PMR towards another diagnosis of arthritis.

Fig 5 : Longitudinal view sub acromial bursitis

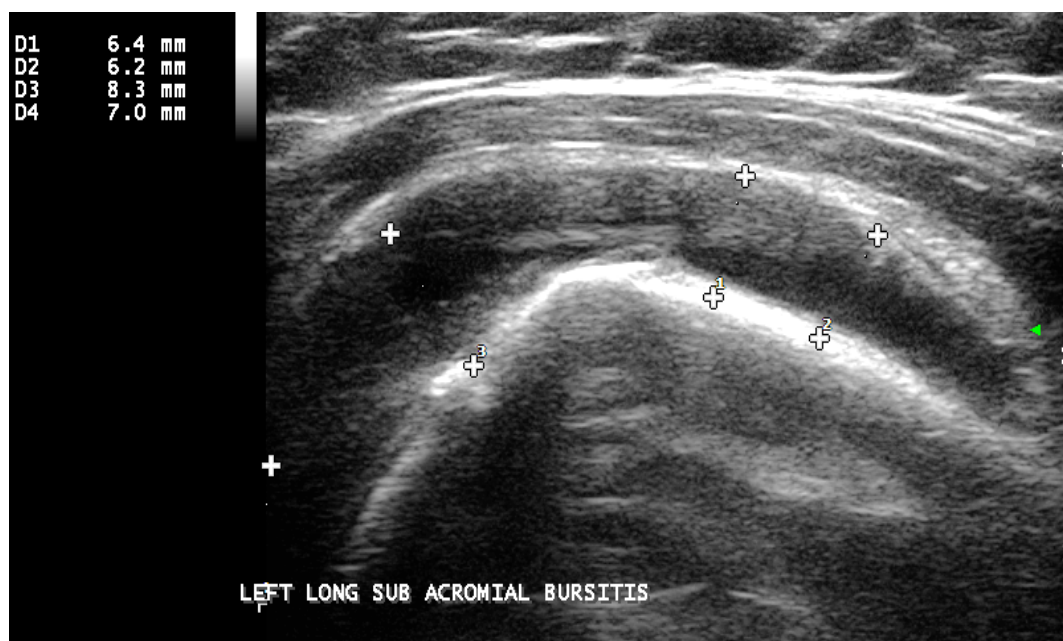


Fig 6 : Subdeltoid bursitis with positive power Doppler

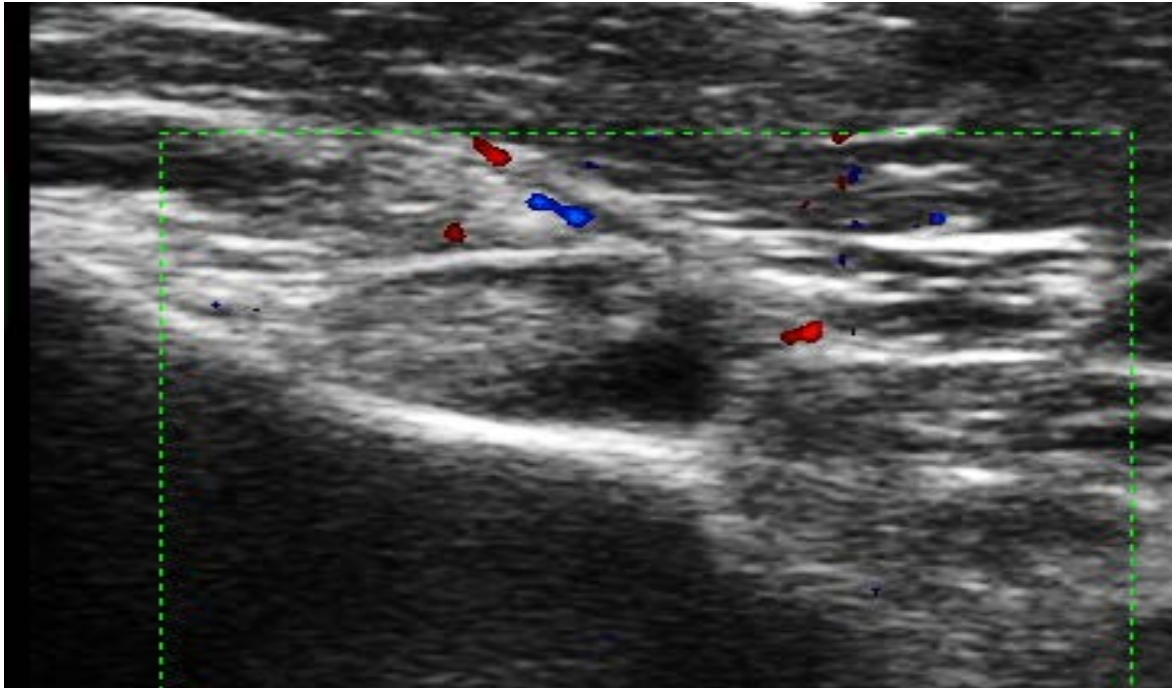


Fig 7 : Ultrasound shows a proliferative bursitis more akin to that seen in RA

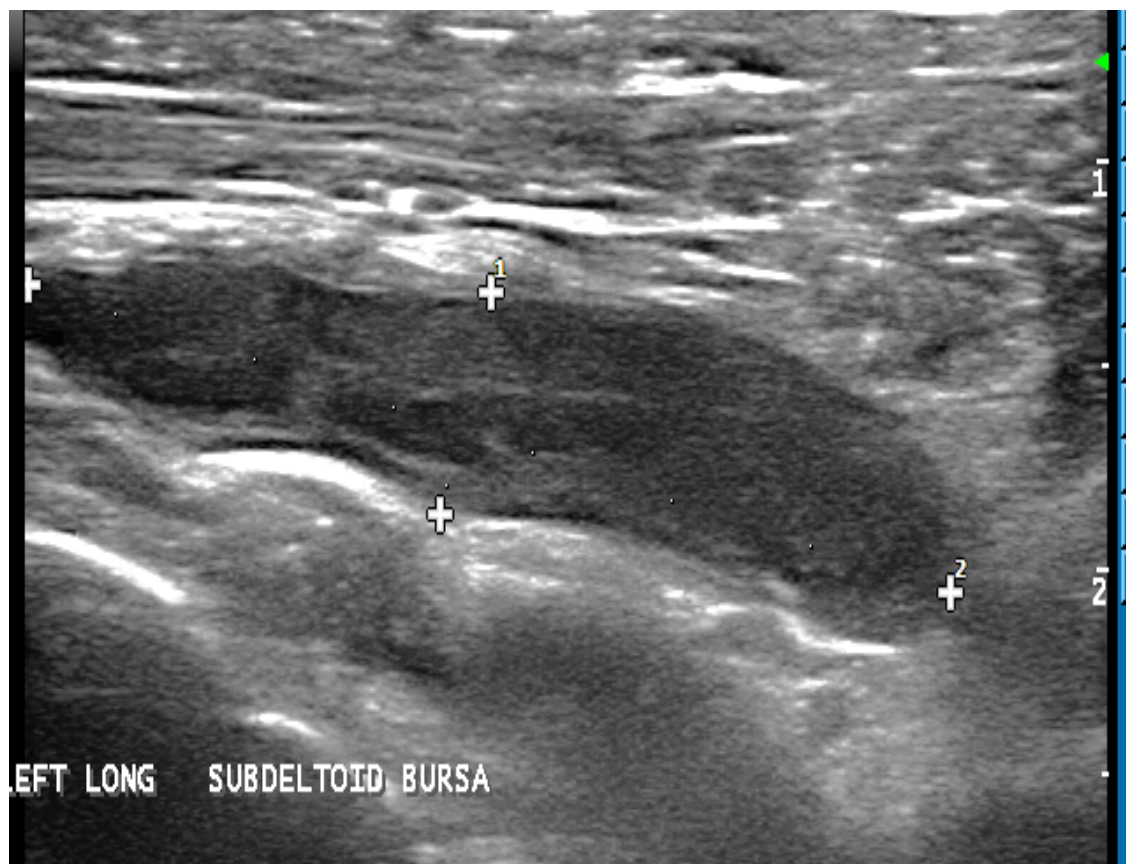


Fig 8 : RS3PE showing subcutaneous oedema with prominent flexor tenosynovitis

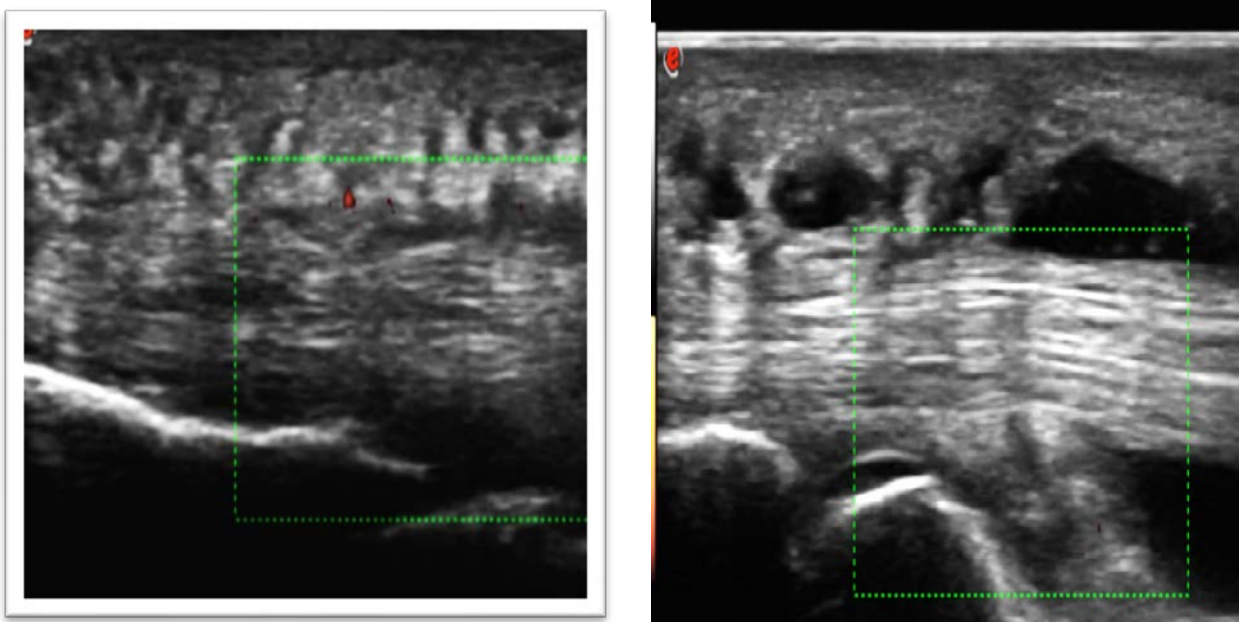
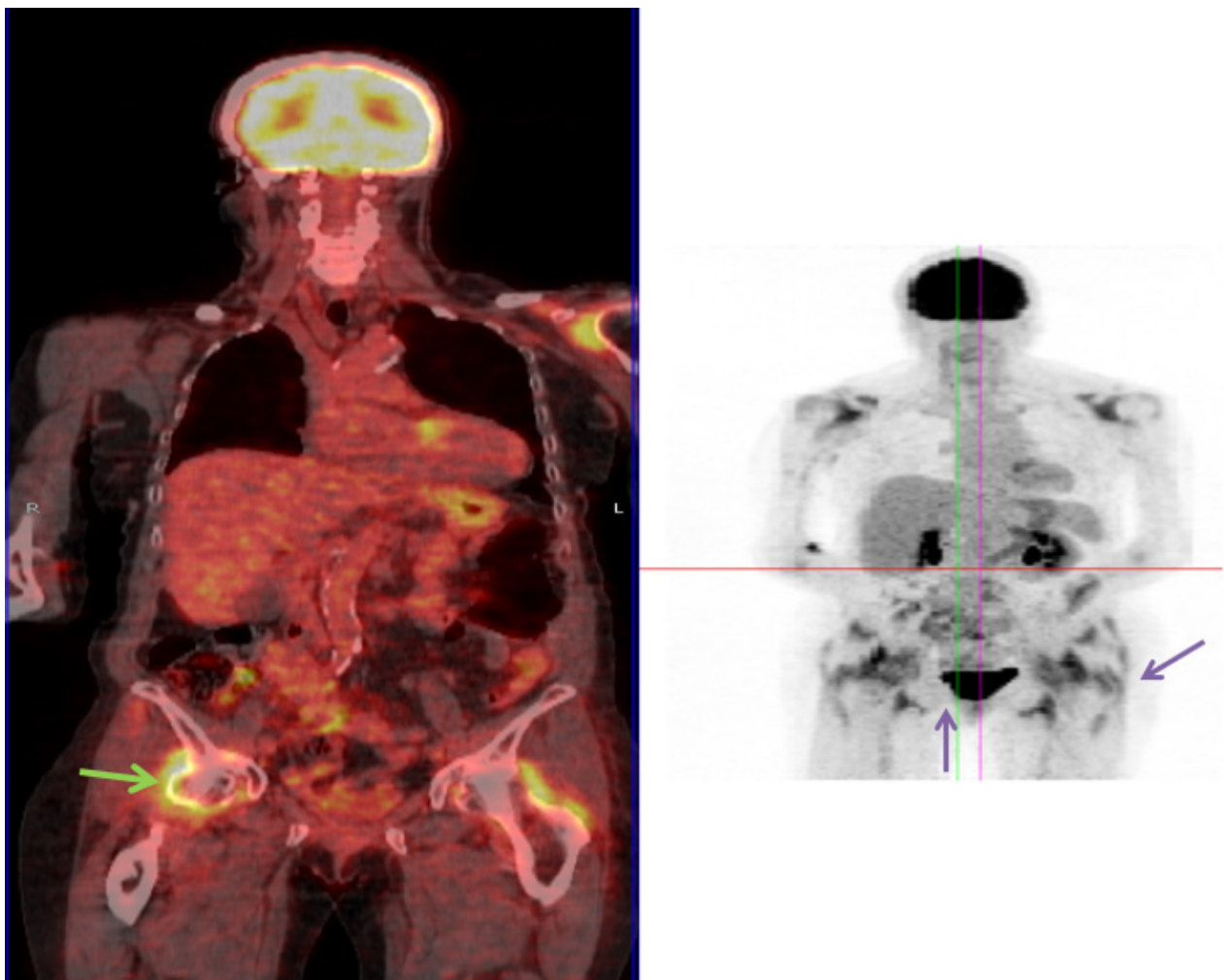


Fig 9: FDG - PET showing typical changes of bursitis, capsulitis and enthesitis in multiple areas, reproduced with permission from joint bone spine 2012, sept 27.



7.3 Imaging studies in GCA

Imaging modalities such as CDUS, CT Angiography, MR Angiography and 18F FDG-PET are emerging as important diagnostic methods and are also useful for assessment of disease activity.

High-resolution CDUS has gained widespread acceptance as a diagnostic tool in GCA. Available CDUS transducers have a resolution of about 0.1 mm, which is 10-fold higher than that of MRI. CDUS can visualise both the vessel wall and the lumen, and may thus demonstrate early vessel wall alterations while the lumen is still unaffected. Other advantages of CDUS include its limited cost, non-invasive nature, the relatively short time required for the investigation and the absence of exposure to ionising radiation.

The use of CDUS in GCA was initiated by Schmidt et al, who showed that inflamed temporal arteries in GCA have a concentric hypoechogenic mural thickening, called a 'halo', which the authors interpreted as resulting from inflammatory vessel wall oedema (Schmidt et al, 1997). The authors reported that the halo sign had a specificity of 100% and a sensitivity of 73% for the diagnosis of GCA, whereas stenoses and occlusions, although common (80% of cases), were less sensitive and specific for GCA. Since then, CDUS has increasingly been used to screen patients with suspected GCA. A meta-analysis of studies published up to 2004 reported a sensitivity of 69% and a specificity of 82% for the halo sign in the temporal arteries for GCA with a positive TAB, and a sensitivity and a specificity of 55% and 94%, respectively, for GCA diagnosed according to the ACR criteria (Karassa et al, 2005). A meta-analysis of prospective studies published through 2009 that examined the CDUS findings of the temporal arteries of patients with suspected GCA using the ACR 1990 classification criteria for GCA as the reference standard, yielded similar results (Arida et al, 2010). More specifically, a positive unilateral halo sign had an overall sensitivity of 68% and a specificity of 91% for GCA, while bilateral halo signs had a sensitivity of 43% and a specificity of 100%. Therefore, while a positive halo sign suggests a diagnosis of GCA in the presence of compatible clinical manifestations, the absence of a halo does not rule it out. In addition, the presence of a bilateral halo sign appears to have a very high specificity for GCA. The Compression sign – a non-compressible halo with persistence of hypoechoic wall swelling despite compression of involved vessel – is now considered a pathognomonic sign of GCA.

Schmidt et al compared the results of temporal artery US examinations with the occurrence of visual ischaemic complications in patients with GCA: anterior ischaemic optic neuropathy, central retinal artery occlusion, branch retinal artery occlusion, diplopia or amaurosis fugax in 222 consecutive patients with newly diagnosed, active GCA (Schmidt et al, 2009). However, the findings of temporal artery US did not correlate with eye complications.

US may also be useful to detect stenosis and occlusion, particularly helpful in detecting axillary and subclavian arteries. Studies have shown abnormalities of axillary arteries in 53% in GCA patients. (Khan A 2015, Czihal M 2012). The sonographic finding is distinct from arteriosclerotic lesions which are irregularly delineated, non-

homogeneous and or calcified wall alterations where as in GCA the abnormalities are circumferential, homogeneous, hypoechogenic thickening of the vessel wall. TABUL study which was a multicentre prospective study of 381 patients, comparing TAB to ultrasound of temporal and axillary arteries for diagnosis of newly suspected GCA, reported that ultrasound had a higher sensitivity for the diagnosis of GCA (54% vs. 39%) than TAB, but a lower specificity (81% vs. 100%) (Luqmani R 2015).

Inflammation of the aorta and its branches may occur in a subset of patients with GCA, although symptoms of aortic involvement can appear years after the initial diagnosis. Therefore, a systematic evaluation of patients with imaging techniques such as MRI, angiography and PET may show that the clinical impact of extracranial involvement in GCA is more than previously thought.

MRI can aid in diagnosing early large vessel vasculitis in GCA. Typical changes in inflamed vessels include thickening and oedema of the vessel wall, which precede the development of angiographically detectable stenoses or aneurysms. Magnetic resonance angiography is used to show alterations in the vessel lumen, such as stenoses and aneurysms. The main limitations of MRI are misinterpretation of vascular branch-points as occlusions, and falsely accentuated stenoses. MRI and CT are particularly useful in evaluating deep, large vessels such as the thoracic and the abdominal aorta, which are frequently involved in GCA.

Some data suggest that high-field strength MRI (3 T or 7T) may also be both sensitive and specific in demonstrating temporal artery inflammation. In the presence of inflammation, the temporal arteries show increased mural thickness and contrast enhancement within and around the vessel wall. Enhanced 3 T MR T2-weighted inversion recovery fast spin echo images have been shown to reveal mural oedema of inflamed cranial arteries, although with a lower diagnostic sensitivity than with contrast-enhanced images. Validation of these findings in large prospective trials is required, especially due to the limited availability of 3T equipment.

Theoretically, MRI could be useful for the diagnosis and also the follow-up of patients with GCA (Bley et al, 2005a; Bley et al, 2005b). However, very few longitudinal studies on patients with GCA monitored with sequential MRI have been carried out. A marked improvement in MRI inflammatory changes has been seen 8 weeks after starting glucocorticoid therapy. However, MRI has no clear role in following up large vessel vasculitis since correlation between MRI findings and clinical and laboratory parameters is poor.

Bley et al compared the results of high-resolution MRI and CDUS in 59 patients with suspected GCA with the final clinical diagnosis based on the ACR classification criteria for GCA (Bley et al, 2008). Thirty-six of the 59 patients (61%) were diagnosed as having GCA. The sensitivity of high-resolution MRI and CDUS was 69% and 67%, respectively, while specificity was 91% in both. TAB findings were positive in 24 of the 41 biopsied patients (59%). The sensitivity of high-resolution MRI and CDUS compared with TAB was 83% and 79%, respectively, and specificity was 71% and 59%, respectively.

FDG/PET can be used to secure the diagnosis of large vessel GCA because of its ability to disclose inflammatory cell infiltration of the vessel wall, which is one of the earliest events characterising large vessel vasculitis (Meller et al, 2003; Moosig et al, 2004; Besson et al, 2011; Prieto-Gonzalez et al, 2014*). However, owing to the high background uptake of FDG in the brain, PET is not helpful for the evaluation of medium vessels (temporal arteries and cranial arteries), and does not provide information about wall structure or luminal flow. In a study of 35 patients with new-onset, untreated GCA, increased vascular FDG uptake was seen in 83% of patients, mainly in the subclavian arteries (74%), the aorta (>50%) and the femoral arteries (37%) (Blockmans et al, 2006). An advantage of PET compared with other imaging modalities is that it can show both the severity and the extent of inflammation. In addition, PET can also be used to assess disease activity over time, including response to treatment. In a study performed in five untreated patients with active large vessel vasculitis and after treatment-induced remission, PET was positive in all patients, but FDG uptake clearly decreased compared with baseline in all patients in remission. In another study of four patients with large vessel vasculitis, glucocorticoid therapy led to clinical and laboratory improvement and significantly reduced tracer uptake in all patients, while the mean number of involved segments decreased from 28 to 15. However, in spite of the decreased FDG uptake, it does not disappear in most cases after treatment and other studies have shown an inconsistent correlation between the PET findings and the clinical and laboratory data as well as the MRI images. Therefore, the role of PET in the follow-up of patients with GCA remains unclear. Nevertheless, PET may be more sensitive than MRI in detecting vessel inflammation in the early stage of large vessel vasculitis

Figure 10: Hypoechoic halos surrounding the vessel lumen

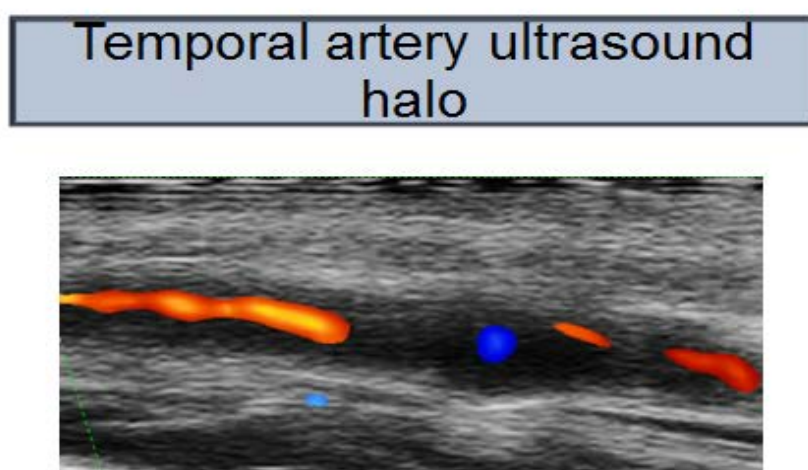


Figure 11: Longitudinal and transverse view – halo sign is visible, hypoechoic homogeneous circumferential.

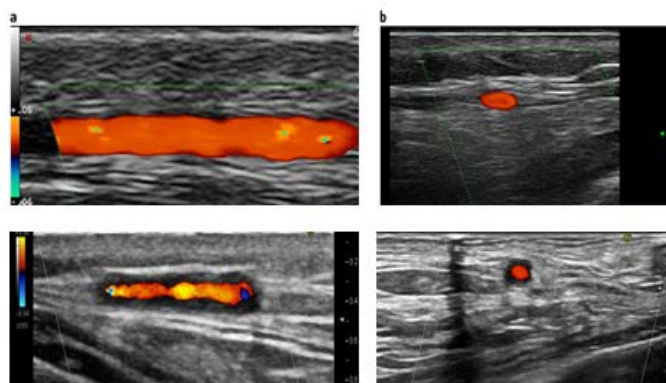


Figure 12: Top left –Longitudinal view of the Axillary artery, increased Intima-medial thickness. Top right shows positive PET scan. Bottom Left and right shows Intima-medial thickness of the axillary artery.

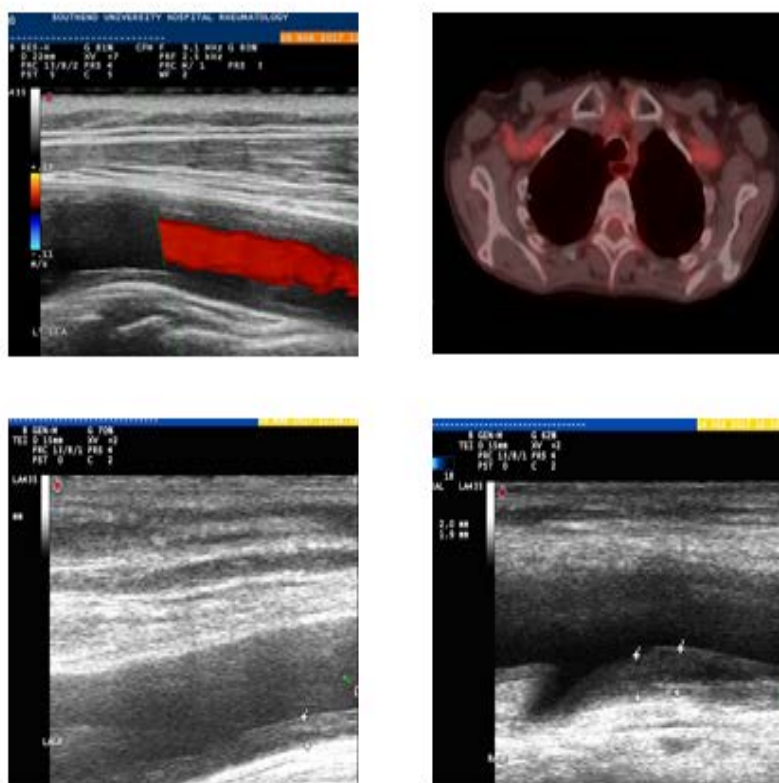
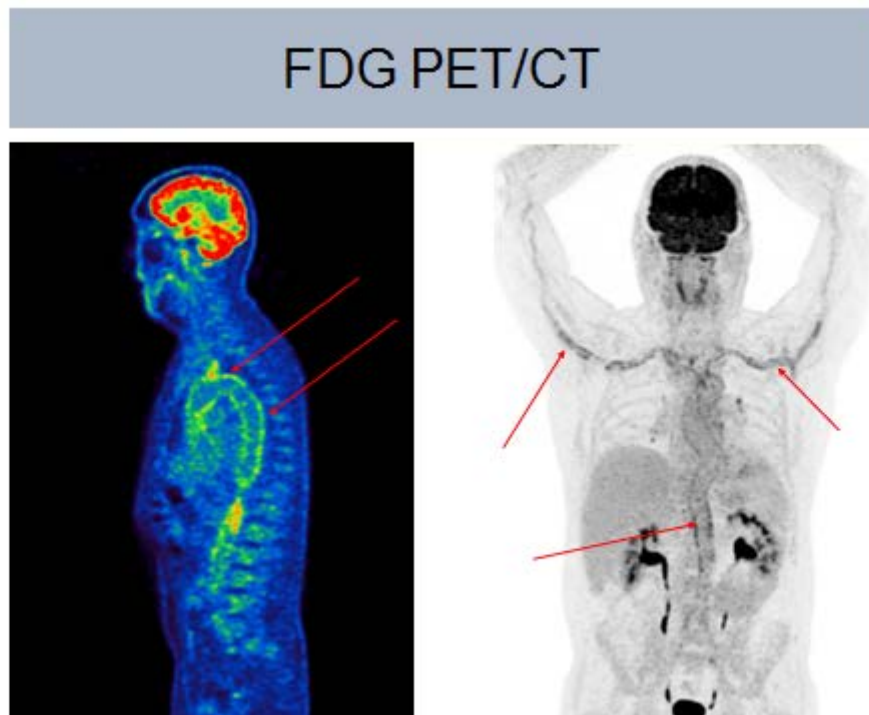


Figure 13: 18 F-Fluorodeoxyglucose positron emission tomography showing the presence of aortitis in a patient with polymyalgia rheumatica with a poor response to low-dose prednisone



There are limited data on the ability of PET to predict the development of complications in vessel segments. However, a study suggested that patients with GCA with increased FDG uptake in the aorta may be more prone to develop thoracic aortic dilatation than patients with GCA without this sign of aortic involvement.

Vascular uptake on PET is not specific for large vessel vasculitis. In a retrospective analysis of 137 patients who underwent PET for various reasons, older patients were found to have increased vascular FDG uptake judged to be secondary to age-related vessel changes, including atherosclerosis. Some characteristics may help to discriminate between atherosclerotic and vasculitic lesions. The vasculitic lesions are usually smooth and linear with an intense FDG uptake, whereas atherosclerotic plaques have a more irregular appearance ('hot spots') with less intense FDG uptake. In addition, the involvement of vessels usually spared by atherosclerosis should raise the suspicion of vasculitis.

Limitations of PET include the lack of visualisation of the temporal and renal arteries, the high costs of the procedure and it's (at the present time) limited availability.

8 Differential diagnosis of PMR and GCA

8.1 Differential diagnoses of PMR

Although the symptoms are very characteristic, several autoimmune disorders, infections, endocrine and malignant disorders can present with similar symptoms and in people aged <60 years inflammatory rheumatic diseases that mimic PMR are more common than PMR itself (table 1) (Gonzalez-Gay et al, 1999a; Gonzalez-Gay et al, 2000b; Gonzalez-Gay et al, 2004c). In particular, PMR should be differentiated from rheumatoid arthritis (especially, elderly-onset rheumatoid arthritis (EORA), late-onset spondyloarthritis (SpA) (Olivieri et al, 2007), calcium pyrophosphate deposition disease (CPPD) (Pego-Reigosa et al, 2005), fibromyalgia, viral myalgia, infective endocarditis (Gonzalez-Juanatey et al, 2001), bilateral rotator cuff syndrome, bilateral adhesive capsulitis ('frozen shoulder'), osteoarthritis of the cervical spine and shoulders, polymyositis, neoplasms including multiple myeloma, hypothyroidism (Ozdogan et al, 2005), late-onset systemic lupus erythematosus (SLE) and Parkinson's disease.

The differential diagnosis between early PMR and EORA is challenging because of a significant overlap of clinical and laboratory findings (Cutolo et al, 2009). Some patients with PMR develop peripheral non-erosive arthritis or tenosynovitis with a carpal tunnel syndrome. Conversely, an initial clinical presentation resembling PMR with marked shoulder involvement is four times more common in EORA than in adult-onset RA. The demonstration of anticitrullinated protein antibodies (ACPA) in elderly patients with inflammatory joint pain also supports the diagnosis of EORA over that of PMR. In one study, 65% of patients with EORA were reported as having ACPA, compared with none of the patients with PMR (Lopez-Hoyos et al, 2004). Similarly, a positive rheumatoid factor, particularly at high titre, would indicate a diagnosis of RA, although the specificity of the rheumatoid factor for RA is lower than that of ACPA, particularly in the elderly. A rapid response to glucocorticoid therapy would also be in keeping with a diagnosis of PMR, although patients with EORA may also improve with glucocorticoids, albeit in a less dramatic fashion. In some cases, a correct diagnosis can only be established at follow-up. A longitudinal study has shown that 6–17% of patients initially labelled as having PMR develop RA over an average of 4 years. The development of joint erosions strongly supports a diagnosis of RA, since arthritis associated with PMR is benign and non-erosive. Similarly, extra-articular manifestations of RA, such as cutaneous nodules, can help to secure its diagnosis.

Table 5 Polymyalgia rheumatica: differential diagnosis and testing

Diagnosis	Clinical features
Inflammatory disorders	
Polymyalgia rheumatica	Age >50 years, predominantly proximal shoulder and hip girdle symptoms, symmetrical; non-erosive joint disease on radiography
Rheumatoid arthritis, especially EORA	Mainly distal joint symptoms; positive for rheumatoid factor and ACPA; erosive joint disease on radiography
Late-onset spondyloarthropathy, including ankylosing spondylitis, psoriatic arthritis	Predominantly low back stiffness and pain; may have large and distal joint symptoms; spinal ankylosis on radiography; psoriasis
Calcium pyrophosphate deposition disease	X-Rays chondrocalcinosis, synovioanalysis
RS3PE syndrome	Peripheral hand or foot pitting oedema
SLE, scleroderma, Sjögren's syndrome, vasculitis	Fatigue, stiffness, multisystem disease; presence of antinuclear antibodies, cytopenias (SLE) and antineutrophil cytoplasmic antibodies
Dermatomyositis, polymyositis	Proximal muscle weakness, rash; high creatine kinase
Other disorders	
Osteoarthritis, spinal spondylosis	Joint pain in shoulder, neck and hips; gelling; degenerative changes on radiography
Rotator cuff disease, adhesive capsulitis (frozen shoulder)	Periarticular pain, restricted range of motion; ultrasound and MRI may show characteristic bursal and synovial inflammation
Infections, including infective endocarditis. Viral syndromes. Tuberculosis	Fever, weight loss, heart murmur, microscopic haematuria, blood cultures. Adapted tests.
Myeloma, lymphoma, leukaemia, occult solid tumours, amyloidosis	Weight loss, fatigue; investigations according to symptoms, sex and age; diffuse aching symptoms not limited to shoulder and hip girdles
Parkinsonism	Stiffness, rigidity, shuffling gait, gradual onset
Fibromyalgia, depression	Fatigue, longstanding pain, tender points, sadness, loss of usual interests
Hypovitaminosis D, osteomalacia, hyperparathyroidism, hyperthyroidism or hypothyroidism	Bone pain, fatigue, blood tests: vitamin D concentrations, parathyroid hormone, calcium, phosphorus, thyroid-stimulating hormone

ACPA, anti-cyclic citrullinated peptide; EORA, elderly-onset rheumatoid arthritis; RS3PE, remitting seronegative symmetrical synovitis with pitting oedema; SLE, systemic lupus erythematosus.

In addition to EORA, late-onset SpA should also be carefully considered in elderly patients with PMR-like manifestations since in this age group SpA may present with typical signs but also with constitutional manifestations, shoulder involvement and, sometimes, distal pitting oedema. The presence of predominant hip pain, sacroiliitis, axial involvement (with or without imaging signs), dactylitis, enthesitis, uveitis and extra-articular manifestations consistent with late-onset SpA (if present) can assist in making a correct diagnosis.

RS3PE can occur in association with PMR, but also with vasculitis, SpA or neoplasms, or be idiopathic. It should be distinguished from lymphoedema, usually found in association with RA or less frequently with psoriatic arthritis. Compared with RS3PE, lymphoedema has a harder feeling on palpation and does not respond to glucocorticoid therapy.

CPPD may occasionally present with polymyalgia-like symptoms. The identification of calcium pyrophosphate dihydrate crystals in the synovial fluid, the demonstration of the typical radiographic findings seen in CPPD, or both, can secure the correct diagnosis.

Late-onset SLE presenting as PMR has been previously reported. The presence of positive antinuclear antibodies in elderly individuals by itself does not exclude PMR. In patients with PMR the presence of leukopenia with lymphopenia and, especially, unexplained high titres of antinuclear antibodies, should prompt a more complete analytical study including proteinuria, anti-native DNA, anti-extractable nuclear antigen (anti-ENA), C3 and C4 laboratory tests. In these cases a detailed clinical history may be of help in eliciting symptoms related to SLE if present. A physical examination may also disclose clinical features such as pleuritis or pericarditis that are common in late-onset SLE which, together with the presence of haematological abnormalities such as leukopenia or thrombocytopenia, should raise suspicion of this condition.

Polymyositis presents with muscle pain, but early morning stiffness is not a feature of this condition, and above all, muscle strength, which is normal in PMR, is typically impaired in polymyositis. Laboratory tests, particularly a raised creatine kinase, and other investigations for muscle disease (if clinical necessary) (electromyography and muscle biopsy) allow confident discrimination of polymyositis from PMR.

Infective endocarditis may mimic PMR. Although fever may be a symptom of PMR in up to 35% of patients, other conditions presenting with fever and polymyalgia symptoms should be considered when there are reasons to suspect an underlying disease, particularly when there is little response to glucocorticoids. In this case, the possibility of an underlying systemic infection, even when fever is low grade, should be ruled out. The presence of unexplained malaise and low grade fever along with musculoskeletal manifestations are good reasons to exclude bacterial endocarditis that may cause musculoskeletal manifestations in up to 30% of patients (blood cultures must be performed if this diagnosis is evoked).

Viral myalgia can occur in the presence of various viral infections, and may be associated with systemic manifestations and raised inflammatory markers. However, viral myalgia is usually diffuse and quickly or rather quickly remits spontaneously.

Osteoarthritis of the cervical spine and shoulders is a common condition in the elderly population. Osteoarthritis of the acromioclavicular joints is associated with the growth of osteophytes impinging ('impingement syndrome') on the underlying rotator cuff, leading to rotator cuff damage and pain. The

combination of neck and shoulder pain can suggest PMR, but the mechanical characteristics of the pain, the absence of prolonged early morning stiffness and the normal inflammatory data assist in ruling out PMR.

Rotator cuff tendinitis can cause shoulder pain radiating down to the elbows, sometimes with nocturnal pain when lying on the affected shoulder. However, in rotator cuff tendinitis the symptoms are often initially unilateral (although they may become bilateral over time), pain is mechanical (although it may become inflammatory later on) and inflammatory markers are not raised.

Adhesive capsulitis ('frozen shoulder') rarely can mimic PMR when it affects both shoulders at the same time, since in the early stages the inflammatory pain dominates the clinical picture of adhesive capsulitis, and the typical restriction of joint movements (especially external rotation) occurs only weeks to months after disease onset. The absence of raised inflammatory markers and of bursitis on US can aid in differentiating adhesive capsulitis from PMR.

Neoplasms, particularly multiple myeloma and renal adenocarcinoma, can very occasionally present with PMR-like clinical features. However, in these cases there is usually limited or absent early morning stiffness, little if any proximal joint restriction, no evidence of bursitis or glenohumeral synovitis in the shoulder on US and poor response to low-dose glucocorticoid treatment. Some patients with a cancer have a paraneoplastic polyarthritis, as may patients with a myelodysplasia.

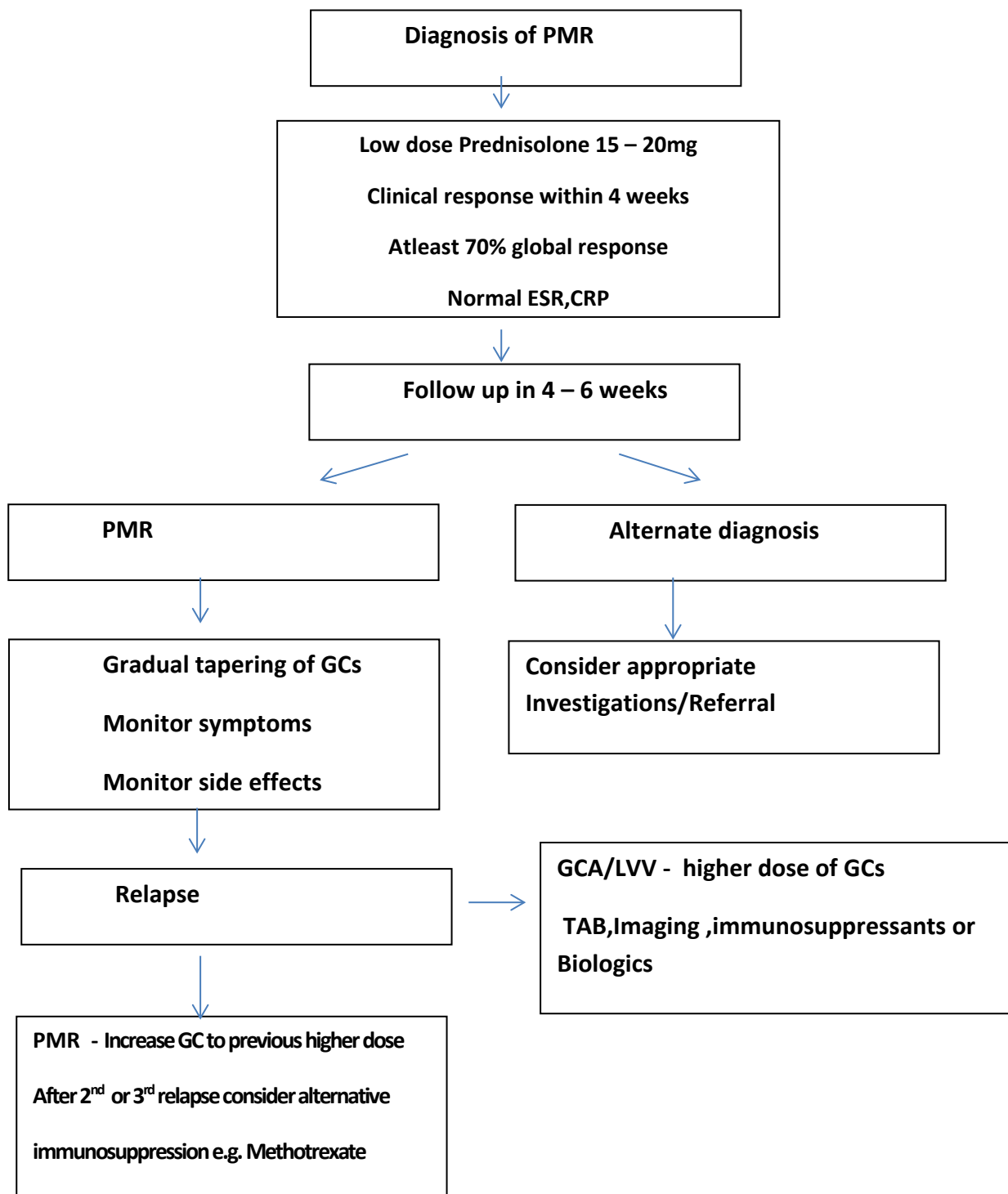
Parkinson's disease may be confused with PMR when muscle stiffness predominates in the shoulder and pelvic girdles and other clinical features of Parkinson's disease, such as tremor, are less conspicuous. In such cases, the lack of improvement in stiffness during the day and the absence of raised inflammatory markers should cast suspicion on a diagnosis of PMR, while a careful search for subtle signs of neurological involvement can lead to the correct diagnosis.

Drugs —for example, statins can also cause symptoms mimicking PMR. Immune checkpoint inhibitors may induce real arthritis as RA, SpA or ...PMR.

Fibromyalgia can cause muscle pain and a feeling of stiffness aggravated by exposure to cold and heavy physical activity, particularly in the neck and shoulder area, but inflammatory indices are not raised. Physical examination in fibromyalgia typically discloses positive tender points in the absence of synovitis.

Hypothyroidism can cause pain and stiffness in the muscles, including those around the shoulders, and can mimic PMR. However, in hypothyroidism muscle stiffness does not substantially improve as the day goes on. In its most pronounced form (Hoffmann's syndrome), hypothyroid muscle disease can present with muscle pain, stiffness and muscle hypertrophy. The differential diagnosis is generally easy because hypothyroid muscle disease is often associated with other clinical features of hypothyroidism. Laboratory tests show normal inflammatory markers, altered thyroid function and moderately raised creatine kinase levels.

A flow chart based on previous reports of the diagnosis and management of patients presenting with polymyalgia-like symptoms, is shown in figure 5.



8.2 Differential diagnosis of GCA

Every patient with suspected GCA requires a confirmatory diagnostic (histologic or imaging) test. The diagnosis of typical high probability GCA is relatively simple, but can be challenging if it presents with atypical features.

Temporal artery involvement is highly suggestive of GCA, although cases of headache due to temporal artery involvement in the presence of primary systemic necrotising vasculitides such as polyarteritis nodosa or granulomatosis with polyangiitis or cases of amyloidosis have been described. In such cases, TAB is invaluable in securing the correct diagnosis.

New-onset headache is also one of the most common presenting symptoms of primary central nervous system vasculitis. However, cerebral vasculitis is rare in GCA.

In elderly patients, LV-GCA accounts for about one-sixth of cases of fever of unknown origin. Therefore, vasculitis should be suspected in older patients with fever of unknown origin who have no evidence of infection or neoplasm. A PET-CT in this context may be very valuable to rule in GCA and exclude other serious pathology.

Visual loss, usually due to AION, is a very early, and often the initial, manifestation of GCA. In patients with visual loss, diagnosing GCA is easy in the presence of other clinical manifestations consistent with GCA and the finding of raised acute phase reactants. There are reports of occult GCA where diagnosis is made only after sight loss. In most such cases direct questioning reveals presence of non-specific constitutional and MSK symptoms that can be missed in the elderly. In these cases, the diagnosis usually rests on the demonstration of raised acute phase reactants and a confirmatory imaging or TA biopsy. AION should be differentiated from non-arteritic AION (NAION). NAION is commoner than AION, occurs almost exclusively in Caucasians at a younger age than GCA and is characterised by a sudden visual loss in one eye without premonitory signs. Contralateral eye involvement in NAION can occur, but is less common than in AION. Fundoscopy usually shows hyperaemic (less often pale) oedema of the optic disc with a small cap size. Systemic manifestations are not associated with NAION. Optical coherence tomography with angiogram is a research tool that may help differentiate the two disorders. Finally, cases of carotid occlusion mimicking GCA have also been described (González-Gay et al, 1998d).

9 Treatment of PMR and GCA

9.1 Treatment of PMR

Glucocorticoids remain to date the cornerstone of treatment for PMR and GCA (Gonzalez-Gay et al, 2006; Hernandez-Rodriguez et al, 2009; Gonzalez-Gay et al, 2010a; Gonzalez-Gay et al, 2010b; Kermani and Warrington, 2013*; Matteson et al, 2016). Non-steroidal anti-inflammatory drugs are of little value in the management of PMR. Treatment guidelines have been published by the British Society of rheumatology (BSR) and a collaborative initiative of the European League Against rheumatism (EULAR) and the American college of Rheumatology (Dejaco C 2015).

Low dose Glucocorticoids are the recommended standard treatment for PMR.

In PMR, an initial dose of 10–20 mg of prednisone or prednisone-equivalent per day is sufficient in the vast majority of cases to control the inflammatory symptoms. Starting doses of prednisone or an equivalent of >10 mg/day have been shown to be associated with fewer relapses and shorter treatment duration, while starting doses of >15 mg/day have been linked to a higher cumulative prednisone dose and more glucocorticoid-related adverse events. Most patients respond to glucocorticoid therapy within a few days, generally in less than 1 week, with complete or nearly complete resolution of their pain and stiffness, although very occasionally a patient may require a prednisone dose of up to 30 mg daily to attain disease control. A rapid response in 24–72 h can help to confirm the diagnosis.

Lack of clinical improvement after treatment with prednisone 20 mg daily for a week should prompt the physician to question the diagnosis of PMR and consider other diagnoses. Higher glucocorticoid dosages may be effective in inflammatory conditions other than PMR and thus are best avoided as they may delay the correct diagnosis. Lack of complete response as well as atypical clinical features, such as peripheral joint disease, pain with little stiffness and muscle weakness, should prompt consideration of alternative diagnoses.

Higher doses of prednisone are not likely to provide an additional benefit in isolated PMR and have, in fact, been linked both to more frequent glucocorticoid-related adverse reactions and to an increased risk of relapse. In addition, glucocorticoid pulse therapy (intravenous methylprednisolone 250 mg daily for 3 days) did not induce clinical remission or reduce the cumulative glucocorticoid dose and is thus not recommended (Cimmino et al, 2004). EULAR/ACR recommend tapering to 10mg/day within 4 – 8 weeks followed by a taper by 1mg every 4 weeks assuming patients are in remission.

Fast tapering schemes are best avoided as they substantially increase the risk of disease relapse.

Persistently raised concentrations of CRP and IL-6 have also been associated with a relapsing disease course in PMR. However, an increase in inflammatory markers in the absence of clinical symptoms does not in itself mandate an increase in the dose of glucocorticoid. It is important to treat the patient's symptoms and not rely exclusively on inflammatory markers to guide treatment. Persistence of a raised ESR may be indicative of an additional condition.

In general, a treatment course of 1–2 years is often required, but some patients might need to continue receiving glucocorticoid (mostly at low doses) for several years and even indefinitely, often maintained on 2.5–5 mg of prednisone daily. The dose should be kept as low as possible to treat the symptoms in remission.

If relapse occurs (Myklebust and Gran, 2001; Kremers et al, 2005), it may be necessary to increase the steroid dosage to the previously effective level. However, it is important to keep glucocorticoid toxicity as low as possible and to implement osteoporosis prevention methods. Management of comorbidities, including

prophylaxis for cardiovascular disease, is also necessary. Blood pressure, blood lipids and blood glucose should be assessed and the patient screened for osteoporosis. Prophylaxis for osteoporosis should be started within the first few weeks of treatment.

Glucocorticoids are notorious for adverse events, which are largely related to the cumulative dose. In a study of 124 patients with PMR treated with glucocorticoid alone, 65% had at least one glucocorticoid-related adverse event. High risk phenotypes (treatment unresponsive at 4 weeks, older age at diagnosis, females, high inflammatory markers, risks for GCs adverse events) may benefit from early initiation of adjunctive immunosuppressants (Dejaco C 2015)

Some attempts have been made to investigate other drugs as glucocorticoid-sparing agents. Two randomised controlled trials (RCTs) have investigated the efficacy of methotrexate (MTX) in PMR (Van der Veen et al, 1996; Caporali et al, 2004). In one of these RCTs, 40 patients with PMR (six of whom also had symptoms of GCA) were randomised to prednisone 20 mg daily with a rapid tapering scheme and either MTX 7.5 mg by mouth weekly or placebo. Twenty-one patients were followed up for at least 2 years, or 1 year after treatment withdrawal. There was no difference between the study arms for time to remission, number of relapses or cumulative glucocorticoid dose. In a subsequent RCT, 62 patients with PMR were treated with an initial dose of prednisone 25 mg daily, which was tapered within 24 weeks in the absence of flares. Thirty patients received placebo and 32 received MTX 10 mg by mouth weekly for 48 weeks. This study showed significant differences in the outcome measures between the two study groups: (a) 28 of 32 patients in the MTX group and 16 of 30 patients in the placebo group were able to discontinue prednisone at 76 weeks; (b) 15 of 32 patients in the MTX group and 22 of 30 patients in the placebo group had at least one flare-up by the end of follow-up; and (c) the median prednisone dose was lower (2.1 g) in the MTX group than that (2.97 g) in the placebo group. Despite these differences, the rates and severity of adverse events were similar in both study arms. These results suggest that MTX may be effective in reducing the incidence of relapses and the amount of prednisone needed to maintain remission when the drug is started at disease onset and given for at least 1 year at a dose of at least 10 mg a week. However, the reduction in the cumulative glucocorticoid dose achieved in this trial was not paralleled by a decreased frequency and severity of glucocorticoid-related adverse events. It remains to be established whether MTX at higher doses might prove more effective or act more rapidly. It is also unclear how effective MTX would be when given in patients with longstanding disease refractory to glucocorticoid.

Small retrospective series have suggested possible efficacy of leflunomide [Adizie T 2012, Diamantopolos AP 2013]. In a series of 14 patients with refractory PMR, partial (GC reduction) and complete (GC discontinuation) responses were observed in 9 and 4 patients respectively with addition of LEF [Adizie T 2012]. In another series of 12 patients with PMR, 34% patients were able to reduce GC doses with improvement in

CRP levels at 10.5 months [Diamantopoulos AP 2013]. RCTs are in setup to explore the role of this medication in PMR and GCA.

A number of studies have reported the use of tumour necrosis factor α (TNF α) blocking agents in PMR (Catanoso et al, 2007). In a pilot study, four patients with longstanding, relapsing PMR and glucocorticoid-related adverse events who were unable to decrease their prednisone dose below 7.5–12.5 mg daily were treated with the anti-TNF α monoclonal antibody infliximab (3 mg/kg intravenously) at baseline and after 2 and 6 weeks (three infusions only) (Salvarani et al, 2003). Three of the four patients were able to stop taking prednisone without experiencing disease relapses. Similarly, the TNF α receptor Fc-fusion protein etanercept 25 mg given subcutaneously twice weekly showed efficacy in six patients with longstanding PMR taking prednisone 7.5–10 mg daily. In one patient, glucocorticoids could be withdrawn, while in five the prednisone dose could be reduced to 2.5 mg daily without any resulting flare. There were two cases of urinary tract infection and one case of influenza.

In contrast to these encouraging results in patients with longstanding PMR, infliximab has not proved more effective than placebo in an RCT of patients with newly diagnosed PMR (Salvarani et al, 2007). In that study, 51 patients with newly diagnosed isolated PMR received prednisone 15 mg/day tapered over 16 weeks in the absence of flares. Infusions of placebo or infliximab (3 mg/kg) were given at 0, 2, 6, 14 and 22 weeks. The primary study outcomes were the numbers of patients with a relapse or who were recurrence-free, while secondary outcomes included the number of patients no longer taking prednisone, the number of flares, the duration of prednisone therapy and the cumulative prednisone dose throughout the planned trial duration of 52 weeks. The results of this study showed no significant effect of infliximab on any of the outcome variables at weeks 22 and 52. There was no significant difference in adverse events between the study arms. This trial had a number of limitations, including the relatively low dose of infliximab used, the rapid tapering of prednisone, the small sample size and the short duration of follow-up.

The authors of this RCT concluded that although too small to be definitive, the trial provided evidence that adding infliximab to prednisone for treating newly diagnosed PMR is of no benefit and may be harmful. They emphasised that if there is a benefit, it is unlikely to be large.

A more recent RCT designed to study the effect of etanercept in newly diagnosed, glucocorticoid naive patients with PMR showed that the PMR activity score decreased by 24% in the patients with PMR treated with etanercept, but did not change significantly in the placebo-treated patients (Kreiner and Galbo, 2010)

However in view of all these apparently contradictory results, the EULAR/ACR treatment guidelines do not recommend anti-TNF therapy in PMR

Tocilizumab is efficient in refractory PMR (Hagihara et al, 2010, Seitz et al, 2011; Toussirost et al, 2016.

Devauchelle-Pensec et al, 2015 have demonstrated in an open-label uncontrolled trial (“TENOR study”) that tocilizumab is efficient as a first-line treatment for PMR. Twenty patients with PMR were treated with three tocilizumab intravenous infusions at an initial dose of 8 mg/kg with 4-weeks intervals followed by oral prednisolone. At 12 weeks, the primary end-point of a PMR activity score <10 was achieved in all patients.

The TENOR study has revealed the efficacy for the first time of a treatment other than glucocorticoid in PMR, but the risk: benefit ratio of tocilizumab has to be considered, especially the risk of infections, leukopenia, elevations of liver transaminases, modifications of serum lipid levels and alterations in cholesterol composition.

9.2 Treatment of GCA

As described for PMR, glucocorticoids are also mainstay treatment in GCA (Salvarani et al, 2008b; Gonzalez-Gay et al, 2010a; Gonzalez-Gay et al, 2010b; Masson, 2012*; Matteson et al, 2016, Bienvenu et al, 2016, Dejaco et al, 2015a, Dejaco et al, 2015b, Das, et al, 2015). They are the preferred treatment because of their ability to rapidly control inflammatory symptoms and prevent most ischaemic manifestations, including visual loss.

In patients with GCA, without severe ischaemic complications, an initial dose of prednisone or its equivalent of 40 mg/day (or 0.7 mg/kg) is usually recommended. But in patients with GCA who present with visual ischaemic complications or other severe ischaemic manifestations, such as cerebrovascular accidents or large artery stenosis of the extremities resulting in occlusion (limb claudication) of recent onset, an initial prednisone dose of 60 mg/day is necessary.

The use of glucocorticoids has dramatically decreased the frequency of severe visual ischaemic complications in patients with GCA. Indeed, a decrease in the incidence of permanent visual loss was seen in Olmsted County, Minnesota (USA), where 19% of patients with GCA were blind during the period 1950–1969 compared with 6% during the period 1980–1985.

Data show that it is not the absolute dose but the time from onset of symptoms to first administration of glucocorticoids that is predictive of improvement in visual loss.

Once visual loss is established, the prognosis for significant visual recovery in patients with GCA despite glucocorticoid therapy is poor. Literature review suggests that glucocorticoid therapy should not be delayed under any circumstances in patients with GCA with suspected visual impairment. The efficacy of high-dose oral prednisone is comparable to that of intravenous pulse glucocorticoid therapy.

Apart from visual loss, most GCA symptoms usually begin to improve within 24–72 h after the start of glucocorticoid therapy. Also, normalization of routine laboratory parameters of inflammation (CRP, and then ESR) occurs within 2–4 weeks after starting this treatment. The glucocorticoid dose can then be gradually tapered. Prednisone is generally reduced by 5 mg every 2–4 weeks down to 25 mg. It can then be reduced by 2.5 mg every 2–4 weeks until the dose is 10 mg and later by about 1 mg every month. However, the duration of glucocorticoid therapy in GCA is variable; nearly half of them relapses, may last for 2–4 years, and sometimes cannot be stopped.

There have been contradictory data regarding benefit of IV over oral GCs in this subgroup with visual impairment (Gonzalez – Gay MA 1998, Liu GT 1994,). A study compared an initial high-dose pulse of intravenous methylprednisolone with standard oral glucocorticoid therapy (Mazlumzadeh et al, 2006). The authors carried out a double-blind, placebo-controlled, randomized, prospective clinical trial: a 3-day course of intravenous methylprednisolone pulses (15 mg/kg of ideal body weight/day) in addition to oral prednisone (n = 14) compared with normal intravenous saline infusions plus oral prednisone (n = 13). The initial intravenous pulse of methylprednisolone therapy yielded more rapid glucocorticoid tapering, a lower median dose at each visit and fewer relapses. However, further studies including larger numbers of patients are required to establish the routine use of intravenous pulse methylprednisolone as initial glucocorticoid therapy for the management of GCA.

Adjunctive therapies:

The incidence of GC related side effects is very high and reported to be around 86% over 10 years; therefore alternative Immunosuppressive agents are desperately needed to reduce the GCs burden. Indeed, alternative glucocorticoid-sparing drugs should be considered in patients with GCA with severe glucocorticoid-related side effects and/or in patients who require prolonged glucocorticoid therapy owing to disease relapse. MTX was evaluated in newly diagnosed GCA in three RCTs, which produced discordant results. The first study by Spiera et al compared 12 patients treated with MTX starting at 7.5 mg/week with nine patients treated with a matched placebo (Spiera et al, 2001).

All patients received high-dose glucocorticoid treatment with the dosage tapered according to clinical response, while the dose of MTX or placebo was increased by 2.5 mg/week for disease flare up to 20 mg/week. There were no significant differences at the end of the study between MTX- and placebo-treated patients in the cumulative glucocorticoid dose and number of weeks to taper the glucocorticoids. Side effects did not significantly differ between groups.

The other two randomized clinical trials of the use of MTX in GCA included larger numbers of patients but had contradictory results. Jover et al studied 42 patients from Madrid (Spain) (Jover et al, 2001). A single weekly dose of oral MTX (10 mg) or placebo was started on diagnosis, maintained throughout the treatment period

and discontinued after 24 months of follow-up if clinical signs of disease activity were absent. All patients started treatment with oral prednisone 60 mg/day during the first 2 weeks and then gradually tapered. This 24-month placebo controlled trial showed a significant reduction in the rate of relapse of GCA and mean prednisone dose in MTX-treated patients compared with a placebo group, but no differences in the severity of the disease and the side effects.

Hoffman et al performed multicentre randomized clinical trial of MTX in GCA (Hoffman et al, 2002). In this study the initial treatment was prednisone 1 mg/kg/ day (≤ 60 mg every day), plus 0.15 mg/kg/week MTX (increased to 0.25 mg/kg/week, for a maximum weekly dosage of 15 mg) or placebo. The median dose of MTX was 15 mg/week. Unfortunately, this multicentre study did not support the adjunctive use of MTX to control disease activity or to decrease the cumulative dose and toxicity of glucocorticoids in patients with GCA.

The data from the above three RCTs were the subject of a formal meta-analysis, which showed that adjunctive MTX treatment at 7.5–15 mg per week reduced the risk of a first relapse in GCA by 35%, and of a second relapse by 51% (Mahr et al, 2007). Adjunctive MTX treatment also reduced the cumulative glucocorticoid dose. However, the incidence of glucocorticoid-related side effects was similar in both groups. Furthermore, the clinical effect of MTX fully appeared only after 24–36 weeks.

Therefore, while MTX appears to be effective in GCA, it does not act rapidly. As a result, MTX cannot be recommended as a replacement for glucocorticoids at disease onset. Equally important, adjunctive MTX therapy has not been shown to decrease the incidence of glucocorticoid-related complications, which raises the question of the real clinical significance of adjunct MTX therapy in GCA. It is unclear whether higher-dose MTX (20–25 mg/week) would be more effective or act more rapidly, or how effective MTX would be when given to patients with longstanding, glucocorticoid-refractory GCA.

Azathioprine given at 150 mg daily has been assessed in a 52-week, double-blind placebo-controlled trial in 31 patients with PMR, GCA or both (De Silva and Hazleman, 1986). All patients had been receiving stable prednisolone for at least 3 months before being enrolled. The results showed a statistically significant difference in the mean prednisolone dose (1.9 ± 0.84 mg in the azathioprine arm vs 4.2 ± 0.58 mg in the placebo arm), but only at week 52. However this study recruited both PMR and GCA patients, therefore it is difficult to ascertain whether there was a true effect in GCA.

Leflunomide

Two case series of leflunomide as a GC sparing in GCA have been published with nine and 12 patients (Adizie T 2012, Diamantopoulos AP 2013). Each study showed improvement in prednisolone dose tapering, suggesting that leflunomide may have a role as steroid sparing.

TNF α inhibitors have also been used in some patients with GCA. The rationale for their use is based on evidence of TNF α synthesis in inflamed temporal arteries and demonstration of raised circulating TNF α levels in patients with GCA.

Three RCTs of TNF- α antagonists failed to show efficacy in GCA [Hoffman GS 2007, Martinez-Taboada VM 2008, Seror R 2014]. The studies used different anti-TNF therapies (ETN, IFX and adalimumab (ADA)), different populations of patients (newly diagnosed in 2 studies) and had different endpoints which limits their interpretability. In a multicentre RCT of 44 patients with new GCA randomized to GCs and IFX (5 mg/kg, 28 patients) or GCs and placebo (16 patients), relapse free survival at 22 weeks (primary outcome) was similar in both groups (43% IFX versus 50% placebo, $p=0.65$) (Hoffman 2007). Infectious AEs were observed in 47% in the IFX group compared to 23% in the placebo arm with serious infections in 11% of the IFX patients and 6% of the patients on placebo. In another RCT of only 17 patients with biopsy-proven GCA randomized to ETN 25 mg twice weekly (8 subjects) or placebo (9 subjects), GC discontinuation at 12 months (primary outcome) was met in 50% in the ETN arm compared to 22% in placebo arm (NS) [Martinez Taboada 2008]. A RCT using ADA 40 mg every other week (34 patients) or placebo (36 patients) for 10 weeks in patients with newly diagnosed GCA, found no differences in remission on less than 0.1 mg/kg of prednisone at week 26 (59% ADA arm and 50% placebo arm, $p=0.46$) [Seror R 2014]. Serious AE occurred in 5 patients (3 serious infections) on ADA and 17 patients (5 serious infections) on placebo.

Anti-TNF therapies have not shown benefit in GCA. The draft BSR GCA guidelines do not advocate the use of anti-TNF blockade in GCA (manuscript in preparation).

The treatment option for patients whose disease is resistant to glucocorticoids (GCs) and who have an insufficient response to standard GCs for induction of remission, and GC-dependent cases after successful induction of remission, remains an open question, with the need for other prospective trials (Kötter et al, 2012*). The new prospects for PMR and GCA treatment include fairly convincing evidence for a role for IL-6 in both PMR and GCA. Interleukin – 6 induces acute phase responses and has a central role in the pathogenesis of GCA (Dasgupta B 1990, Garcia – Martinze A 2010, Weyand CM 2000, Weyand CM 2011). The IL-6 blocker tocilizumab (TCZ) (a humanized anti-IL-6 receptor monoclonal antibody) has been reported to be effective in several published case series with large vessel vasculitis (Unizony et al, 2012, Loricera et al, 2015, Regent et al, 2016).

A single-centre phase II randomized placebo-controlled study has demonstrated the efficiency of TCZ in the induction and maintenance of remission in patients with 23 newly diagnosed GCA (Villiger et al, 2016). GCs were tapered and discontinued using a standardized protocol. The primary outcome of complete remission at a prednisolone dose of 0.1 mg/kg/day at week 12 and was met in 85% of patients in the TCZ group compared to 40% in the placebo group ($p=0.03$). Relapse-free survival at week 52 was observed in 85% patients in the TCZ group compared to 20% with placebo ($p=0.001$). Adverse effects were observed in 15 patients (75%) in the

TCZ group (26 events; 7 serious adverse effects) and 7 patients (70%) in the placebo group (23 events; 10 serious adverse effects). Infectious were observed in 10 patients in the TCZ group compared to 1 in the placebo arm.

In a recent randomized, double blind, placebo controlled, phase 3 trial, the Giant cell arteritis Actemra (GiACTA) trial showed beneficial results with Tocilizumab (J Stone et al 2017).

251 patients with newly diagnosed or relapsing disease were randomized 1:1:2:1 to 26 week prednisone taper and placebo, 52 week prednisone taper and placebo, 26 week prednisone taper and TCZ 162 mg subcutaneously weekly or 26 week prednisone taper and TCZ 162 mg subcutaneously every other week. Primary endpoint was the proportion of patients in sustained remission (week 12 to week 52) in the TCZ group compared to the 26 week prednisone and placebo group (significance level set to 0.005) and the key secondary outcome of sustained remission was assessed against the 52 week GC taper group . Sustained remission occurred in 56.0% of patients in the TCZ-weekly arm and 53.1% in the TCZ-every-other-week arm, compared with 14.0% in placebo-26-week prednisone taper and 17.6% in placebo-52-week prednisone taper (P<0.001 for comparisons of either active treatment to placebo at each time point). The cumulative median prednisone dose over 52 weeks was 1862 mg in each of the TCZ groups compared with 3296 mg in the placebo-26-week group (p<0.0001) and 3818 mg in the placebo-52-week group (P <0.0003). Any adverse effects was observed in the majority of patients as follows: 98.8% weekly TCZ group, 95.9% every other week TCZ group, 96% of the 26-week prednisone arm and 92.2% of the 52-week prednisone arm .Serious adverse effects were seen with 15.0% of TCZ-weekly, 14.3% of TCZ-every-other-week, 22.0% of placebo-26-week taper, and 25.5% of placebo-52-week taper patients. Serious infectious were observed in 7% and 4.1% of the weekly and every other week TCZ arms respectively, and, 4% and 11.8% of the 26 week and 52 week prednisone arms respectively. Long-term follow-up is required regarding safety and sustained remission.

Another large phase III, randomized, placebo-controlled trial evaluating a different IL-6 antagonist, sirukumab is currently under way (ClinicalTrials.gov identifier NCT02531633).

Activated T-cells have also been implicated in the pathogenesis of GCA. In a multicentre, randomized, study, 49 patients were treated with prednisone and abatacept (ABA) (10 mg/kg intravenously on days 1, 15, 29 and week 8) [Langford CA 2017]. At 12 weeks, 41 patients who were in remission were randomized to ABA (intravenously monthly, N=20) or placebo (N=21). Prednisone was tapered by using a standardized protocol. Relapse-free survival at 12 months was 48% in the ABA group compared to 31% in the placebo group (p=0.049). Median duration of remission was also longer for the treatment group (9.9 months) compared to placebo group (3.9 months) (p=0.023). Overall, adverse effects were observed in 35 patients (129 events; 23 serious adverse effects). This included 33 infections; 2 of which required hospitalization .There were no differences in frequency of AE between the two arms. The results of this study are promising.

IL-12 and IL-23 in the Th1 and Th17 responses are also recognized in the pathogenesis of GCA, therefore ustekinumab, a monoclonal antibody against IL-12/23p40, was studied in an open-label study of 14 patients with GCA with a median prednisolone dose of 20 mg/day and median of 2 relapses. 86% of the patients had also failed other adjunctive immunosuppressive therapy. After a median follow-up of 13.5 months (range 7-26 months), none of the 14 patients experienced a relapse, prednisolone was lowered to median 5 mg/day and 4 patients (29%) were able to discontinue prednisolone completely. There were 6 adverse effects; 4 of which were infectious (Conway R 2016)

Aspirin may be considered for the adjuvant treatment of patients with GCA. Thus, two retrospective studies suggested that low-dose aspirin may prevent ischaemic complications due to GCA (Nesher et al, 2004; Lee et al, 2006). In one study, only 8% of the aspirin-treated patients presented with cranial ischaemic complications, compared with 29% of the non-aspirin-treated patients. Similarly, after the start of glucocorticoid treatment, cranial ischaemic complications developed in only 3% of the aspirin-treated patients compared with 13% of the patients treated with glucocorticoid alone. In another retrospective study, 16.2% patients receiving antiplatelet or anticoagulant therapy had a GCA-related ischaemic event compared with 48.0% not receiving such treatment. Therefore, according to these results, antiplatelet therapy started before GCA diagnosis may reduce the risk of severe ischaemic events in patients with GCA. Thus, in view of the above-mentioned data, we recommend the prescription of aspirin (75–125 mg/day) in patients with GCA, although there is no formal evidence of efficiency from other studies (Berger et al, 2009; Salvarani et al, 2009) and RCTs are lacking (Mollan et al, 2014).

Bone protection treatment should be considered in patients with GCA as long-term glucocorticoid therapy induces bone loss. Therapeutic agents aimed at restoring balanced bone cell activity, either by directly decreasing the rate of osteoblast apoptosis (such as cyclical parathyroid hormone) or by increasing the rate of osteoclast apoptosis (such as bisphosphonates), are potentially useful in the management of people with GCA or PMR receiving long-term glucocorticoid therapy.

10 Course and mortality in GCA and PMR

Approaches to rapid diagnosis and treatment have recently been shown to reduce the incidence of sight loss associated with GCA. In one study, there was a reduction in incidence of blindness from 37% in the historical cohort to 9% following introduction of fast track pathway (Patil P 2015) Similarly implementation of an outpatient fast track ultrasound GCA clinic in Norway resulted in significant reduction in permanent visual impairment in GCA patients compared with those treated conventionally (RR0.12, 95%CI: 0.01 – 0.97) with a

reduction in inpatient days (Diamantopoulos 2016). These studies suggest that early diagnosis and intervention in GCA management can reduce permanent visual loss.

Frequencies of severe infections and rates of infection-related mortality are increased during the first year after the diagnosis of GCA (Schmidt et al, 2016). The risk of infection in this multicentre, prospective, double-cohort study increases in GCA patients with older age or in the presence of diabetes, or if the average dose of corticosteroids is over > 10 mg/day after twelve months of treatment.

Relapses are common in GCA and PMR (Gonzalez-Gay et al, 1999c; Salvarani et al, 2005b; Martinez-Lado et al, 2011). The rate of relapse is higher in those with fast tapering of the steroids. However, disease flares can occur throughout the course of glucocorticoid therapy and be independent of the glucocorticoid regimen. Typical flares of the disease are associated with raised ESR and CRP as well as with disease-related manifestations. A population-based study confirmed a high frequency (41%) of relapses or recurrences in patients with biopsy-proven GCA. Those patients with GCA who had relapses or recurrences did not show clinical differences in comparison with the remaining patients with biopsy-proven GCA. However, the total duration of glucocorticoid therapy was significantly longer in the patients who had relapses or recurrences of the disease. The median dose of prednisone and the median duration of glucocorticoid treatment at the time of the first relapse were 5 mg/day and 16 months, respectively. Headache (52%) was the most common feature at the time of first relapse of GCA. PMR manifestations occurred in 30% of the patients with biopsy-proven GCA at the time of first relapse, but none developed visual loss. The presence of anaemia (haemoglobin <12 g/dL) at the time of disease diagnosis was the best predictor of relapse or recurrence of GCA.

Despite the increased risk of irreversible visual loss and the increased frequency of aortic aneurysmal disease in patients with GCA, most long-term survival studies have shown no excess mortality in GCA or PMR (Delecoeuillerie et al, 1988; Schaufelberger et al, 1995; Matteson et al, 1996; Gonzalez-Gay et al, 1997a; Bahlas et al, 1998; Gran et al, 2001; Gonzalez-Gay et al, 2007a).

As with many other rare diseases, it is important to understand the natural history of the disease. Few longitudinal prospective studies, French GRACG, Slovenian and Spanish prospective cohorts have provided valuable information regarding clinical features, risk of relapse and complications. However there is an unmet need to study further biomarkers, histopathological diagnosis, prognostic markers, standardized data collection and patient reported outcomes.

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SUMMARY POINTS

- Polymyalgia rheumatica (PMR) is an inflammatory disorder characterised by pain, aching and morning stiffness in the shoulder girdle and often in the pelvic girdle and neck. Recent classification criteria has provided differentiation of PMR from several possible mimics of this disease and a stepwise assessment which includes inclusion and exclusion criteria and use of low-dose steroids. Examination should also include evaluation of the temporal arteries, peripheral pulses and auscultation for bruits. If vascular abnormalities are present, evaluation for GCA should be undertaken.
- Giant cell arteritis (GCA) is a vasculitis mainly involving the large and medium arteries.
- GCA and PMR are common and often overlapping conditions in elderly Western populations.
- A genetic component—in particular, in patients with biopsy-proven GCA, has been reported.
- GCA is an antigen-driven disease with local T cell and macrophage activation in the vessel wall, with proinflammatory cytokines playing an important role.
- The clinical features of GCA, chiefly headache, are mainly due to involvement of the cranial arteries.
- Permanent visual loss, generally due to anterior ischaemic optic neuropathy, is the most feared complication of GCA.
- Aortic arch syndrome, aortitis, which involves the thoracic aorta more often than the abdominal aorta, is also described, with risk of stenosis, dissection and or aneurysm formation. This has also been seen in the vertebral arteries in patients with GCA.
- Vertebral and basilar artery lesions can be responsible for fatal cerebrovascular events.
- The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are generally raised in most patients with GCA and PMR; however, some cases with low ESR have been reported.
- A temporal artery biopsy remains the 'gold standard' to secure the diagnosis of GCA.
- High-resolution colour Doppler ultrasonography has gained widespread acceptance as a diagnostic tool in GCA.
- Positron emission tomography with ¹⁸F-fluorodeoxyglucose (FDG/PET) can be used to secure the diagnosis of large vessel GCA.
- Glucocorticoids remain the cornerstone of treatment in PMR and GCA.
- In PMR, an initial dose of 10–20 mg/day of prednisone or its equivalent is adequate in the vast majority of cases to control the inflammatory symptoms.
- In patients with GCA, without complicated lesions, an initial dose of prednisone or its equivalent of 40 mg/day for 3–4 weeks is usually recommended.
- In patients with severe ischaemic lesions, an initial dose of prednisone or its equivalent of 60 mg/day as a single or divided dose for 3–4 weeks is usually recommended.
- In general, treatment for 1–2 years is often required, but some patients may need (mostly at low doses) for several years or more.
- Relapses (flares) are not uncommon in GCA and PMR. Alternative glucocorticoid-sparing drugs—in particular, methotrexate, should be considered in patients with GCA with severe glucocorticoid-related side effects and/or in patients who require prolonged glucocorticoid therapy owing to disease relapse.

Future Research:

1. There remains a need for additional tests or biomarkers, especially where or when the diagnosis is not clear-cut.
2. The new EULAR/ACR classification criteria will facilitate uniform entry into clinical trials of novel therapies which are so urgently required for the condition. There appears to be an overlap with GCA and large-vessel vasculitis as well as inflammatory arthritis.
3. Bursal Biopsy studies are in progress
4. Development of treatment protocols and preventive strategy

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module

EULAR on-line course on Rheumatic Diseases

Polymyalgia rheumatica and giant cell arteritis

Gouri Koduri, Bhaskar Dasgupta, Charles Masson

A previous version was coauthored by Brian Hazleman, Nicolo Pipitone, Carlo Salvarani, Javier Rueda and Miguel A Gonzalez-Gay

IN-DEPTH DISCUSSION I

Giant cell arteritis with large-vessel involvement

Involvement of large vessels (the aorta and its main branches) is not uncommon in giant cell arteritis (GCA), but may easily remain unrecognized in the early stages because it is often per se asymptomatic until vascular complications become manifest. Inflammatory markers do not reliably discriminate between GCA with and without large-vessel vasculitis, while large-vessel biopsy is virtually unfeasible. Therefore, one has to rely on imaging studies to secure a precocious diagnosis.

The earliest lesions of large-vessel GCA are thought to consist of inflammatory cell infiltration, oedema, and thickening of the vessel wall without changes in vessel lumen. Angiography can visualize the vessel lumen but not the vessel wall; therefore it is not helpful to make an early diagnosis. Instead, Colour-Doppler sonography (CDS), computerized tomography (CT) and magnetic resonance (MR) complemented by angiography are able to depict both the vessel wall and the lumen, and may thus reveal early signs (mural thickening and oedema of the vessel wall) of large-vessel vasculitis. F-18 Fluorodeoxyglucose (FDG) positron emission tomography (PET) cannot reliably delineate the vessel wall, but is very sensitive in revealing active inflammation in the affected vessels.¹ The EULAR recommendations for the management of large vessel vasculitis include the use of PET, together with MRI, for diagnosing large-vessel vasculitis.² However, the absence of standardized methods for interpreting the images constitutes a limitation of PET.

Increased vascular FDG uptake has been observed in 83% of 35 patients with newly diagnosed, untreated GCA.³ The subclavian arteries were most commonly affected (74%), but increased uptake was also noted in the aorta (>50%) and to a lesser extent in the axillary, carotid, iliac and femoral arteries.

In another study on (mostly untreated) 176 patients with new-onset GCA, CDS of the subclavian, axillary, and proximal brachial arteries showed in 53 (30%) patients a long, homogeneous wall swelling, consistent with active vasculitis.⁴

In a more recent study CDS pattern suggestive of vessel wall inflammation was observed in 21 of the 38 patients with GCA (55%).⁵ CDS signs of large vessel vasculitis (LVV) were found in vessel regions of both upper and lower limb vessels. 5 Follow-up DS was performed 6 months after the baseline examination in 9 of the 12 patients with LVV and showed the persistence of most findings despite normalized signs of systemic inflammation ⁵.

The higher prevalence at diagnosis of large-vessel disease found using PET compared to CDS may be related to the very high sensitivity of PET in detecting vessel inflammation as well as to its capacity to visualize arterial segments (such as the thoracic and abdominal aorta), which are not, or only limitedly accessible to CDS.

While large-vessel inflammation has been shown to occur precociously in the course of GCA, vascular complications are usually fairly late events. ^{6,7} In a retrospective cohort study of 168 GCA patients followed up for a mean of 7.6 years, 46 (27%) cases presented with large-vessel complications.⁶ In this series, aortic

aneurysm, dissection, or both occurred in 30 (18%) cases, while large-artery stenosis was found in 21 (13%) patients.⁶ The mean time from the diagnosis of GCA to the occurrence of complications was 5, 6.3 and 1.1 years for thoracic aorta involvement, abdominal aorta involvement, and large-vessel stenoses, respectively. Of those patients who had aortic disease, 18 (11%) had thoracic aorta and 16 (10%) abdominal aorta involvement. Dissection occurred in 9 (5%) of patients with thoracic aortitis, but only in one patient with abdominal aortitis. Thoracic aorta dissection was fatal in 7 (4%) patients.⁶ Of note, simultaneous involvement of the thoracic and abdominal aorta as well as of aneurysms and stenoses was very rare. Large-vessel stenoses were found to affect 21 (13%) of patients; only one patient had lower-limb involvement.

Other studies have confirmed overall similar incidence rates per patient/year of large-vessel complications.^{7,8} According to one of these studies the risk of developing an aneurysm of the thoracic and of the abdominal aorta was 17 and 2.4 times higher, respectively, in patients with GCA than in non-diseased controls.⁸

However, these studies were retrospective and there was not a standardized evaluation process to assess for the presence of either aortic aneurysm or large-artery stenosis in GCA patients, which can have led to under ascertainment of subclinical cases. In a more recent prospective study including 54 GCA patients with a median follow-up of 5.4 years, 22% of cases were found to have aortic aneurysms using a protocol which included a chest radiograph, an abdominal ultrasonography scan and a CT scan if any complication was suspect.⁹

GCA patients with large-vessel involvement may only present with systemic symptoms such as fever, constitutional syndrome, and laboratory evidence of inflammation.¹⁰ Pain in the back or lower back, as well as carotidynia, are inconsistent symptoms. Large vessel stenosis can lead to ischemic manifestations such as claudication of an extremity with an arterial bruit, a blood pressure difference between the two sides, decreased or absent pulses, and Raynaud's phenomenon. It is important to emphasize that headache, visual loss, and jaw claudication occur less commonly in GCA patients with large-vessel involvement than in those presenting with classical cranial GCA.¹¹ Temporal artery biopsy is also less frequently (42% of cases) positive compared to classic cranial GCA.¹¹

Treatment of large-vessel GCA is based on corticosteroids given with the same regimen used in GCA without cranial ischemic manifestation. Symptoms and findings related to arterial stenoses usually respond favourably to corticosteroids, but in selected cases interventional vascular procedures may be required. Patients with aortic aneurysms should be managed similarly to patients with non-arthritic aneurysms.

Vigilant monitoring is required to capture early manifestations of large-vessel arteritis, since large-vessel arteritis may develop at any time in the disease course.¹² ESR and C-reactive protein should be monitored regularly, while chest X-rays and CDS of the aortic arch, of the supra-aortic vessels, and of the abdominal aorta should be done yearly. If large-vessel vasculitis is strongly suspected, MR, CT and/or PET should also be

performed. In patients with established large-vessel arteritis, response to therapy should be assessed by serial measurements of inflammatory markers and by the appropriate imaging techniques.

CDS, MR and CT may be used to monitor stenoses and aneurysms, with the caveat that mural thickening and oedema may persist for long periods of time despite attainment of remission.¹ PET may be more specific to reveal ongoing inflammation. However, inflammatory signs on imaging and PET studies do not necessarily portend the development of new lesions, while apparently inactive vessel segments may subsequently develop complications.¹ Moreover, PET findings shows weak correlations with clinical and laboratory criteria of disease activity and with MRI findings. Thus, PET seems to be no value in the follow-up of GCA patients.

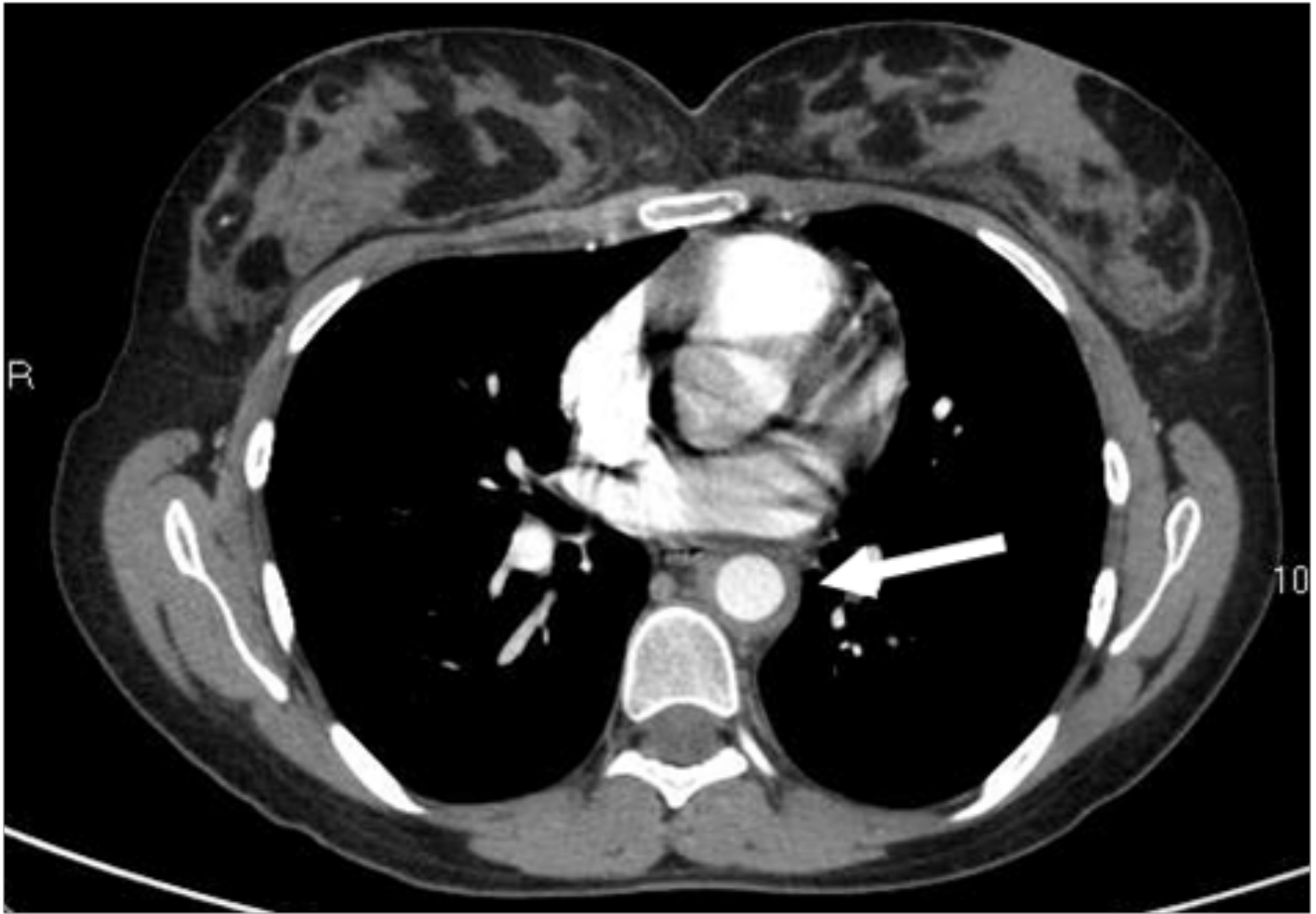
Image 1. Increased (grade 3 on a 0-3 scale) F-18 fluorodeoxyglucose (F-18FDG) uptake on a positron emission tomography (PET) scan of a patient with large-vessel vasculitis involving the thoracic aorta. This finding is highly specific for active vasculitis.

(Image courtesy of Dr. A. Versari, Nuclear Medicine Department, Arcispedale S. M. Nuova, Reggio Emilia, Italy)



Image 2. Thickening of the thoracic aorta (arrow) on a computerized tomography scan of a patient with large-vessel vasculitis involving the thoracic aorta (same patient as in Image 1). This finding is highly specific for vasculitis.

(Image courtesy of Dr. F. Nicoli, Chief Radiologist, Arcispedale S. M. Nuova, Reggio Emilia, Italy)



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module

EULAR on-line course on Rheumatic Diseases

Polymyalgia rheumatica and giant cell arteritis

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A previous version was coauthored by Brian Hazleman, Nicolo Pipitone, Carlo Salvarani, Javier Rueda and Miguel A Gonzalez-Gay

IN-DEPTH DISCUSSION II

GCA and sight loss

‘How do you prevent a stroke in the eye’ – Way Forward.

Headache was identified as an important differentiating feature in the 1990 ACR Classification criteria for GCA. Unfortunately, these criteria have been misused as diagnostic criteria, leading to the mistaken widespread understanding of GCA as primarily a 'headache disease' omitting key constitutional, polymyalgic and major organ threatening features such as jaw pain, visual symptoms and sight loss and large vessel vasculitis. Loss of sight occurs in about 15 – 35 % of patients with GCA and is the most feared complication in GCA (1).

Sight loss in at least one eye still occurs in 15–20% of the cases, because of anterior ischemic optic neuropathy or, less commonly, due to central retinal artery occlusion or ischemic retrobulbar neuropathy (2). In untreated patients with unilateral visual loss, involvement of the contralateral eye may occur, 1–10 days after the initial event, in up to one third of the cases. Irreversible sight loss almost always occurs prior to glucocorticoid therapy. Unfortunately, established sight loss is most often irreversible (2). Sight loss can be preceded by non-specific constitutional symptoms, often missed in the very elderly, and can therefore be the presenting symptom of GCA. Visual impairment can be preceded by diplopia, blurred vision amaurosis fugax, and other ischemic symptoms such as jaw and tongue claudication pain (3). The absence of visual/ischemic symptoms, however, does not preclude the occurrence of visual complications. It has been observed that patients with sight loss reported transient visual symptoms and headache less frequently than patients without visual complications (4). Patients with sight loss are older, as likely in men as in women and more frequently have hypertension and other co-morbidities and a positive temporal artery biopsy. Untreated patients with unilateral visual loss have a 50% risk of blindness in the other eye, usually occurring after a few days (5, 6). Less common ischaemic complications of GCA include TIAs, cerebrovascular strokes, infarction of the tongue and scalp necrosis, Large vessel involvement and aortitis leading to back pain and limb claudication (7).

Patients with GCA related sight loss suffer loss of independence and residential home placement, severe depression, adverse effects from high dose glucocorticoids, severely reduced QALYs because of sight loss. In addition to these personal costs, there are also large direct and indirect healthcare and social costs related to blindness and a major impact on the immediate family.

The key to improving the outcomes of GCA patients is rapid diagnosis and treatment. However, diagnosis is often difficult as the symptoms are similar to many common conditions routinely seen by GP's and Healthcare professionals. The three key areas to address for reducing GCA related sight loss are improved public awareness, improved professional awareness/training and provision of a fast track GCA clinic.

Diagnostic delays and factors have been extensively investigated in strokes, ischaemic heart disease and cancers (8, 9). This led to the development of public health interventions to raise awareness. Similar health care provision is required for GCA to prevent sight loss which can be legitimately regarded as an ischemic 'stroke in the eye'.

In a recent Meta –analysis the importance of understanding the extent of diagnostic delay, and the reasons associated with delay, has been undertaken (10). The mean delay in receiving a diagnosis of GCA ranged from 1.2 (SD 1.6) to 34.7 (34.2) weeks. This meta-analysis demonstrated that those with cranial GCA received a diagnosis after 7.7 weeks (2.7 to 12.8, $P < 0.001$) and those with non-cranial GCA after 17.6 weeks (9.7 to 25.5, $P < 0.001$). They found that even when patients present with distinct cranial symptoms, the delay in finally receiving a GCA diagnosis remains substantial (8 weeks) and is longer still for those with non-cranial symptoms (18 weeks). Such findings are of concern, as previous research has reported that as few as half of GCA patients can experience temporal headaches (11).

On average, patients experience a 9-week delay between the onset of their symptoms and receiving a diagnosis of GCA. Even when the patient has a ‘classical’ cranial presentation, delay remains considerable. In view of the potentially serious consequences of a missed GCA diagnosis, a reduction in diagnostic delay would be beneficial and could result in overall cost savings for healthcare systems (12)

This meta- analysis provides a new evidence-based benchmark of diagnostic delay of GCA against which future efforts to reduce this problem can be measured and supports the need for improved public awareness and fast-track diagnostic pathways.

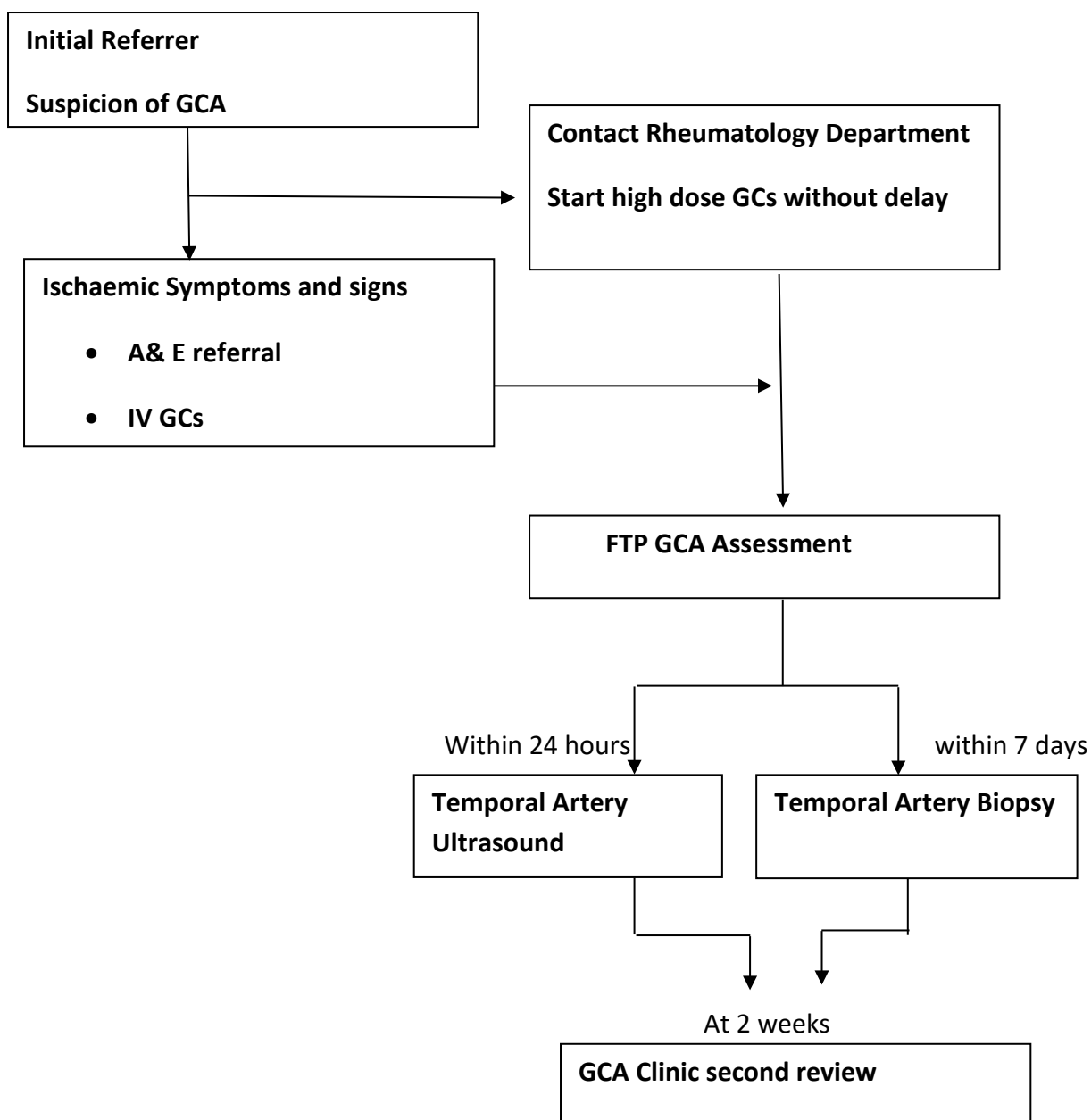
Patients who already have sight loss at the time of diagnosis, have a poorer prognosis and may even have increased mortality. Most guidelines recommend oral prednisone 40 – 60 mg, once daily with the higher dose used in patients with ischaemic symptoms (13). In primary care practice a dose of 60 mg daily should be used in most patients with suspected GCA and if necessary this can be adjusted once the patient has been assessed in secondary care. Improvement in symptoms often begins within hours to days after commencing GCs, with a median time to initial response to an average initial dose of 60 mg/day is 8 days (14).

The proven ability of timely administration of GCs to prevent blindness in GCA is a yardstick against which any other treatment must be measured. While awaiting development of safer therapies we should concentrate efforts in reducing ‘symptom to steroid’ time. A fast track pathway for management of GCA is one such example (**see Figure**).

GCA should be treated as an ischemic emergency just like cerebrovascular event or myocardial infarction. Implementation of fast-track GCA pathways in rheumatology departments have significantly reduced the risk of permanent sight loss in patients with suspected GCA (15, 16). For GCA, a secondary care ‘fast-track’ referral pathway, combined with GP education, specialists, raising awareness reported a significant reduction in the number of patients experiencing permanent sight loss compared to those going through usual care. Though multifactorial, the reduction in diagnostic delays played a role in achieving this reduction in sight loss. This has also been found to be cost effective. Thus the pathway ‘saves money and saves sight’!

Fast track pathway also helps to minimise the steroid burden in those who do not have GCA or other GCA mimics. Where there is more than a low probability suspicion of GCA, we advocate starting oral glucocorticoids immediately and referral to the fast track clinic since a delay in treatment will have greater consequences than a few days/hours of unnecessary GCs in someone where the diagnosis is thereafter quickly excluded. For GCA patient's preservation of vision and maintenance of Independence are the most important ranked quality of life (QOL) concerns (17). For guidance in adequate triage and referral, a GCA probability score will be helpful and is in development (from the Southend Fast track Clinic) using weighted criteria items such as demographics, mode of onset, symptomatology, ischemic features, inflammatory markers and presence/absence of competing diagnoses such as infection, neoplasia and other head and neck conditions.

*Figure: South end Fast track pathway, *image courtesy BSR Case study*



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module

EULAR on-line course on Rheumatic Diseases

Systemic consequences of the inflammatory process

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1 Amyloidosis

LEARNING OBJECTIVES

- Outline the classification of systemic amyloidosis
- Outline the pathogenesis of amyloidosis
- Outline the epidemiology of systemic amyloidosis
- Describe the clinical manifestations of systemic amyloidosis
- Describe diagnostic approaches to systemic amyloidosis
- Describe treatment options in systemic amyloidosis

1.1 Classification of amyloidosis

Various forms of amyloidosis are characterised by extracellular deposition of fibrillar proteins. Amyloid deposits may be detected by polarisation microscopy, where deposits result in typical green birefringence upon Congo red staining. At least 30 different amyloid proteins have been identified and amyloidosis is classified according to the nature of the major fibrillar protein component (table 1). Amyloidosis can be localised or systemic, inherited or acquired. The interest of the rheumatologist in amyloidosis is twofold: (a) chronic inflammatory rheumatic diseases, such as rheumatoid arthritis (RA), may be associated with (mainly) AA amyloidosis, and (b) some forms of amyloid disease may have musculoskeletal manifestations due to the deposition of amyloid in the joints and periarticular tissues (Falk et al. 1997*; Sipe et al. 2010; Wechalekar et al. 2016*).

As localised amyloidosis only rarely affects the joints, in this module we will discuss features of systemic amyloidoses only, primarily the AA, AL, A β 2M and ATTR forms.

1.2 Pathogenesis of systemic amyloidosis

In amyloidosis, the various proteins misfold and undergo irreversible transition to insoluble and proteolysis-resistant fibrils. In contrast to the heterogeneity of the various precursors, all amyloid fibrils share similar ultrastructure and properties. Amyloid fibrils are rigid, non-branching, 7–13 nm in diameter and of indeterminate length. They are insoluble under normal conditions and their specific highly ordered ultrastructure is responsible for binding Congo red dye in a spatial manner, yielding the characteristic birefringence under polarised light.

Table 1 Classification of systemic amyloidosis (Adapted from Perfetto et al, *Nat Rev Rheumatol* 2010;6:417–29*)

Amyloid type	Fibril protein precursor	Clinical syndrome
AL	Monoclonal immunoglobulin light chains	Associated with plasma cell dyscrasias
AH	Monoclonal immunoglobulin heavy chains	Associated with plasma cell dyscrasias
AA	Serum amyloid A protein	Associated with chronic inflammatory conditions
A β 2M	β 2-Microglobulin	Associated with chronic haemodialysis
ATTR ATTR-SSA	Genetically variant transthyretin Wild-type transthyretin	Familial (autosomal dominant) amyloid polyneuropathy Senile systemic amyloidosis
ACys	Genetically variant cystatin	Hereditary cerebral haemorrhage with cerebral and systemic amyloidosis
AGe	Genetically variant gelsolin	Familial (autosomal dominant) systemic amyloidosis Cranial nerve involvement, lattice corneal dystrophy
ALys	Genetically variant lysozyme	Familial (autosomal dominant) systemic amyloidosis Non-neuropathic, prominent visceral involvement
AApoAI	Genetically variant apoA-I	Familial (autosomal dominant) systemic amyloidosis Non-neuropathic, prominent visceral involvement
AApoAII	Genetically variant apoA-II	Familial (autosomal dominant) systemic amyloidosis Non-neuropathic, prominent renal involvement
AFib	Genetically variant fibrinogen A α chain	Familial (autosomal dominant) systemic amyloidosis Non-neuropathic, prominent renal involvement

High levels of amyloid precursors, including serum amyloid A (SAA) protein, immunoglobulin (Ig) light chain or β 2-microglobulin (β 2M), can be detected in the circulation. For example, the median plasma concentration of SAA in healthy individuals is <5 mg/L, while this may increase to >2000 mg/L during the acute phase response. Amyloid precursors may interact with other non-fibrillar components, such as serum amyloid P (SAP) protein or glycosaminoglycans (GAGs) (figure 1). GAGs promote fibril formation and strengthen their stability.

Amyloid deposition in various tissues may occur under different circumstances.

1. A sustained abundance of otherwise structurally normal proteins, such as SAA or β 2M, may occur during chronic inflammation or renal insufficiency under dialysis, respectively.
2. Some aberrant proteins, such as monoclonal Ig light chains or genetically variant forms of fibrinogen α -chain may form amyloid deposits.
3. Naturally weak amyloidogenic proteins, such as transthyretin (TTR) may be expressed in normal amounts over a prolonged period of time, as seen in senile amyloidosis (Perfetto et al, 2010*, Wechalekar et al. 2016*).

Figure 1 Process of systemic amyloid deposition. Excess production of circulating amyloid precursors occurs under different circumstances leading to misfold protein oligomers. These oligomers bind to serum amyloid P (SAP) and glycosaminoglycans (GAGs) and then are deposited in various internal organs. ApoA, apolipoprotein A; β 2M, β 2-microglobulin; SAA, serum amyloid A; TTR, transthyretin.

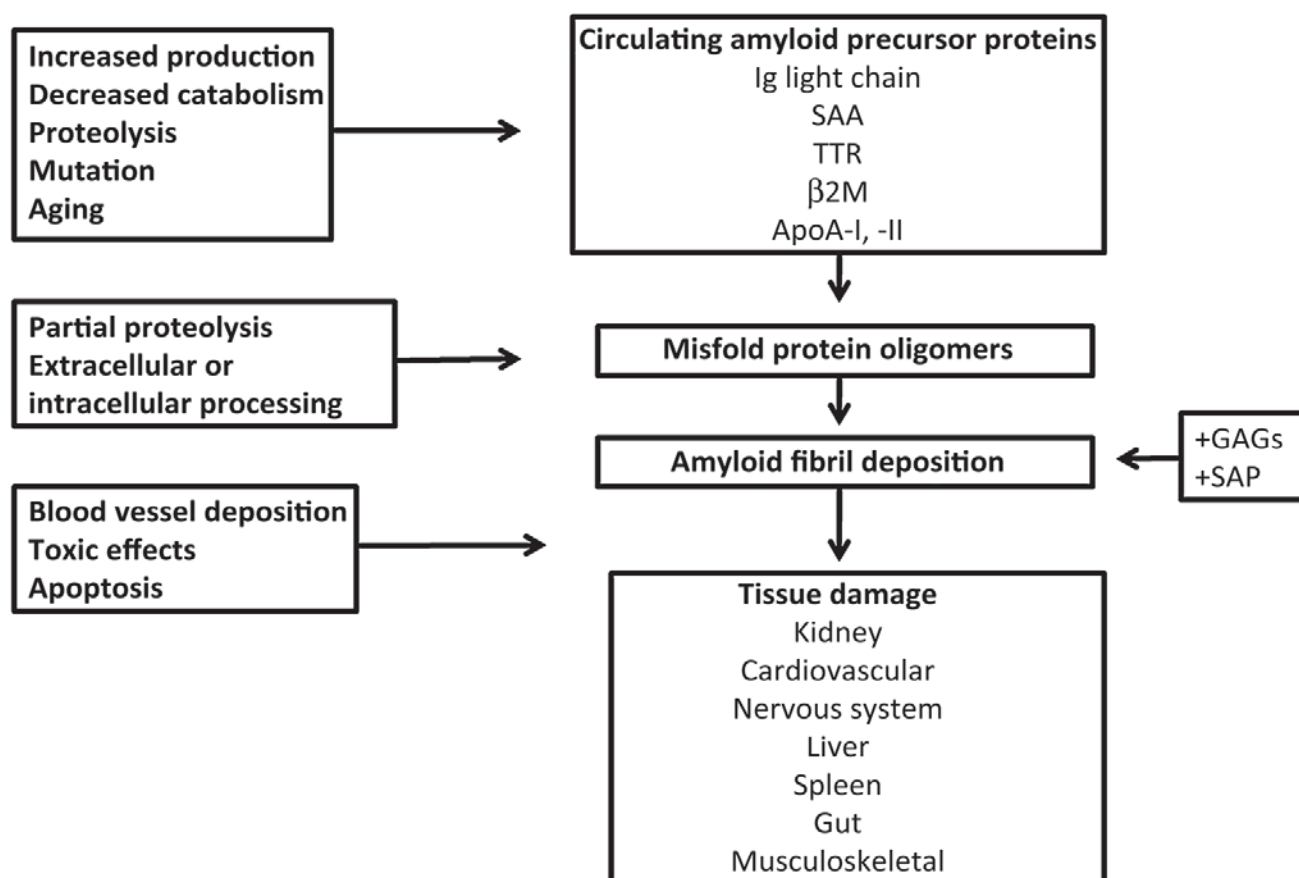


Table 2 Clinical manifestations of systemic amyloidosis (Adapted from Perfetto et al, Nat Rev Rheumatol 2010;6:417–29*)

Amyloid type	MSS	Renal	CV	PNS	ANS	Liver	Spl	Skin	GI	Thy	Adr	Eye	Test	Tong	FX def.
AA	–	+++	+	–	++	++	++	–	+	+	+	–	–	±	–
AL	++	+++	+++	++	++	++	+	±	++	+	+	–	±	+++	+
A β 2M	+++	–	±	–	–	±	±	–	–	±	±	–	–	–	–
ATTR	±	+	+++	+++	+++	–	–	–	–	–	–	++	–	–	–
ATTR-SSA	–	–	+++	+	–	–	–	–	–	–	–	–	–	–	–
ALys	–	+++	±	–	–	++	+	–	++	–	–	–	–	–	–
AApoAI	–	++	++	+	–	++	++	–	–	–	–	–	++	–	–
AApoAII	–	++	+	–	–	–	–	–	–	–	–	–	–	–	–
AFib	–	+++	+	–	–	+	+	–	–	–	–	–	–	–	–

Adr, adrenal; ANS, autonomic nervous system; CV, cardiovascular; FX def, factor X deficiency; GI, gastrointestinal; MSS, musculoskeletal system; PNS, peripheral nervous system; Spl, spleen; Thy, thyroid; Tong, tongue.

+++ very common, ++ common, + rare, ± very rare, – does not occur.

Table 3 Conditions associated with systemic AA amyloidosis

Rheumatic diseases	Auto inflammatory syndromes
Rheumatoid arthritis	Familial Mediterranean fever
Ankylosing spondylitis	Hyper-IgD syndrome
Psoriatic arthritis	Muckle–Wells syndrome
Adult-onset Still's disease	TNF receptor-associated periodic syndrome (TRAPS)
Reactive arthritis	Familial cold auto inflammatory syndrome (FCAS)
Juvenile idiopathic arthritis	
Gout	Inflammatory bowel diseases
Systemic lupus erythematosus	Crohn's disease
Sjögren's syndrome	Ulcerative colitis
Systemic sclerosis (scleroderma)	
Systemic vasculitides	Malignancies
Behçet's disease	Lung, colon and urogenital cancer
	Basal cell cancer
Chronic infections	Carcinoid tumour
Tuberculosis	Castleman's disease
Leprosy	Gastrointestinal stromal tumour
Bronchiectasis	Hairy cell leukaemia
Chronic cutaneous ulcers	Hodgkin's disease
Chronic pyelonephritis	Waldenström macroglobulinaemia
Osteomyelitis	Mesothelioma
Q fever	Renal cell carcinoma
Subacute bacterial endocarditis	Sarcoma of the liver
Whipple's disease	Hepatic adenoma
Immunodeficiency states	Other conditions
Common variable immunodeficiency	Cystic fibrosis
Cyclic neutropenia	Epidermolysis bullosa
Hyper-IgM M syndrome	Injected drug abuse
Hypogammaglobulinaemia	Jejunioileal bypass
Sex-linked agammaglobulinaemia	Kartagener's syndrome
HIV/AIDS	Paraplegia
	Sickle cell anaemia
	SAPHO syndrome
	Atrial myxoma
	Sarcoidosis
	Retroperitoneal fibrosis

Ig, immunoglobulin; TNF, tumour necrosis factor.

1.3 Epidemiology, clinical features and prognosis of amyloidosis

Organ and tissue manifestations of amyloidosis are shown in table 2 and figure 1, whereas major clinical syndromes associated with various forms of systemic amyloidosis are included in table 3.

1.3.1 AA amyloidosis

Systemic AA amyloidosis is most commonly associated with chronic inflammatory diseases, including rheumatic, autoimmune and hereditary autoinflammatory disorders, and is also a potential complication of chronic infections and malignancies due to chronic elevations of acute phase reactants, including SAA. In a cohort of 374 patients with AA amyloidosis, 60% of cases were related to chronic inflammatory arthritis, 15% to chronic sepsis, 9% to periodic fever syndromes, 5% to Crohn's disease, 6% to miscellaneous diseases and 6% unknown (Lachmann et al. 2007). A recent large retrospective study identified a pattern of reducing incidence and changing epidemiology with older age of patients at presentation and death, more frequent end stage renal disease (ESRD), as well as a change in aetiology (less juvenile idiopathic arthritis (JIA) patients, more chronic infections due to intravenous drug use) (Lane et al. 2017).

Conditions associated with AA amyloidosis are listed in table 3. SAA is an apolipoprotein of a high-density lipoprotein, which, similarly to C-reactive protein, is synthesised by hepatocytes under the regulation of proinflammatory cytokines, such as tumour necrosis factor α (TNF α), interleukin 1 (IL-1) and IL-6.

RA, ankylosing spondylitis and other arthritides account for approximately 70% of all AA amyloidosis cases. The reported prevalence of amyloidosis in RA varies from study to study depending on the diagnostic procedure used and clinical status. A decreasing incidence of amyloidosis in RA has been demonstrated based on consistent decline of the annual number of biopsies positive for amyloid deposits. The prevalence of the asymptomatic phase of AA amyloidosis in RA ranges between 0.5% and 14%. In ankylosing spondylitis, renal amyloidosis is the most common renal manifestation with a 5-year survival rate of only 30%.

The predominant feature of amyloidosis at diagnosis is renal dysfunction, which manifests as proteinuria or renal failure (figure 2). In 97% of patients >500 mg protein/day was excreted or the serum creatinine concentration was >1.5 mg/dL, or both. Patients with AA amyloidosis may have higher serum creatinine levels at diagnosis and require dialysis earlier than those with AL amyloidosis. If untreated, AA amyloidosis may progress towards ESRD.

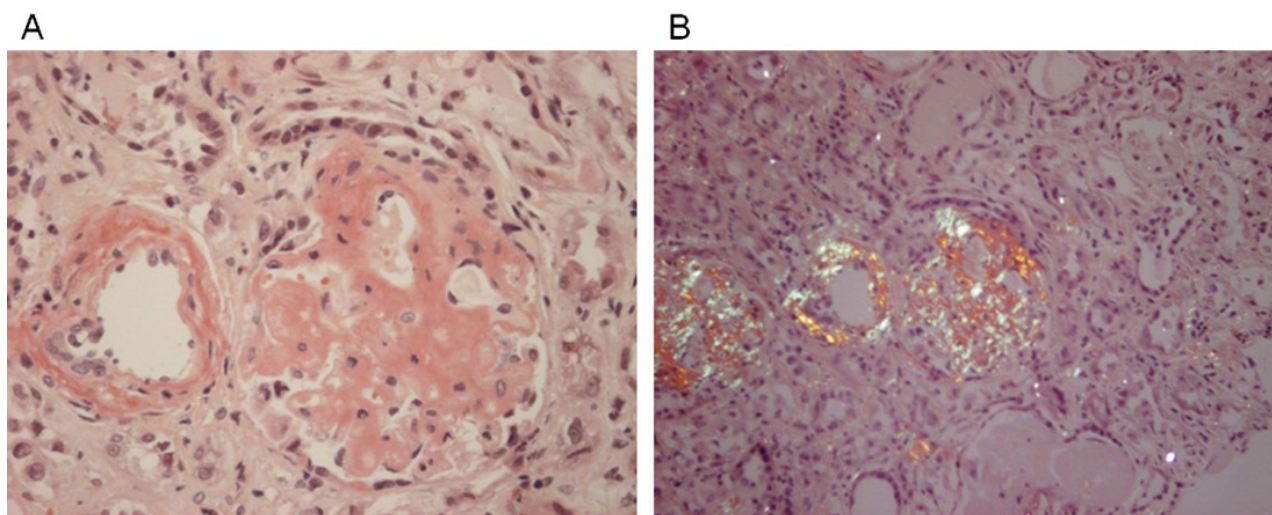
Autopsy series or radiolabelled SAP scintigraphy show the presence of amyloid deposits in the liver and spleen, but these deposits rarely lead to clinical manifestations. While hepatic amyloid deposits are found in 25%, hepatomegaly is present in about 10% of all cases of AA amyloidosis. Jaundice or abnormal aminotransferase levels are extremely rare. Splenic involvement is suspected if Howell–Jolly bodies are found in the peripheral blood smear or when frequent infections occur.

Gastrointestinal features include malabsorption, pseudo-obstruction, diarrhoea or vomiting secondary to submucosal amyloid infiltration. Amyloid deposits within vessel walls may lead to gastrointestinal perforation and bleeding.

Cardiac infiltration is present in only 1% of patients with AA amyloidosis, which is much less frequent than in AL amyloidosis. Clinical presentation is right heart failure with lower limb oedema. Cardiomyopathy is an unfavourable prognostic factor.

Few studies have assessed survival rates in AA amyloidosis. The mean survival time in 1991 was 24 months, but it had increased to 79 months by 2008. Higher age, heart involvement and raised serum creatinine levels predict a worse prognosis. Thus, early referral of patients with AA amyloidosis to a nephrologist and co-operation between rheumatologists, internists and nephrologists are needed (Tanaka et al, 2003*; Obici et al, 2005; Perfetto et al, 2010*).

Figure 2 Renal amyloid deposition in a patient with AA amyloidosis secondary to rheumatoid arthritis. (A) Congo red staining. (B) Green birefringence under polarisation microscope. (Courtesy of Dr J Kovács, Department of Pathology, University of Debrecen Medical Centre, Debrecen, Hungary).



1.3.2 AL amyloidosis

AL amyloidosis is the most common type of systemic amyloidosis in Western countries. About 20–30% of patients with myeloma have AL amyloidosis. In this type of amyloidosis, fibrils are derived from monoclonal Ig light chains. AL amyloidosis is usually diagnosed at the age of 60, mostly in men.

The characteristic manifestations of AL amyloidosis are nephrotic syndrome, congestive heart failure, peripheral neuropathy and hepatic involvement (table 2). Multisystem involvement is common (>50%). Renal manifestations including proteinuria and uraemia are seen in about 70% of patients. AL amyloid deposits in the myocardium lead to restrictive cardiomyopathy. Low voltage in the limb leads or poor R-wave progression in the precordial leads is seen on ECG. In 60–70% of patients, echocardiography shows abnormal myocardial relaxation, thickened ventricular walls, pericardial effusion, abnormal myocardial texture and, in late-stage disease, a restrictive filling pattern. Symptomatic involvement of the autonomic and peripheral nervous

systems (20%) includes orthostatic hypotension, axonal and demyelinating peripheral neuropathy or bilateral carpal tunnel syndrome. Hepatomegaly and/or increased transaminase levels are present in almost one-quarter of the patients. Macroglossia is a characteristic feature, which is seen only in AL amyloidosis (table 2).

Rheumatologists may encounter various musculoskeletal manifestations, including joint, bone and soft tissue involvement in 9% of cases. Amyloid infiltration of periarticular and synovial tissues may result in joint swelling and stiffness. The 'shoulder pad' sign is attributable to amyloid infiltration of the tendons and capsules of the shoulders leading to characteristic appearance. Cutaneous ecchymosis around the eyes is also known as 'raccoon eyes'. The shoulder pad sign, raccoon eyes and macroglossia, together found in 10% of patients, are pathognomonic for AL amyloidosis.

Uncommon manifestations include jaw claudication, xerostomia, xerophthalmia, skin manifestations resembling scleroderma, amyloid myopathy mimicking polymyositis, muscle pseudohypertrophy and abnormal bleeding due to acquired factor X deficiency.

Patients with AL amyloidosis have the worst prognosis as heart failure is associated with a median survival time of only 6 months (Falk et al, 1997*; Perfetto et al, 2010*).

1.3.3 β 2-Microglobulin amyloidosis

β 2M amyloidosis is caused by the deposition of fibrillar β 2M and is a serious complication of long-term haemodialysis. The precise mechanism leading to β 2M amyloidosis is still unclear. Amyloid fibril formation has been associated with the duration of renal failure, current age, age at initiation of haemodialysis, duration of haemodialysis and bioincompatibility of dialysis membranes.

The most common manifestations involve the musculoskeletal system (table 2). Early manifestations include carpal tunnel syndrome and arthralgia in the shoulders and other large joints. Arthralgia may later evolve into erosive arthropathy. Spinal involvement is characterised by degeneration of the intervertebral discs and erosions with reactive sclerosis of vertebral plates and little osteophyte formation. Eventually, collapse of vertebral bodies and spondylolisthesis may occur (Perfetto et al, 2010*).

1.3.4 Hereditary amyloidosis

Hereditary amyloidosis is a heterogeneous group of diseases caused by a mutant TTR protein produced by the liver. Mutations may occur in genes encoding apolipoprotein A (apoA)I, apoAII, gelsolin, fibrinogen, lysozyme and cystatin C (table 2). The most important manifestations in ATTR amyloidosis are myocardial dysfunction, peripheral and autonomic neuropathy, secondary skin ulcers and Charcot arthropathy in the lower extremities. Wild-type TTR protein may also form amyloid fibrils leading to senile systemic amyloidosis (Falk et al, 1997*; Perfetto et al, 2010*).

1.4 Diagnostic procedures

Advanced organ involvement has often ensued by the time a clinical diagnosis of amyloidosis is made, so keeping a high index of suspicion is important. Specific combinations of symptoms should trigger suspicion for the diagnosis, such as nephrotic syndrome and heart failure; peripheral and autonomic neuropathy; thick-walled heart failure with normal or low-voltage electrocardiogram; recurrent carpal tunnel syndrome; a combination of carpal tunnel syndrome and heart failure in elderly people; and relevant family history (Wechalekar et al. 2016*). In these patients, biopsy and histological diagnosis is mandatory. Other laboratory tests and imaging should be performed to identify the type of amyloidosis, refine diagnosis and identify clinical manifestations (table 4).

Table 4 Evaluation of patients with suspected amyloidosis*

1.	Characteristic patients	<ul style="list-style-type: none"> • Chronic rheumatic disease • Long-term dialysis • Monoclonal gammopathy
2.	Characteristic clinical manifestations	<ul style="list-style-type: none"> • Non-diabetic nephrotic syndrome • Low voltage on ECG • Echocardiography showing left ventricular hypertrophy • Hepatomegaly, abnormal levels of alkaline phosphatase, γ-glutamyl transferase • Howell–Jolly bodies in peripheral blood smear • Splenomegaly • Chronic demyelinating polyneuropathy and/or orthostatic hypotension • Macroglossia, ‘shoulder pad’ sign, cutaneous ecchymosis • Xerostomia, joint involvement, jaw claudication, skin involvement
3.	Biopsy-histology	<ul style="list-style-type: none"> • Abdominal subcutaneous fat aspiration with Congo red staining • Other biopsies (rectal, renal, liver, salivary gland)
4.	Additional laboratory tests to identify type of amyloidosis	<ul style="list-style-type: none"> • Immunofixation of serum and urine, Ig free light chain assay (AL amyloidosis) • Serum amyloid A assay (AA amyloidosis) • Genetic testing (ATTR amyloidosis) • Serum β2-microglobulin level (Aβ2M amyloidosis)
5.	Imaging	<ul style="list-style-type: none"> • Echocardiography • Abdominal ultrasound (kidney, liver, spleen) • Musculoskeletal ultrasound (joints) • CT, MRI (spinal involvement in β2M amyloidosis) • ^{18}F-FDG PET imaging (pulmonary amyloidosis) • Multimodality imaging (all types) • EMG/nerve conduction study (carpal tunnel syndrome, polyneuropathy)

EMG, electromyogram; Ig, immunoglobulin; FDG PET, fluorodeoxyglucose positron emission tomography.

*See details of the diagnostic algorithm in the text.

1.4.1 Histology

Histological examination of biopsy specimens stained with Congo red under polarised microscopy is the standard method for establishing the diagnosis of amyloidosis. The amyloid deposits are often in a perivascular distribution with some degree of heterogeneity.

Although biopsy specimens can be obtained from compromised organs such as the liver, heart or kidneys, increased blood vessel fragility associated with amyloid deposition carries a risk of bleeding. Therefore, abdominal subcutaneous fat aspiration (ASFA) is preferable. ASFA detects amyloid deposits in patients with AA, AL or ATTR amyloidoses with a sensitivity of 57–88% and a specificity of 100%, whereas it usually gives negative results in A β 2M amyloidosis. The preferred tissue for histology in A β 2M amyloidosis is the synovium. If the ASFA is negative or contraindicated because of local skin infection, haematoma or large umbilical hernia, then biopsy of minor salivary glands may be useful. In AA and AL amyloidosis, salivary gland biopsy has a sensitivity of 86%, and this technique is also useful in ATTR amyloidosis. Rectal biopsy (75–85% sensitivity) was more widely used in the past, but should be deep enough to include the submucosa to be of value. Biopsy of the kidney or liver is sensitive when laboratory tests show dysfunction of the biopsied organ (figure 2). Life-threatening bleeding can occur, and therefore these procedures should be reserved for patients in whom ASFA, salivary gland or rectal biopsy fail to establish the diagnosis. Peripheral nerve biopsies vary in their diagnostic value and may result in residual dysaesthesia.

Some histological techniques may enhance diagnostic performance. ‘Permanganate-sensitive’ deposits stained with Congo red lose their birefringence after oxidation with potassium permanganate. This pattern occurs with AA and A β 2M amyloid. In contrast, AL and ATTR amyloid are ‘permanganate-resistant’. This test was useful in distinguishing between AA and AL amyloidosis, but today it has been replaced by immunohistochemical techniques. In patients with systemic amyloidosis, immunohistochemical studies with antibodies to AA and to the Ig light chains λ and κ are usually sufficient, as they identify the vast majority of amyloid deposits composed of AA fibrils or Ig light chains, but they can be not definitive in AL amyloidosis (Bély and Apáthy, 2000; Sipe et al, 2010). The proteomic method of mass spectrometric analysis of amyloidotic material is the new gold standard for fibril typing (Wechalekar et al. 2016*).

1.4.2 Additional laboratory tests

Knowledge of the type of amyloidosis is a prerequisite to optimal treatment. As AA, AL and ATTR amyloidosis may have similar clinical manifestations (table 2), determination of the type of amyloidosis is particularly important. If characteristic clinical manifestations are present, the biopsy is positive for Congo red staining and green birefringence occurs under polarised light, various laboratory tests may be performed in order to determine the type of amyloidosis (table 4, figure 1).

Immunofixation of serum and urine, as well as an Ig free light chain (FLC) assay should be performed in order to confirm AL amyloidosis. If the diagnosis is uncertain, bone marrow biopsy could be performed (table 4). In patients with chronic inflammatory disease and proteinuria and/or chronic renal failure, increased serum SAA confirms systemic AA amyloidosis (table 4). If AL and AA amyloidoses are excluded, owing to negative immunofixation, an Ig FLC assay and SAA, genetic testing for mutant TTR, apoA-I, apoA-II, gelsolin, lysozyme and cystatin C should be performed in order to confirm ATTR amyloidosis (table 4).

Among laboratory tests, serum troponin, N-terminal portion of type B natriuretic peptide, Ig FLC, β 2M and SAA levels also reflect an unfavourable prognosis (Falk et al, 1997*; Perfetto et al, 2010*).

1.4.3 Imaging

Echocardiography is the 'gold standard' test for diagnosing cardiac involvement. An echocardiogram demonstrating marked left ventricular wall thickening, biatrial enlargement, thickened valve leaflets and a pericardial effusion in the context of reduced ECG voltages is highly persuasive of cardiac amyloid. If either a thickened interatrial septum or a granular highly echogenic myocardium is also present, this makes the diagnosis even more likely (Selvanayagam et al. 2007). Diffuse myocardial granular sparkling has 87% sensitivity and 81% specificity for the diagnosis of cardiac amyloidosis. Senapati et al. (2016) recently studied the use of the regional strain ratio assessed by means of speckle tracking analysis as a means of obtaining better prognostic data than that provided by standard echocardiography. MRI is another highly sensitive technique for the determination of heart involvement. Characteristic MRI features include impaired biventricular systolic function, thickened atrioventricular valves, increased atrial septal thickness and left ventricular mass, and widespread subendocardial hyperenhancement, representing infiltration with amyloid protein.

The SAP component contributes to the stability of amyloid deposits in vivo. This unique property of the SAP component led to the development of a scintigraphic technique capable of detecting amyloid deposits anywhere in the body. Although the definitive diagnosis of amyloidosis continues to depend on histological examination of biopsy specimens, radiolabelled SAP component scintigraphy is both sensitive and specific for detecting amyloid deposits and can be useful in monitoring disease.

Abdominal ultrasound (US) is necessary to investigate renal, splenic and hepatobiliary manifestations of systemic amyloidosis. Musculoskeletal US is a reliable method for detecting amyloid deposits in joints—for example, in the shoulders and wrists of patients with $A\beta$ 2M amyloidosis. Electrophysiology is needed to confirm carpal tunnel syndrome or polyneuropathy as manifestations of the peripheral nervous system primarily associated with ATTR and AL amyloidoses (tables 2 and 4).. As described above, spinal involvement including intervertebral space narrowing, erosions with reactive sclerosis, vertebral plate cysts, vertebral body

collapse and spondylolisthesis may occur in A β 2M amyloidosis. CT may be helpful for assessing the extent of destruction, while MRI may show amyloid deposits in the disc, synovium and ligamentum flavum.

Recently, 18F-fluorodeoxyglucose positron emission tomography (PET) scanning has been introduced to detect pulmonary amyloidosis (table 4). More studies are under way to determine the value of PET in amyloidosis diagnostics.

(Perfetto et al 2010*; Howard et al, 2012; Baqir et al, 2014).

1.5 Current and new treatments

1.5.1 General therapeutic strategies

No treatment specifically stimulates the clearance of amyloid deposits and, therefore, strategies focus on reducing the supply of the respective amyloid fibril precursor protein while supporting or replacing the function of the affected organs. Although these treatments may have significant toxicity and the clinical benefit is often delayed by months or years after the supply of the fibril precursor has been reduced, this strategy often slows disease progression, permits gradual regression of amyloid deposits and eventually, leads to improved survival.

In systemic amyloidosis secondary to inflammatory rheumatic diseases, the strategy involves administration of anti-inflammatory drugs, including non-steroidal anti-inflammatory drugs and glucocorticoids, as well as various traditional or biologic immunosuppressive agents. Among the biological agents, TNF α inhibitors suppressed proteinuria and gastrointestinal amyloid deposition in AA amyloidosis secondary to arthritis. Targeting IL-1 with anakinra and, more recently, canakinumab seems particularly interesting in autoinflammatory syndromes complicated by amyloidosis. As IL-6 is also involved in the pathogenesis of amyloidosis, as well as arthritis, IL-6 receptor inhibition by tocilizumab may also be promising.

There have been approaches to inhibiting fibrillogenesis in amyloidosis. As described above, proteoglycan GAG chains are universal constituents of amyloid deposits (figure 1). New sugar analogues of N-acetylglucosamine inhibit the binding between heparan sulfate or the heparan sulfate proteoglycan perlecan and amyloid fibril proteins, and orally administered low molecular weight anionic sulfonate or sulfated compounds can substantially inhibit the development of experimentally induced murine AA amyloid. A GAG mimetic agent eprodisate has been developed and introduced to human trials, but results are still awaited (Dember et al. 2007).

Although direct induction of amyloid deposit regression has not yet been a feasible approach, there have been attempts to target the SAP component described above. The non-fibrillar SAP is universally present in amyloid deposits, persists within these deposits for prolonged periods and can be identified by SAP scintigraphy. Small

molecular compounds that inhibit the binding of SAP to amyloid fibrils are under investigation (Fiter et al, 1995; Kyle et al, 1997; Stankovic and Grateau, 2011).

1.5.2 Treatment of AA amyloidosis

In AA amyloidosis secondary to inflammatory rheumatic diseases, the major goal of treatment is to control the underlying disease. Chronic suppression of SAA production leads to the regression of amyloid load and deposition as determined by SAP scintigraphy. This will eventually lead to clinical improvement and improved long-term survival.

Various immunosuppressive agents, including colchicine, methotrexate (MTX), cyclophosphamide, chlorambucil and leflunomide, have been used in an attempt to control secondary AA amyloidosis associated with arthritis. These agents reduced SAA levels. Apart from scattered early case reports showing limited efficacy, no large trials have been conducted. Colchicine treatment was only effective in secondary renal amyloidosis with low proteinuric stage, but not in amyloidosis associated with rheumatic diseases. Colchicine is mainly used to treat AA amyloidosis secondary to familial Mediterranean fever (FMF).

Biological agents have emerged as effective drugs for the treatment of secondary renal and gastrointestinal AA amyloidosis. Among TNF α inhibitors, etanercept and infliximab reduced proteinuria and inhibited gastrointestinal amyloid deposit formation in patients with arthritis. The IL-1 inhibitor anakinra has been successfully used in cases of amyloidosis secondary to auto inflammatory syndromes, including TNF receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), FMF, Muckle–Wells syndrome and familial cold auto inflammatory syndrome. The T cell costimulation inhibitor abatacept was also effective in some cases of AA amyloidosis secondary to arthritis. Because of its potent anti-IL6 action, tocilizumab may be efficacious in treating AA amyloidosis regardless of the underlying cause. It has successfully controlled AA amyloidosis complicating RA, JIA and adult-onset Still's disease (AOSD). Tocilizumab improved nephrosis, as well as gastrointestinal amyloid deposition and diarrhoea.

In a phase II/III clinical trial, the effects of eprodisate, a small molecule GAG mimetic, were compared with those of placebo in patients with systemic AA amyloidosis. Although the specified primary end point for efficacy was not achieved, eprodisate significantly slowed the progression of renal disease in comparison with placebo. Thus, inhibition of interactions between GAGs and amyloid fibrils using small molecule anionic sulfates or sulfonates remains a promising therapeutic approach in all types of amyloidosis

(Fiter et al. 1995; Gottenberg et al 2003; Keersmaekers et al, 2009; Unverdi et al. 2013; Nakamura et al. 2014; Courties et al. 2015).

1.5.3 Treatment of AL amyloidosis

In AL amyloidosis, chemotherapy reduces the production of amyloid precursor proteins, which improves target organ function and survival. Future therapeutic strategies will aim to inhibit fibrillogenesis by stabilising precursor proteins or to promote amyloid clearance. Determination of serum Ig FLC levels has important prognostic value and also reflects the response to chemotherapy.

Among therapeutic strategies, high-dose melphalan followed by autologous stem cell transplantation was effective in haematological patients with AL amyloidosis. Complete haematological response leading to prolonged survival could be achieved in 40% of patients. As cardiac involvement was associated with higher treatment-related mortality, such patients should receive other chemotherapy regimens. The main causes of cardiac worsening are heart failure and ventricular arrhythmias (VAs), but there is still debate concerning the need and indication for implantable cardioverter-defibrillator (ICD) therapy (Hamon et al. 2016). Other pharmacological strategies include the combination of melphalan with glucocorticoids; however, this treatment resulted in a 28% response rate. In relapsing cases, thalidomide may be an effective alternative, but it has been poorly tolerated by patients with polyneuropathy. A new and less toxic thalidomide analogue, lenalidomide induced haematological responses in 67% of patients. The proteasome inhibitor bortezomib, registered for the treatment of multiple myeloma, produced responses in 50% of patients when administered in monotherapy and in >80% of patients in combination with dexamethasone (Fitter et al, 1995; Perfetto et al, 2010*; Kastritis and Dimopoulos 2016).

1.5.4 Treatment of A β 2M amyloidosis

In A β 2M amyloidosis, the approach is to prevent amyloid deposition by removing β 2M using high-flux dialysis membranes and adsorption columns. There is insufficient evidence that these manipulations will indeed decrease amyloid deposits (Perfetto et al, 2010*).

1.5.5 Treatment of ATTR amyloidosis

Liver transplantation seems to be the only way to remove the source of mutated TTR from the blood. Blockade of TTR fibrillogenesis may be a feasible approach in the future. Small molecules that stabilise the tetramer structure of TTR would inhibit its dissociation and would prevent the formation of cytotoxic monomeric species. Such agents include tafamidis, diflunisal and a combination of doxycycline and tauro-ursodeoxycholic acid (TUDCA). Finally, novel RNA inhibiting therapies targeting the synthesis of transthyretin in the liver are under development (Wechalekar et al. 2016*).

1.5.6 Treatment follow-up

As described above, some laboratory biomarkers may reflect the progression and prognosis of various types of amyloidosis. Thus, these markers may be used to monitor therapeutic response. Circulating SAA, β 2M levels and the Ig FLC assay may be repeatedly used to monitor therapeutic response in AA, A β 2M and AL amyloidosis, respectively (table 4).

In AA amyloidosis secondary to chronic rheumatic diseases, organ involvement may develop after a period of time. Therefore, these patients must be periodically monitored for new clinical symptoms and laboratory tests, such as renal function and microalbuminuria, must be carried out. These patients are at high risk of rapid acceleration of amyloidosis, and new organ manifestations may occur at any time (Tanaka et al, 2003*; Perfetto et al, 2010*).

SUMMARY POINTS

- Systemic amyloidosis is characterised by extracellular deposition of insoluble fibrils.
- Amyloidosis is classified by the nature of amyloid precursor proteins.
- The type of amyloidosis greatly influences the required treatment and outcome.
- The diagnosis of amyloidosis needs histological confirmation.
- Extensive investigation should be performed to determine systemic organ manifestations.
- Treatments aim to reduce the supply of amyloid precursor proteins.
- Future therapeutic strategies aim to inhibit fibrillogenesis by stabilising precursor proteins or to promote amyloid clearance.

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2 Atherosclerotic disease in patients with inflammatory arthritis and systemic lupus erythematosus

LEARNING OBJECTIVES

- To describe the epidemiology of cardiovascular disease in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and systemic lupus erythematosus (SLE)
- To describe the contribution of traditional cardiovascular risk factors to the excess cardiovascular risk
- To describe the contribution of disease-specific processes to the excess cardiovascular risk
- To describe the effects of treatments on endothelial function
- To describe the effects of treatments on cardiovascular risk factors and cardiovascular morbidity
- To describe measures for preventing cardiovascular disease in patients with inflammatory arthritis and SLE

2.1 Cardiovascular mortality

2.1.1 Rheumatoid arthritis

Mortality in rheumatoid arthritis (RA) is increased compared with the general population. Standardised mortality ratios (SMRs) in observational studies ranged from 1.3 to 3.0 but recent meta-analyses show somewhat lower SMRs (1.2-1.7) (Avina-Zubieta et al. 2008; Widdifield et al. 2015; Dregan et al. 2017; Gwinnutt et al. 2017). Excess mortality is largely due to cardiovascular diseases (CVDs), particularly atherosclerotic ischaemic heart disease. The Norfolk Arthritis Register has confirmed an increase in all-cause and CV mortality in patients satisfying the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA; there were 40% more deaths than expected in rheumatoid factor (RF)/anti-citrullinated peptide antibody (ACPA)-positive than in RF/ACPA-negative patients, suggesting that antibody status plays an important role in CV mortality (Humphreys et al. 2014). There has been debate on the trend of cardiovascular (CV) mortality in RA. A systematic review and meta-analysis suggests a decrease in incident mortality of 2.3% a year (95% CI 2.1% to 2.6%) and a meta-SMR of 1.47 (95% CI 1.19 to 1.83), with no decrease over time in the meta-regression (Dadoun et al. 2013). More recent data support also a reduction in CV-related mortality (Myasoedova et al. 2017)

2.1.2 Spondyloarthropathies

Mortality has been less investigated in the spondyloarthropathies but is also high, although less so than in RA. Reported SMRs for ankylosing spondylitis (AS) are between 1.5 and 1.9 (Bakland et al. 2011; Haroon et al.

2015; Exarchou et al. 2016) and even lower in psoriatic arthritis (PsA), between 0.8 and 1.6. In a recent study from Swedish registries, SMRs for overall and cardiovascular mortality were 1.22 and 1.64 respectively and they were associated with disease activity (Juneblad et al. 2016).

2.1.3 Systemic lupus erythematosus

Mortality in patients with systemic lupus erythematosus (SLE) typically has a bimodal pattern: this is driven by infectious complications in the early phases, but CVD is by far the most important contributor to the second (late) peak of mortality. Although mortality has improved greatly in SLE over the past few decades, it is still 2–5 times higher than in the general population with CV morbidity being also significantly higher (Symmons and Gabriel 2011).

2.2 Cardiovascular morbidity

2.2.1 Rheumatoid arthritis

A number of studies have indicated that patients with RA are at higher risk of developing CV diseases such as myocardial infarction (MI), cerebrovascular disease, peripheral arterial disease (PAD) and congestive heart failure (CHF). In a meta-analysis, RA patients had a 48% increase in the risk of incident CVD compared with the general population, 68% for MI, 41% for a CV event and 87% for CHF (but only in women)(Avina-Zubieta et al. 2012*). In a recent comparison between sex and age-matched patients with RA or osteoarthritis (OA) in a Chinese population, the adjusted ORs (95%CI) for CVD, stroke, IHD, CHF, and atherosclerosis were 1.86(1.42-2.43), 1.11(0.71-1.74), 1.47(0.97-2.24), 2.09(1.03-4.22), and 2.49 (1.97-3.13), respectively (Zou et al. 2017).

The prospective Dutch CARRÉ (CARDiovascular research and Rheumatoid arthritis) study of 353 patients with RA diagnosed between 1989 and 2001, investigated the magnitude of this risk by comparing prevalent CVD and diabetes (a well-established CV risk factor) with the findings of the Hoorn population-based cohort study of CVD and its risk factors (van Halm et al. 2009): its findings suggested that the risk of CVD in RA patients is increased to an extent comparable to that seen in diabetes. This has recently been confirmed in the much larger nationwide Danish study: the overall, fully adjusted incidence rate ratio of MI in patients with RA was 1.7 (95% CI 1.5 to 1.9), the same as that found in patients with diabetes 1.7 (95% CI 1.6 to 1.8) (Lindhardsen et al. 2011). Various other studies have found that patients with RA have a 2–4 times greater risk of developing MI than the general population, and that the occurrence of multivessel coronary disease is twice as frequent in patients with RA who have had an MI than in patients with an MI but without RA, thus indicating accelerated atherosclerosis. In addition, the fatality rate after MI is almost twice as high in patients with RA in both the short term (30 days) and the long term (up to 10 years). Although ischemic heart disease (IHD) in RA probably follows a decreasing trend (Holmqvist et al. 2017), it is still high comparing to the general population. It is

important to note that patients with RA are less likely to report angina, and twice as likely to experience a silent MI and sudden death.

CHF is also an important co-morbidity in RA. A population-based, retrospective incidence cohort study of 575 patients with RA and 583 controls using the criteria of the Framingham Heart Study found that the incidence of CHF was, respectively, 2.0 and 1.2 per 100 person-years (rate ratio 1.7, 95% CI 1.3 to 3.2.), the cumulative incidence after a follow-up of 30 years was, respectively, 34% and 25% (HR = 1.9) and the risk was higher in RF positive patients (Nicola et al. 2005). Recent results from two Swedish cohorts also show increased risk for both ischemic and non-ischemic CHF (HRs 1.71 and 1.88 respectively). There appears to be a rapid increase of risk for non-ischemic CHF in newly diagnosed RA patients, not fully explained by their IHD risk but associated with high disease activity (Mantel et al. 2017). A major drawback of heart failure studies in RA is that the diagnosis is usually based on clinical criteria, thus making it less reliable than a diagnosis based on echocardiographic criteria. Diastolic heart failure with preserved ejection fraction seems to be more prevalent reflecting the influence of chronic inflammation on the myocardium (Nurmohamed et al. 2015*; Midtbø et al. 2016b), while high ACPA titres were associated with increased left ventricular (LV) mass index (Geraldino-Pardilla et al. 2017).

It is important to remember that the prevalence of CVD may vary from country to country, as was recently demonstrated by a large cross-sectional study of 4363 patients from 15 countries. The overall prevalence of CVD (defined as MI, angina, coronary heart disease, coronary bypass surgery or stroke) was 9%, but ranged from 3.6% to 17.8%: <5% in France and Argentina, and >10% in Finland, Germany, Poland, the UK and the USA (del Rincón et al. 2007; van Halm et al, 2009; Peters et al, 2010).

2.2.2 Spondyloarthropathies

Available data on CV morbidity in AS and PsA indicate increased CV risk, perhaps comparable to that of RA (Peters et al. 2004).

Han et al. (2006)* used the large American PharMetrics medical reimbursement administrative database of 1843 patients with AS to find prevalence odds ratios of 1.3 for ischaemic heart diseases, 1.4 for CHF, 1.6 for atherosclerosis and 1.3 for cerebrovascular disease in comparison with the controls. Increased CV risk in AS is related to higher inflammatory activity (Bakland et al. 2011). A systematic review and meta-analysis of observational studies that compared the risk of coronary artery disease in patients with AS versus non-AS controls showed that AS was associated with a 1.41-fold [95% CI: 1.29-1.54] increased risk of coronary artery disease compared with non-AS patients (Ungprasert et al., 2015). A Swedish population study also found a more than twofold higher prevalence of IHD (Bremander et al. 2011). In contrast, a population-based cohort study using the British Clinical Practice Research Datalink found only a non-significant trend for IHD in women with AS, after adjusting for NSAID use (Essers et al. 2014).

A number of studies indicate that AS is also associated with various non-atherosclerotic CV manifestations. The inflammatory processes in AS may affect different structures of the heart: the most characteristic lesions are conduction defects and aortic insufficiency, but other less common manifestations are pericarditis, cardiomyopathy and mitral valve disease. Conduction disturbances may occur in AS because of inflammation and fibrosis of the membranous portion of the interventricular septum, thus affecting the atrioventricular node. The reported prevalence rates vary from 1% to 33%, and may be related to the presence of HLA-B27. One recent study found no increase in comparison with historical controls, whereas a study of 131 consecutive patients with AS found intraventricular conduction disturbances in up to 30% (Atzeni et al. 2010; Szabo et al. 2011). These data have been confirmed by a recent meta-analysis showing that, compared to controls, patients with AS have an increased prevalence of diastolic left ventricular dysfunction, which may be a precursor of CHF (Heslinga et al. 2014). Aortic insufficiency develops because the aortic inflammatory process affects the aortic wall directly behind and above the sinuses of Valsava. The reported prevalence rates range from 1% to 10%, and increase with age, disease duration and presence of peripheral arthritis.

The number of publications concerning CV morbidity in patients with psoriasis and PsA has increased in recent years. A database investigation of 648 patients with PsA found a 2.5 increased standardised prevalence of MI, and the same group also showed that the CV risk was higher than in patients with psoriasis alone. A questionnaire-based survey of 753 patients with PsA showed that the prevalence rates of ischaemic CVDs were comparable with those found in patients with RA (Atzeni et al. 2011). A meta-analysis showed an increased risk of MI in patients with psoriasis (OR = 1.25, 95% CI 1.03 to 1.52) or PsA (OR = 1.57, 95% CI 1.08 to 2.27) in comparison with the general population, but inconclusive results for stroke (Horreau et al. 2013).

Disease activity was independently associated with CV morbidity in a Canadian large PsA cohort study (Eder et al. 2016). A recent meta-analysis of observational studies confirmed increased morbidity risks for MI, cerebrovascular disease and heart failure (pooled OR 1.68 [95% CI 1.31-2.15], 1.22 [1.05-1.41] and 1.31 [1.11-1.55], respectively) in patients with PsA (Polachek et al. 2017).

Patients with psoriasis have increased incidence of both heart failure (HR :1.22-1.53) and arrhythmia (HR: 1.25-1.46) depending on disease severity and presence of arthritis (Khalid et al. 2014; Chiu et al. 2015).

2.2.3 Systemic lupus erythematosus

Prospective cohort studies of patients with SLE have shown high rates of CV morbidity, with a prevalence of CV events of 6–10% and an annual incidence of 1.5%. In fact, SLE is associated with the highest CV morbidity risk amongst rheumatic diseases (Koenig et al. 2015).

CV risk was 5–6 times higher in the Pittsburg cohort of patients with SLE than in the Framingham cohort and, in women aged 35–44 years, it was 50 times higher than in controls. A Swedish study of SLE patients followed

up for 6 years found that MI occurred nine times as often as in the general population, while the prospective Nurse's Health study found that the risk was lower (a 2.2-fold increased risk). The higher incidence of MI is associated with a longer disease duration and glucocorticoid treatment. Epidemiological studies cannot determine whether the increased risk of CVD is due to accelerated atherosclerosis or to a greater susceptibility to thrombotic complications but histopathological studies suggest the presence of subclinical atherosclerosis (Bruce et al. 2003; Roman et al. 2003; Mosca et al. 2010*; Skaggs et al. 2012*; Matsuura et al. 2014). A recent Danish nationwide cohort study identified high risk for MI (HR: 2.2), stroke (HR: 2.1) and CV mortality (HR: 1.6) in patients with SLE. The risk for MI, CV mortality but not for stroke is particularly increased in SLE patients with lupus nephritis (Hermansen et al. 2017).

2.3 Preclinical atherosclerosis

Carotid artery intima media thickness (IMT) is a suitable means of assessing early preclinical atherosclerosis and a predictor of future CV disease. A landmark general-population study found that every 0.20 mm increase in cIMT is associated with a 30% increase in new CV events and, when IMT is divided into quintiles from <0.87 mm to >1.18 mm, the relative risk for new CVD is tripled between the fifth and first quintile. Consequently, given the increased CV risk in patients with RA, a number of investigators have measured cIMT in more than 20 studies and, taken together, have found that it is almost 0.1 mm thicker in patients than matched controls. This increase seems to be related to disease activity parameters but is much less than expected in the light of the doubled CV risk: this suggests that the problem may also be due to plaque instability.

The presence of carotid plaques has been linked to IHD and poor CV-related survival in RA patients (Evans et al. 2011). Del Rincón et al. (2007) observed that the rate of IMT progression was related to disease duration, and ranged from 0.15 mm/10 years in patients who have had the disease for <7 years to 0.30 mm/10 years in patients who have been affected for >20 years. Patients with longstanding RA, therefore, have more atherosclerosis than patients of the same age but with shorter disease duration, thus indicating that RA accelerates atherosclerosis. The clinical relevance of preclinical atherosclerosis was also assessed in a cohort of RA patients. A coronary event occurred in six of the 10 patients with a baseline IMT of >0.91 mm, but in none of those with a baseline IMT of <0.77 mm (Gonzalez-Juanatey et al. 2009*). A prospective study also identified increased subclinical atherosclerosis in RA patients by measuring both IMT and flow-mediated dilatation (FMD) after a 5-year follow up. The extent of this effect could be predicted by the presence of traditional CVD factors, as well as inflammatory load over time (Södergren et al. 2015). However, further large-scale studies are necessary to confirm these findings.

The number of publications concerning preclinical atherosclerosis in patients with AS or PsA is limited. Arida et al. (2015) showed that carotid IMT, but not plaque burden, was significantly increased in AS compared to controls but only in active disease patients (based on BASDAI \geq 4). FMD of the brachial artery has also been

found significantly impaired in AS patients. This is an important finding as it is thought that endothelial dysfunction is the initiating step in atherosclerosis (Bodnár et al. 2011). Various controlled studies of patients with PsA have shown increased IMT and significantly impaired FMD. However, none of these studies showed a clear correlation with disease activity, possibly because of a type II error.

Patients with SLE and CV manifestations (eg, MI, angina, stroke and/or arterial claudication) have increased IMT in comparison with patients with SLE without CV manifestations and controls. Subclinical atherosclerosis (as identified by carotid plaques) has also been proven to occur early in SLE patients and is probably driven by disease-related factors (Roman et al. 2003). A recent study indicated that the relative risk of carotid and femoral atherosclerotic plaques in SLE was comparable to that of RA and diabetes (RR=1.80, 95% CI 1.05-3.08) (Tektonidou et al. 2017).

Non-invasive imaging techniques that measure atherosclerosis (IMT), endothelial dysfunction (FMD) and arterial stiffness (pulse-wave velocity) are useful for detecting preclinical vascular disease in arthritides and autoimmune diseases (Soltész et al. 2011; Kerekes et al. 2012). The use of carotid US helps reclassify a considerable proportion of patients to a more appropriate CVD risk group in RA (Corrales et al. 2014), AS (Rueda-Gotor et al. 2016) and PsA (Martínez-Vidal and Fernández-Carballido 2017). The updated EULAR recommendations for CVD risk management suggest to consider screening for asymptomatic atherosclerotic plaques with carotid US as part of the CVD risk evaluation for RA patients (Agca et al. 2017*).

2.4 Cardiovascular risk factors

2.4.1 Rheumatoid arthritis

2.4.1.1 Dyslipidaemia

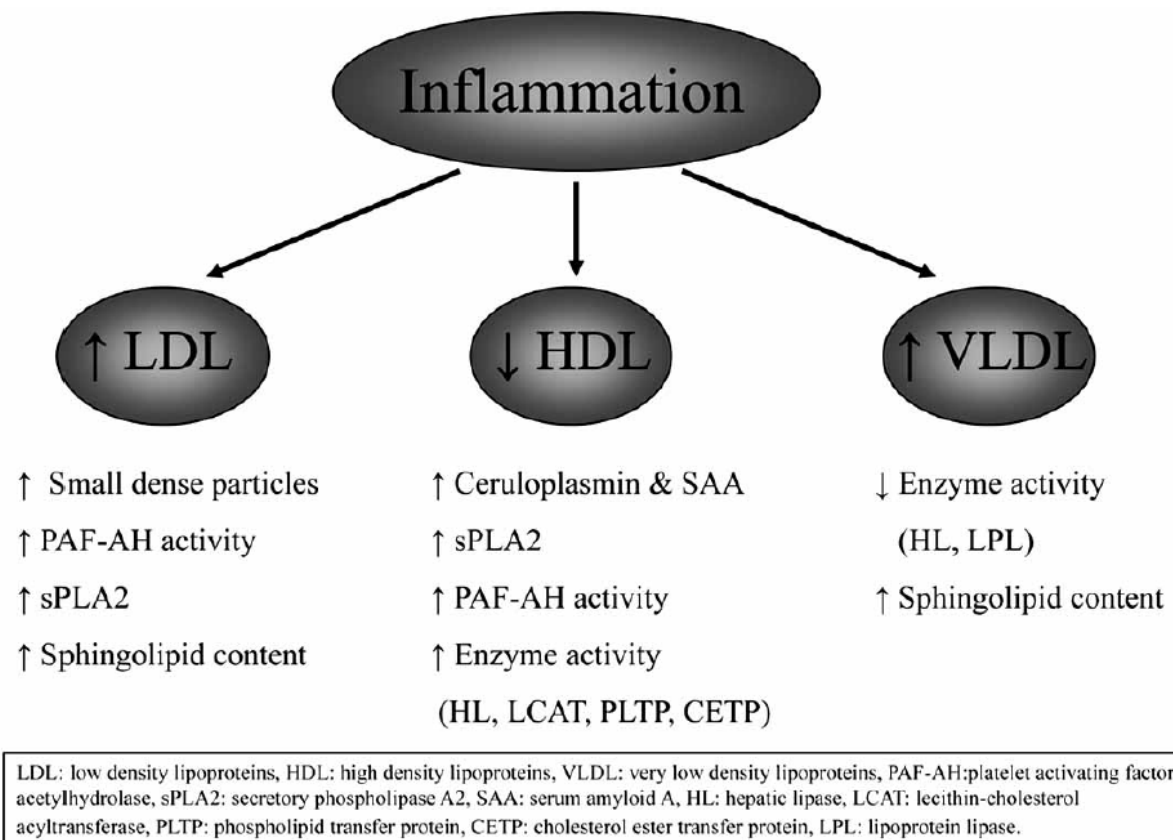
In the general population, high levels of total cholesterol (TC) and LDL cholesterol (LDL-C) and low levels of high-density lipoprotein (HDL) cholesterol (HDL-C) are associated with an increased risk of CVD. In RA however, this relationship paradoxical ('lipid paradox') due to an inverse relationship between lipid levels and disease activity: greater disease activity is related to lower TC and LDL-C levels (figure 3) (Myasoedova et al. 2011*; Myasoedova 2017*). The presence of even more depressed HDL-C levels leads to a higher (unfavourable) atherogenic index (TC/HDL-C ratio). The explanation of this 'paradox' may lie on genetic factors, decreased LDL synthesis and/or increased lipid clearance in patients with active RA, with a recent study demonstrating the latter (Charles-Schoeman et al. 2015). Furthermore, protecting LDL from oxidation is one of the anti-atherogenic roles of normal HDL-C, which can be distinguished from the so-called proinflammatory HDL-C that does not have this property and may actually promote inflammation. Proinflammatory HDL-C was detected in 20% of 48 patients with RA and in only 4% of 72 controls (Kerekes et al. 2014*).

It seems that dyslipidaemia is already present in early RA, which raises the question as to whether it starts in the preclinical phase. Lipid profiles and their relationships with inflammation and serological markers in subjects who later developed RA were investigated. The samples of the patients with future RA had higher TC, triglyceride and apoB levels and lower HDL-C compared to matched controls at least 10 years before the onset of symptoms. Although the differences were small, they may be clinically relevant (Choy and Sattar 2009; Robertson et al. 2013).

Measurement of plasma apolipoprotein A-I (apoA-I), present in HDL-C particles, and apolipoprotein B (apoB), which is found in LDL-C, very low-density lipoprotein (VLDL) and chylomicron particles, may help to assess the total number of pro- and anti-atherogenic particles. There is accumulating evidence that apoB is a better predictor of CV events than LDL-C, and that the apoB/apoA-I ratio is an accurate predictor of CVD insofar as apoA-I might be protective and apoB might increase susceptibility to new CV disease. RA disease activity inversely correlated with apoA-I and HDL-C levels, thus suggesting genetic coupling between dyslipidaemia and the development of RA. Furthermore, it has recently been shown that four RA susceptibility genes (PTPN22, TRAF1/C5, STAT4 and the shared epitope) are associated with TC, LDL-C, apoA-I and apoB levels (Toms et al. 2011a*, 2011b*; Kerekes et al. 2014*).

A growing body of literature shows that reducing inflammation by disease-modifying antirheumatic drugs (DMARDs), including early glucocorticoids, has beneficial effects on the lipid profiles of RA patients, leading to an increase in TC and LDL-C and a more pronounced increase in HDL-C and, consequently, a lower (more favourable) atherogenic index (Chen et al. 2015*; Provan et al. 2015; Souto et al. 2015; Charles-Schoeman et al. 2016a*).

Figure 3 The effects of inflammation on the structure, composition and function of lipids (Reprinted with permission from Toms TE et al, *Curr Vasc Pharmacol*. 2010 May;8(3):301–26)



2.4.1.2 Smoking

Smoking is a well-known risk factor for both CVD and RA. RA patients are more frequently current or ex-smokers than the general population (Boyer et al. 2011). There is a causal link between smoking and RA and smoking has been associated with more severe clinical RA presentation and decreased response to DMARD treatment. However, possibly because of the many overlying interactions with other factors, it has been difficult to clearly establish quantitatively the contribution of smoking to CVD risk in RA populations (Nurmohamed et al. 2015*). In a recent meta-analysis, CV morbidity in RA increased with smoking (RR=1.50) (Baghdadi et al. 2015*).

2.4.1.3 Hypertension

The prevalence of arterial hypertension in RA patients ranges from 4% to 73%, although the recent international COMORA study calculated it at 40.4% (Dougados et al. 2014*). However, data on whether it is more frequent than the general population has been conflicting (Boyer et al. 2011; Protogerou et al. 2013). Undoubtedly, it is an important CVD risk factor and was recently associated with asymptomatic CV organ damage in RA (Panoulas et al. 2010; Midtbø et al. 2016a). The mechanisms behind its pathophysiology in RA are various and include the poor adaptive ability of the arterial system in blood flow changes, increased

arterial stiffness and peripheral vascular resistance, the presence of specific genetic polymorphisms, the activation of inflammatory pathways and the effect of RA treatment (Panoulas et al. 2007, 2008c*).

Unfortunately, hypertension is both underdiagnosed and undertreated in RA (Van Breukelen-van der Stoep et al. 2016) and more aggressive management appears mandatory.

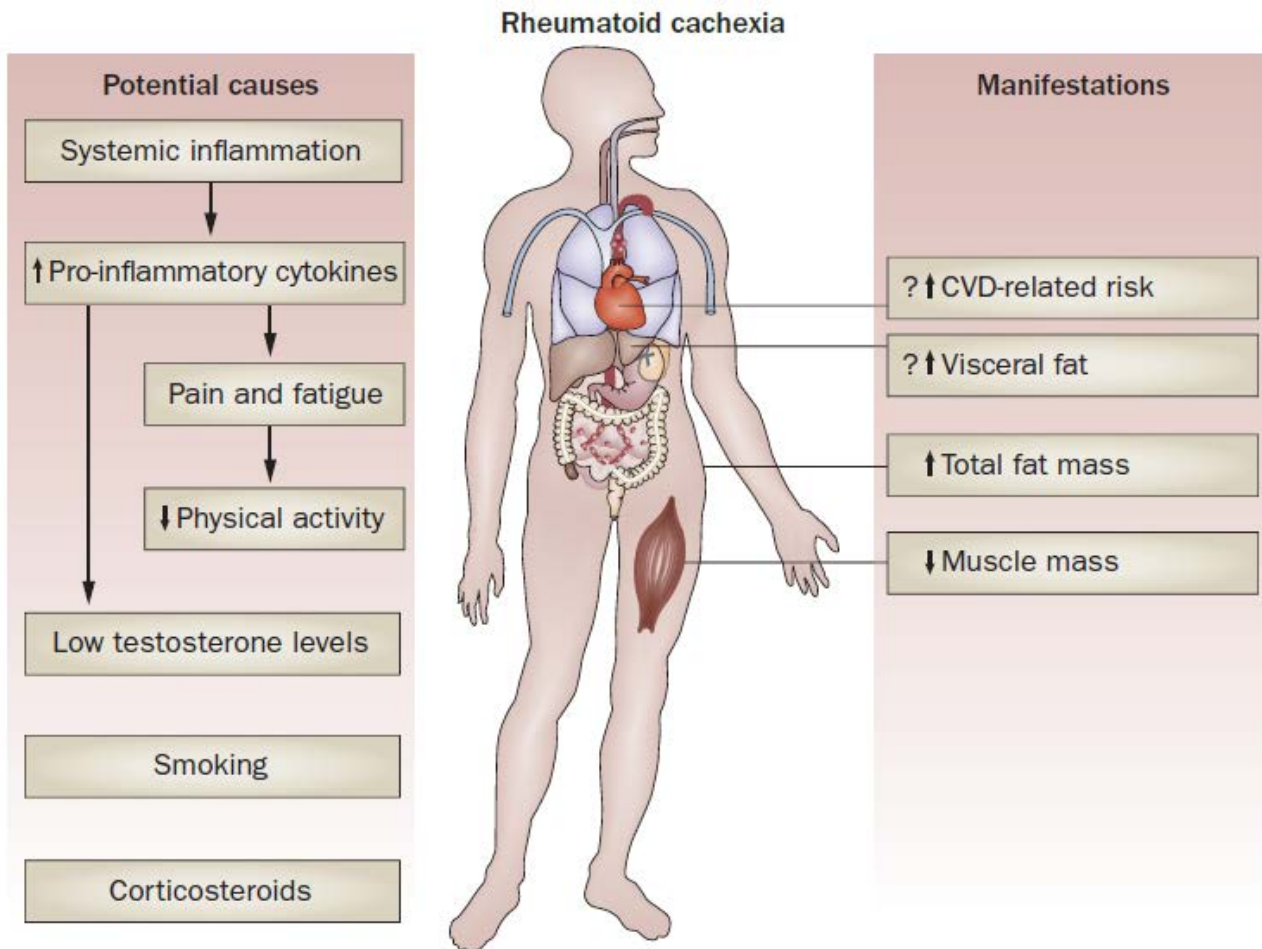
2.4.1.4 Body mass index (BMI), obesity and physical inactivity

As with lipid changes, the effect of BMI in CVD risk in RA populations seems also paradoxical. In the general population, normal-to-low BMI is protective in terms of CVD risk. In contrast, low BMI in RA has been associated with higher risk for CV morbidity. This is explained by the effect of systemic inflammation on adipose tissue leading to muscle atrophy and fat accumulation (low muscle mass, high fat percentage) which has been termed rheumatoid cachexia (figure 4) (Kremers et al. 2004; Summers et al. 2010). These pathophysiological changes are underappreciated with the use of the general population's BMI thresholds and alternative tools, such as the waist-to-hip ratio, may be more representative. This increased visceral adiposity and sarcopenic obesity is positively associated with hypertension, increased insulin resistance, metabolic syndrome and inflammatory load (Stavropoulos-Kalinoglou et al. 2009, 2011*). Furthermore, the physical inactivity that characterises RA patients for a number of reasons (joint pain and stiffness, fear of disease exacerbation, psychological barriers) has also been associated with increased CVD risk (Metsios et al. 2009; Hernández-Hernández et al. 2014). Several studies have also proven that high intensity structured exercise is beneficial in reducing long-term inflammation and in improving both micro- and macro-vascular function in RA (Khoja et al. 2016). Thus, physical activity should be encouraged in this population and is a part of the lifestyle interventions recently recommended by EULAR (Agca et al. 2017*).

2.4.1.5 Diabetes, insulin resistance and metabolic syndrome

As with obesity, insulin resistance and metabolic syndrome appear to be associated with RA, a process mainly driven from systemic inflammation (Dessein et al. 2003; Chung et al. 2008; Giles et al. 2015). This is a bidirectional relationship, as insulin resistance causes low-grade inflammation, but also high RA disease activity precipitates the effects of metabolic syndrome (Zegkos et al. 2016*). Moreover, both synthetic and

Figure 4 Summary of current knowledge regarding the underlying mechanisms and clinical manifestations of rheumatoid cachexia. The question marks denote areas in which the current state of knowledge is still preliminary. (Reprinted with permission from Summers GD et al, *Nat Rev Rheumatol.* 2010 Aug;6(8):445–51)



biological DMARD treatment in RA reduces the risk for development of diabetes and improves insulin resistance, as has been shown in several studies (Toms et al. 2009; Burska et al. 2015; Chen et al. 2015*; Bissell et al. 2016).

2.4.1.6 RA-specific risk factors

The chronic high-grade inflammatory state of RA and disease severity, as proven by joint involvement and extra-articular manifestations are established CVD risk factors in this population. Several inflammatory and serological RA markers (ESR, CRP, RF, ACPA) have been positively associated with CVD risk, while reduced time-averaged disease activity in RA is associated with less CV events (Solomon et al. 2015). RA and atherosclerosis share common inflammatory pathways (Skeoch and Bruce 2015), while immune activation/dysregulation, such as that seen in RA, is considered an important CVD risk factor. RF and ANA impose increased risk for IHD, CHF and peripheral vascular disease, independent of a diagnosis of RA (Liang et al. 2009), while ACPA positivity has been shown to promote atherosclerosis (Spinelli et al. 2017).

As disease severity is associated with increased mortality, it is reasonable to assume that the genes associated with disease severity are also associated with mortality. The HLA-DRB1 alleles encoding shared epitopes (SEs) are the most important and their effect to CVD mortality increases in combination with other risk factors. The HLA-DRB1*0101/*0401 and 0404/*0404 genotypes are very strong predictors of mortality with HRs of, respectively, 5.1 and 7.6, probably by relating to T cell-mediated vascular inflammation and damage. More recently discovered susceptibility risk alleles for RA located at the CCL21 locus are also associated with increased CV mortality. A number of studies have found that the gene polymorphisms associated with a higher CV risk in patients with RA, such as the TNF -308 (rs1800629), rs599839 A/G polymorphism, MIA3 rs17465637 A/C and it has been suggested that the risk may also be influenced by the CCR5Δ32 deletion, MTHFR 1298 A > C and IL6-174 gene polymorphisms (Rodríguez-Rodríguez et al. 2012). Associations of several genetic polymorphisms with hypertension and dyslipidaemia have also been described in patients with RA (Panoulas et al. 2008a, 2009a, 2009b; Toms et al. 2011b*, 2012). However, all of these associations need to be confirmed in much larger studies.

2.4.2 Spondyloarthropathies

The published data concerning the lipid profiles of patients with AS or PsA are somewhat contradictory, possibly because of differences in disease activity in the populations studied (Atzeni et al. 2011; Bodnár et al. 2011). As in RA, it seems that the degree of inflammation plays a role in the magnitude of dyslipidaemia. Lipid levels and inflammation markers (C-reactive protein and serum amyloid A (SAA)) were investigated during anti-TNF treatment in 92 patients with AS, in a subgroup of whom HDL-C composition was also analysed. All the inflammatory markers decreased during anti-TNF treatment; TC, HDL-C and apoA-I levels significantly increased; while SAA concentrations in HDL particles were high at the start of treatment, but subsequently decreased. This may be important because SAA replaces apoA-I in HDL particles and thus impairs the anti-atherogenic properties of HDL-C: consequently, by decreasing SAA concentrations the atheroprotective effects of HDL-C are restored.

A few small studies have shown that hypertension occurs more often in patients with AS or PsA than in the general population. The large database of Han et al has confirmed these observations by showing that hypertension is 30% more common in such patients (Han et al. 2006*). Data from the large NOCAR project showed that hypertension and obesity were more frequent in PsA compared to RA and AS. In the same study, hypertension was associated with disease activity in RA and AS (Wibetoe et al. 2017*). Insulin resistance and the metabolic syndrome have been traditionally associated with psoriasis but data in AS are too limited to allow any definite conclusions.

2.4.3 Systemic lupus erythematosus

The increased prevalence of CV disease is well established in SLE even after correction for traditional risk factors. Several associations with disease related clinical, genetic and immunological features have been described (Giannelou and Mavragani 2017*).

A Canadian case–control study of 250 consecutive patients with SLE and 250 controls found higher rates of hypertension and diabetes mellitus in patients who were less physically active and had higher levels of VLDL-cholesterol, triglycerides and homocysteine. The CV risk estimate based on the Framingham score was not significantly different between the groups.

High cholesterol levels and a diagnosis late in life are two factors that are consistently associated with an increased CV risk in patients with SLE. A prospective study of 134 patients showed that cholesterol levels consistently >5.2 mmol/L independently predict MI or unexplained sudden death, which occurred in 28% of the patients with consistently high cholesterol levels and in only 3% of those with consistently normal cholesterol levels. Nevertheless, conventional risk factors do not fully explain the increased CV risk associated with SLE: in a cohort of 296 patients with SLE followed up for mean period of 8.6 years, the RR (95%CI) adjusted for conventional risk factors were: 10.1 (5.8 – 15.6) for MI, 17.0 (8.1-29.1) for CV death and 7.9 (4.0-13.6) for stroke (Esdaile et al. 2001).

A case–control study comparing 8688 patients with acute MI and 33 923 controls in the UK General Practice Research Database found that the 41 patients with SLE were 2.67 times more likely to experience an acute MI than their controls after correcting for the presence of traditional risk factors. However, the odds ratio for CV events increased to 18.24 (95% CI 1.48 to 225) in patients with SLE and dyslipidaemia. The factors that might have accounted for the excess CV risk included early menopause, impaired renal function, hypercholesterolaemia and hyperhomocysteinaemia (Fischer et al. 2004).

One study found that patients with SLE with coronary artery calcifications were older and had a higher prevalence of conventional CV risk factors than their counterparts without calcifications. Coronary artery calcifications were also associated with hyperhomocysteinaemia, renal impairment and longer disease duration. The Study of Lupus Vascular and Bone Long-Term Endpoints involved a cohort of 149 cases and 124 controls, and showed that greater disease-related damage at the first study visit (as measured by the modified systemic damage index) may predict an increased risk of coronary artery calcium progression, whereas greater disease activity at the first study visit (as measured by hypocomplementaemia and use of glucocorticoids) may predict an increased risk of aorta calcium progression (Lertratanakul et al. 2014).

The published data for smoking are contradictory but, as in the general population, smoking is related to an increased presence of plaques.

Insulin resistance is a well-established CV risk factor in the general population, and has been documented in patients with SLE. However, it is not associated with disease activity, or past or current glucocorticoid treatment, although it does correlate with high C-reactive protein levels. The excess CV risk in patients with SLE may be at least partially related to insulin resistance, which may in turn be due to chronic inflammation (Skaggs et al. 2012*). Also, SLE damage accumulated overtime contributes to insulin resistance in an independent way (Sánchez-Pérez et al. 2017).

A recent meta-analysis of 17 187 patients followed up for a median of 8 years showed that 25.4% experienced a CV event (MI in 4.1% and stroke in 7.3%). The most important predictors were: OR (95%CI) male gender 6.2 (1.49 – 25), hyperlipidaemia 3.9 (1.57 – 9.71), a family history of cardiac disease 3.6 (1.15 – 11.32), hypertension 3.5 (1.65 – 7.54) and SLE-related features such as the presence of autoantibodies 5.8 (3.28 – 7.78) and neurological disorders 5.2 (2.0 – 13.9), whereas there was low correlation with organ damage 1.4 (1.09 – 4.44), SLE activity 1.2 (1.2 – 1.2) or age at the time diagnosis 1.1 (1.07 – 1.17). These findings are important for patient management as they may help to reduce negative outcomes (Ballocca et al. 2015).

2.4.3.1 Lipid profiles and proinflammatory HDL

Lipid profile abnormalities in patients with SLE include low HDL-C, and high VLDL and triglyceride levels. Changes in the structure of the lipoprotein particles seem to contribute to higher atherosclerotic risk (Giannelou and Mavragani 2017*). Dysfunctional proinflammatory HDLs occur in ~50% of patients with SLE (compared to 5–7% of healthy controls), and lead to an approximately 17-fold increase in the risk of carotid plaque (Matsuura et al. 2014).

2.4.3.2 Antiphospholipid antibodies

Most anticardiolipin antibodies target the self-antigen β 2 –glycoprotein I (β 2 GPI), large amounts of which are found in the subendothelial region and at the intima–media junction of atheroma plaque specimens removed during endarterectomy. B2GPI co-localises with CD4+ T cells and may be the target of an autoimmune response that promotes the formation of atheromatous plaque. Antibodies to β 2 GPI increase oxidised LDL capture by macrophages, which is one of the steps in plaque formation.

Clinical studies have led to conflicting results: one study found that increased IMT correlated with the presence of lupus antibodies, but another found that the presence of atheromatous plaque did not correlate with the presence of anticardiolipin antibodies or circulating anticoagulant. A prospective study of 380 patients with SLE found a close correlation between a history of thrombosis and the presence of anticardiolipin antibodies or lupus anticoagulant, but neither of these was associated with IMT, or with the presence of carotid plaque or coronary artery calcifications (Veres et al. 2004; Matsuura et al. 2014).

2.5 Antirheumatic treatment and cardiovascular risk

2.5.1 Acetaminophen (Paracetamol)

Despite previous studies that hinted on a potential association between acetaminophen and CVD risk, more recent data from large databases confirm the lack of a relationship between the use of acetaminophen and IHD or stroke. This renders the drug useful and safe in pain management of patients with CV comorbidity and/or risk factors (Fanelli et al. 2017).

2.5.2 Glucocorticoids (GCs)

The place of GCs is a matter of continuing debate because of their CV side effects—namely, hypertension, dyslipidaemia, insulin resistance and diabetes. However, these side effects are particularly associated with prolonged and high-dose exposure, as shown in a study of RA patients with long term follow-up. The CV risk was associated with glucocorticoid exposure (HR = 1.68, 95% CI 1.14 to 2.47), and increased with higher current (HR per 5 mg increase 1.14, 95% CI 1.05 to 1.24) and cumulative dose (HR per 1 g increase 1.06, 95% CI 1.02 to 1.10) (Avina-Zubieta et al. 2013). Moreover, long term exposure even to medium dose corticosteroids was associated with hypertension in RA patients (Panoulas et al. 2008b), but not with the presence of metabolic syndrome (Toms et al. 2008). On the other hand, GCs rapidly and effectively suppress inflammation in RA and their use might be justified for short-term treatment and at the lowest possible dose—for example, as a ‘bridging treatment’ between the start of, and response to, DMARD treatment. In a recent EULAR task force publication, it is recognised that GCs association with CVD risk might partly be explained by confounding by indication as patients with high disease activity are more likely to be treated with them. Furthermore, risk of harm with GC exposure was considered high for doses >10mg/day, uncertain for 5-10mg/day and low for <5mg/day, with caution advised for the high risk CVD patients even at the low dose (Strehl et al. 2016*).

Similarly in SLE, glucocorticoid treatment may promote the development of atheroma as a result of its deleterious effects on lipid metabolism, blood pressure and glucose metabolism, but it can also reduce the CVD risk by controlling the inflammatory process. The risk may be once again dose-related, as doses of >10 mg/day have been associated with increases in TC, apoB and triglycerides. Two studies have found a significant association between glucocorticoid exposure and CV risk, and a third showed a lower prevalence of carotid plaque in patients less exposed to glucocorticoids or who had not received cyclophosphamide (Skaggs et al. 2012*).

2.5.3 NSAIDs and COXIBs

Despite the relative decrease of the use of NSAIDs/Coxibs for RA, their role in symptomatic management remains important. However, their use has been associated with increased CVD risk in the general population.

A recent study on a large population concluded that moderate doses of celecoxib were not linked to higher CVD risk compared to ibuprofen and naproxen, while the risk of GI bleeding was lower (Nissen et al. 2016).

The field in RA patients remains controversial. A Danish longitudinal cohort study has shown a statistically significantly lower CV risk associated with overall NSAID use (HR 1.22 (1.09-1.37) vs 1.51 (1.36-1.66); $p < 0.01$), whereas the use of rofecoxib (1.57 (1.16-2.12)) and diclofenac (1.35 (1.11-1.64)) was associated with an increased CV risk in patients with RA (Lindhardsen et al. 2014). A recent meta-analysis of more than 15 large trials aimed at determining the CV risk associated with the use of NSAIDs in patients with RA, psoriasis or PsA found that the RR (95% CI) of all-CV morbidity in patients treated with all NSAIDs, COX-2 inhibitors or non-coxib NSAIDs was respectively 1.18 (1.01 – 1.38), 1.36 (1.10 – 1.67) and 1.08 (0.94 – 1.24), and the RR (95% CI) of MI, stroke and major CV events (MACE) was respectively 1.13 (0.93 – 1.37), 2.15 (1.19 – 3.87) and 1.56 (0.82 – 2.97), suggesting that NSAIDs, especially coxibs, increase the risk of all types of CV morbidity (Roubille et al. 2015*). Furthermore, a population based study suggested a protective effect of traditional NSAID use on vascular mortality in AS patients above 65 years of age. Coxibs were not associated with an increased risk for vascular mortality (Haroon et al. 2015).

As there are no clear data on the safety of NSAID use in patients with rheumatic diseases and comorbidities, the use of NSAIDs should be assessed individually on the basis of the indication for pain relief and the risk factors associated with adverse effects. The recent EULAR recommendations advocate their use with caution in RA and PsA patients with documented CVD or presence of risk factors (Agca et al. 2017*). As for AS, NSAIDs hold their place as first-line treatment, but still individual assessment of balance between expected clinical benefit and CVD risk is needed (van der Heijde et al. 2017).

2.5.4 DMARDs

The QUEST-RA trial identified a reduction on the risk of CV morbidity with prolonged exposure to several DMARDs, including MTX, leflunomide and sulfasalazine (Naranjo et al. 2008). Increasing evidence suggests that effective suppression of inflammation lowers the risk of CVD (Micha et al. 2011). In a prospective study of 1240 patients with RA, where 190 died during the 18-year follow-up period, CV mortality was 70% less in the patients receiving MTX than in those not receiving the drug. Another study has shown that patients who fail to respond to MTX have a poor prognosis. Roubille et al. (2015*) published a meta-analysis of observational and randomized controlled trials indicating a reduction of RR for all CV events, MI and CHF (but not stroke or MACEs) in RA patients treated with MTX. It has also been shown that MTX, unlike other DMARDs, associates with reduced propensity of metabolic syndrome (Toms et al. 2009). A recent study proposed that MTX specifically protects the vascular endothelium against inflammatory injury via induction of AMPK- regulated protective genes (Thornton et al. 2016).

Others studies have investigated the effects of DMARDs on CV risk factors, such as diabetes, metabolic syndrome and dyslipidaemia. Both leflunomide and cyclosporine can induce high blood pressure, and should therefore not be considered the DMARDs of first choice in patients with hypertension or at increased CV risk. Cyclosporine has also been associated with increased susceptibility to atherosclerosis and the development of hyperlipidaemia. The use of hydroxychloroquine in RA has been associated with improved lipid and glucose profiles, anti-thrombotic effects, and protection against the onset of atherosclerosis. Finally, sulfasalazine is not the optimal anti-inflammatory agent in patients with CVD, but no studies are available concerning its use in patients with RA and CV involvement (Atzeni et al. 2010).

2.5.5 TNF-inhibitors

Given the important role of TNF in the aetiology of atherosclerosis, one would expect that TNF blockade would lower the risk of CVD risk (Szekanecz et al. 2009*). An American retrospective cohort showed that the use of TNF inhibitors is associated with a lower risk of CV events in patients with RA than the use of DMARDs (Bili et al. 2014) and this was recently confirmed from data from the largest British biologics registry that showed decreased risk for MI for TNF inhibitor compared to synthetic DMARD treatment (Low et al. 2016).

Furthermore, in the aforementioned meta-analysis (Roubille et al. 2015*), TNF inhibition was significantly associated with a reduction in the risk (RR; 95% CI) of all CVDs (0.70; 0.54 - 0.90), as well as in MI (0.59; 0.36 - 0.97), strokes (0.57; 0.35 - 0.92) and major adverse cardiac events (0.30; 0.15 - 0.57), while no significant effect was observed on CHF. Taken together, the published findings suggest that TNF blockers have favourable effects on the risk of CVD in RA. However, despite the findings of the meta-analysis, the lack of suitable prospective, controlled studies prevents any definite conclusions (Tam et al. 2014).

A recent meta-analysis of available studies revealed similar benefits from TNF inhibition in psoriasis and PsA, as it was associated with lower risk for CV events and MI in particular, compared both to topical and to methotrexate treatment. Also, a trend towards lower mortality was identified (Yang et al. 2016).

The potentially favourable effect of TNF blockers on CV risk might be due to attenuated IMT progression (or even a reduction in IMT) because of the similarities in the underlying inflammatory processes of RA and atherosclerosis. The few studies that have investigated the effect of TNF blockade on IMT in patients with RA indicate no progression or even regression of the IMT, but these involved small numbers of patients and had suboptimal methodological designs. The effect of anti-TNF drugs on arterial stiffness was evaluated by means of pulse wave velocity and the augmentation index, and showed, despite the limitations of the studies, that the balance of evidence suggested that TNF antagonists might have a beneficial effect on arterial stiffness and therefore CV risk (Dulai et al. 2012). The findings of a recent study suggest that the beneficial effect of TNF inhibition on arterial stiffness may be independent of its effect on disease activity (Vassilopoulos et al. 2015).

Also, RA patients on TNF inhibitors exhibited a 37% lower adjusted rate of progression of cIMT after a follow up of 3.2 ± 0.3 years (Giles et al. 2011).

TNF inhibitors are probably effective in preventing or even reversing the progression of IMT in patients with AS or PsA who respond to treatment. A prospective study with a median follow-up of 4.9 years found that carotid IMT progressed more slowly in 56 AS patients who continued treatment with anti- TNF drugs than in nine who discontinued anti-TNF treatment (van Sijl et al. 2015).

Furthermore, long-term anti-TNF treatment is associated with increased HDL and TC levels, low LDL levels and an unchanged atherogenic index (Chen et al. 2015*; Provan et al. 2015; Souto et al. 2015; Charles-Schoeman et al. 2016a*). After long-term treatment, triglyceride levels increased and apoB/A levels decreased. The presumed cardioprotective effects of anti-TNF in RA do not seem to be explained by quantitative lipid changes since long-term treatment has no effect on LDL levels or the atherogenic index. Increased HDL levels may have some beneficial effects, but this needs to be confirmed by prospective studies with long-term follow-up (Daïen et al. 2012). Adalimumab has been shown to improve HDL cholesterol efflux capacity (CEC), reduce cholesterol loading capacity (CLC) and inhibits macrophage cholesterol uptake, and infliximab may also restore impaired CEC in RA patients (Voloshyna et al. 2014). A recent meta-analysis has shown that anti-TNF therapy improves insulin sensitivity as indicated by a reduction in HOMA (Burska et al. 2015), however, there is evidence to suggest that this is not so in obese RA patients (Stavropoulos-Kalinoglou et al. 2012).

2.5.6 Tocilizumab, abatacept and rituximab

IL-6 inhibition has been shown to increase TC, LDL-C and TGs, without changing the atherogenic index and interestingly exhibiting lower Lp(a) levels compared to no biological therapy (Chen et al. 2015*; García-Gómez et al. 2017). Despite these changes and possibly through control of inflammatory pathways, tocilizumab has beneficial effects on endothelial function, as measured by FMD, and on arterial stiffness, as measured by PWV. This effect seems to appear very early in treatment with tocilizumab (Provan et al. 2015; Bacchiega et al. 2017).

Rituximab (RTX), a B lymphocyte-depleting drug, and abatacept (ABA), a selective T lymphocyte costimulation modulator, are both very effective at reducing inflammation and may therefore reduce the risk of CVD in patients with RA who respond to treatment. RTX was found to have beneficial effects on the lipid profile of RA patients, as it reduced the atherogenic index after 6 months of treatment and altered the composition of HDL-C to less atherogenic and proinflammatory (Rateman et al. 2013). A study has also shown that RTX reduces the progression of accelerated atherosclerosis in patients with RA, as measured by the improvement in the percentage FMD and the decrease in common carotid IMT (Benucci et al. 2013). In another recent study, rituximab reduced ccIMT and this was accompanied by decreased disease activity and CRP levels (Novikova et al. 2016).

Data for ABA remain scarce and conflicting. In a small report, trends for higher TC, LDL-C and HDL-C with lower atherogenic index were identified, but arterial stiffness by PWV increased after 6 months of treatment. A possible explanation lies to an insufficient decrease in disease activity and systemic inflammation (Mathieu et al. 2013). A recent study of insurance database data found that elderly RA patients treated with abatacept are at lower risk of developing MI than those treated with anti-TNF drugs (Zhang et al. 2016*).

2.5.7 Other biologics

The JAK inhibitor tofacitinib has been approved for the treatment of RA in a number of countries. Like tocilizumab, tofacitinib greatly increases the levels of LDL-C (19-21%) and HDL-C (11-14%), but improves cholesterol ester catabolism and markers of antiatherogenic HDL function. Data from clinical studies and databases do not, at this stage, suggest an increased CV risk in RA patients (Charles-Schoeman et al. 2015, 2016b; Souto et al. 2015).

Published data on newer biologics remain scarce. The use of anti IL-17A agents (secukinumab and ixekizumab) in clinical trials have not identified any safety signals relating to cardiovascular events. The rate of MACEs with these agents was low and comparable to that of TNF-inhibitors in a recent meta-analysis in patients with psoriasis (Rungapiromnan et al. 2017). There are no available data on belimumab, a B-lymphocyte stimulator (BLyS) inhibitor recently licensed for use in SLE.

Table 5 concentrates on the cardiovascular effects of synthetic and biologic DMARDs.

2.6 Cardiovascular risk management

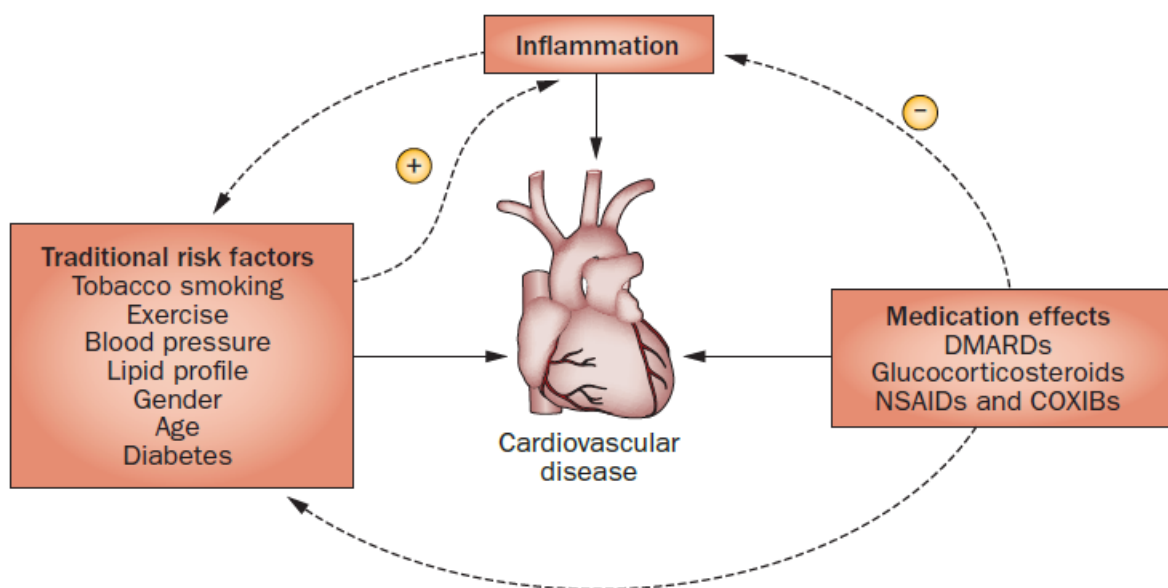
CV risk in patients with inflammatory arthritis is about twice that seen in the general population and, in patients with RA, seems to be similar to that of type 2 diabetes, a well-established CV risk factor. Traditional CV risk factors only partially explain the excess CV risk and another important factor seems to be the inflammatory process (Table 6 and figure 5). RA, AS and PsA should therefore be seen as new, independent CV risk factors requiring appropriate CV risk management and this is recognised in the recent 2016 guidelines of the European Society of Cardiology (Piepoli et al. 2016). However, the ideal actions to ensure proper CV risk management in inflammatory arthritis remain an area of controversy.

Table 5. Cardiovascular effects of biological and non-biological antirheumatic drugs (published on the book 'The heart in Autoimmune Rheumatic diseases' second edition edited by F. Atzeni, A. Doria, M. Nurmohamed, P. Paoletto, Elsevier 2016, Chapter 20, Cardiac Effect of antirheumatic drugs, S Szekanecz)

Drug	Preclinical	Clinical
NSAIDs		↑ Increased CV risk ↑ Hypertension ↑ Heart failure ↑ Arrhythmias
Corticosteroids		↑ CV risk ↑ Hypertension ↑ Hyperglycaemia. diabetes ↑ Heart failure ↑ Arrhythmias
Antimalarials		↓ CV risk ↑ conduction disorders
Sulfasalazine		↑ Thrombocytopenia
Methotrexate	↓ atherosclerosis in rabbits	↓ CV risk ↑ hypotension ↑ pericarditis
Leflunomide		↑ Hypertension
Cyclosporine A		↑ Hypertension
TNF-α blockers	↓ atherosclerosis in mice, rabbits	↓ CV risk ↓ insulin resistance ↓ platelet activation ↓ endothelial cell adhesion molecules ↑ heart failure (NYHA III-IV) ↑ dyslipidaemia ↑ hypertension ↑ infusion-related (if intravenous)
Rituximab	↓ atherosclerosis in mice	↑ infusion-related
Tocilizumab		↑ dyslipidaemia ↑ infusion-related
Abatacept	↓ atherosclerosis in mice ↓ blood pressure in mice	↑ hypertension ↑ infusion-related
Canakinumab	↓ atherosclerosis in mice	↑ endothelial function ↓ pro-atherogenic biomarkers
Tofacitinib		↑ dyslipidaemia

Table 6 Cardiovascular risk factors in inflammatory arthritis

MODIFIABLE RISK FACTORS	NON-MODIFIABLE RISK FACTORS
Traditional risk factors (Smoking, arterial hypertension, obesity, dyslipidaemia, insulin resistance/diabetes)	Age
Surrogate risk factors (Physical inactivity, stress, depression, hypothyroidism, hyperhomocysteinemia, kidney disease)	Sex
Inflammation	Family history
Medication effects (NSAIDs, glucocorticoids, DMARDs)	Genetic polymorphisms

Figure 5 Contributors to cardiovascular risk in inflammatory arthritides (Reprinted with permission from Nurmohamed MT et al, Nat Rev Rheumatol. 2015 Aug;11(12):693-704)

2.6.1 Lifestyle modifications

Increasing patients' awareness for the CV risk associated with their disease should be the cornerstone of CV risk management. Patient and allied health professional educational programs should be implemented to increase volition to behavioural change (John et al. 2011, 2013). Patients should be advised to quit smoking and provided with the opportunity to attend smoking cessation programs. Regular exercise and other modifications to avoid sedentary behaviour (Fenton et al. 2017) are highly recommended in the light of recent data showing their ability to reduce long term inflammation and improve both macro- and micro-vascular function (Metsios et al. 2014*). There is also a strong effect of exercise on reducing other traditional risk

factors (Stavropoulos-Kalinoglou et al. 2013*). Although there are no specific data on a positive effect of dietary modifications on the CV risk related to inflammatory arthritis, a Mediterranean diet (high consumption of fruit, vegetables, legumes, cereals, olive oil and fish) has been shown to reduce CVD in the general population and may have a positive effect on disease activity. Avoidance of excessive alcohol intake, weight control and psychological stress also provide significant benefit.

2.6.2 Control of traditional/modifiable risk factors

Arterial hypertension and dyslipidaemia are major CVD risk factors of multifactorial origin, are underdiagnosed and undertreated in rheumatic diseases and do not have specific treatment targets for these populations. Thus, blood pressure control should follow the management recommendations for the general population. Older studies have indicated that ACE inhibitors and angiotensin II (ATII) receptor blockers should be the preferred treatment choice for RA patients mainly because of their modest anti-inflammatory properties. In view of the lack of newer data, EULAR preferred to omit this preference in its recent recommendations.

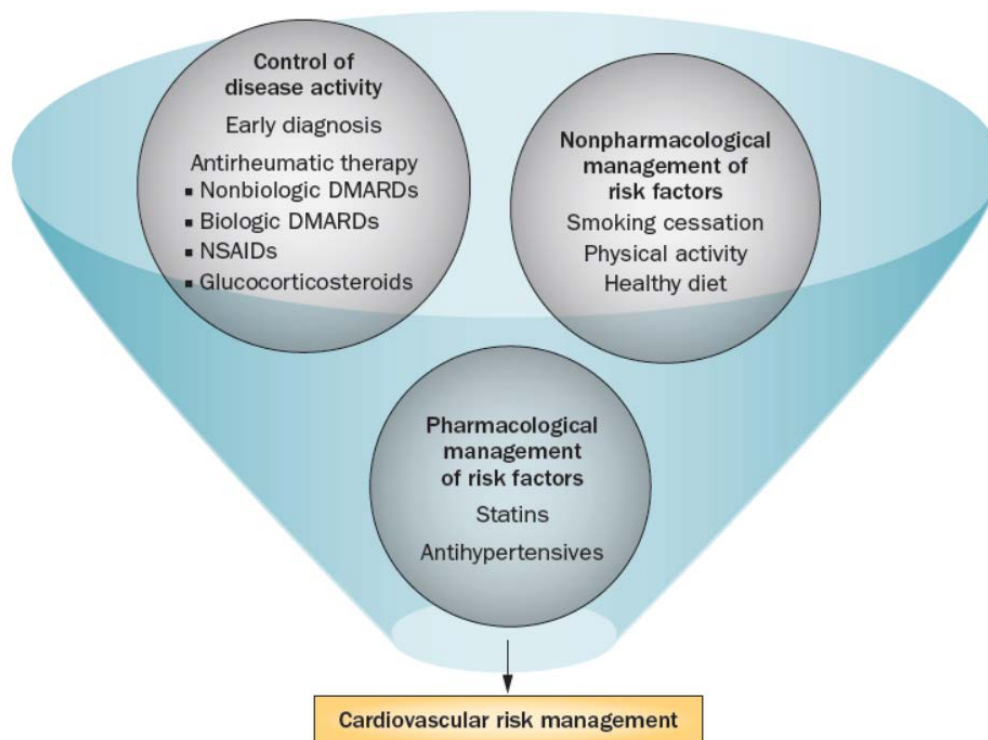
Observational studies suggest that lipid lowering agents, such as statins, associate with reduced cholesterol levels, atherosclerotic burden and CV morbidity and mortality in RA (Schoenfeld et al. 2015), AS and PsA (Rollefstad et al. 2013; Oza et al. 2017). Long-term lipid lowering treatment with rosuvastatin on patients with inflammatory joint disease and established atherosclerosis improved both arterial stiffness and carotid plaque size (Rollefstad et al. 2015). Statins are also considered to have pleiotropic anti-inflammatory properties which may confer additional benefit in patients with inflammatory arthritis (Lv et al. 2015), although this is disputed. Current evidence suggests that statin initiation in these conditions should follow the same guidance as in the general population. In SLE, data are more controversial. Atorvastatin did not show improvement in subclinical atherosclerosis measures (coronary artery calcification, cIMT) or disease activity (SLEDAI) after 2 years of treatment in the Lupus Atherosclerosis Prevention Study (LAPS), an RCT of 200 patients (Petri et al. 2011). On the other hand, statins have been found to improve endothelium-dependent vasodilation by FMD and resting brachial artery diameter (Ferreira et al. 2007) and PWV (Castejon et al. 2017) in SLE patients. Finally, in a recent retrospective cohort of Taiwanese SLE patients with hyperlipidaemia, statin treatment was shown to be associated with decreased mortality, CVD and end stage renal disease (ESRD) (Yu et al. 2015). Despite the inconsistencies, there is a reasonable basis to recommend lipid lowering treatment for CVD risk reduction in SLE in a similar fashion as with RA.

Because of the detrimental effects of insulin resistance and diabetes mellitus and their increased risk in RA patients (Ozen et al. 2016), screening for these co-morbidities with serum glucose and glucose tolerance tests should also be considered.

2.6.3. Control of inflammation

Systemic inflammation is closely associated with atherosclerosis and increased CVD risk. There is increasing literature to support the beneficial role of decreasing the inflammatory burden in patients with inflammatory joint disease with the use of synthetic and biologic DMARDs (Agca et al. 2017*). It seems that low disease activity slows down or improves atherosclerosis regardless of the antirheumatic treatment used (Arida et al. 2017).

Figure 6 Principles of cardiovascular risk management by rheumatologists (Reprinted with permission from Nurmohamed MT et al, Nat Rev Rheumatol. 2015 Aug;11(12):693-704)



In general, CVD risk management in patients with RA (figure 6) should represent an interdisciplinary task involving cardiology, rheumatology and primary care and ensure adequate involvement of the patient as well as effective communication between the managing physicians (Semb et al. 2014*).

Box 1 EULAR recommendations for cardiovascular risk management (Agca et al. 2017*)

OVERARCHING PRINCIPLES

- A. Clinicians should be aware of the higher risk for CVD in patients with RA compared with the general population. This may also apply to AS and PsA.
- B. The rheumatologist is responsible for CVD risk management in patients with RA and other IJD.
- C. The use of NSAIDs and corticosteroids should be in accordance with treatment-specific recommendations from EULAR and ASAS

RECOMMENDATIONS

1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA.
2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy.
3. CVD risk estimation for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available
4. TC and HDLc should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids measurements are also perfectly acceptable
5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model
6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA
7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation for all patients
8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population
9. Prescription of NSAIDs in RA and PsA should be with caution, especially for patients with documented CVD or in the presence of CVD risk factors
10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked



SUMMARY POINTS

- Patients with inflammatory arthritis (rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA)) should be considered as having approximately twice the risk for cardiovascular disease (CVD) as that observed in the general population. Patients with systemic lupus erythematosus (SLE) should be considered as being at very high risk for CVD.
- RA, AS, PsA and SLE should be acknowledged as new, independent cardiovascular (CV) risk factors.
- Traditional CV risk factors may be increased in patients with inflammatory arthritis or SLE.
- The inflammatory process significantly contributes to the increased CVD risk.
- Effective treatment with synthetic or biologic disease-modifying antirheumatic drugs reduces the risk of CVD in patients with inflammatory arthritis.
- Regular CV risk screening is required for patients with inflammatory arthritis or SLE.
- CV risk management, if necessary, should be part of routine care in these patient groups.
- CV risk management entails lifestyle modification, tight disease control and CV risk factor management to predetermined targets.

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3 Anaemia: pathophysiology, diagnosis and treatment

LEARNING OBJECTIVES

- Describe the most important mechanisms underlying pathophysiology of anaemia associated with chronic inflammation
- Establish the diagnosis of inflammatory anaemia based on clinical history, differential diagnosis, interpretation of laboratory values
- Treat anaemia according to aetiology and the underlying rheumatic disease

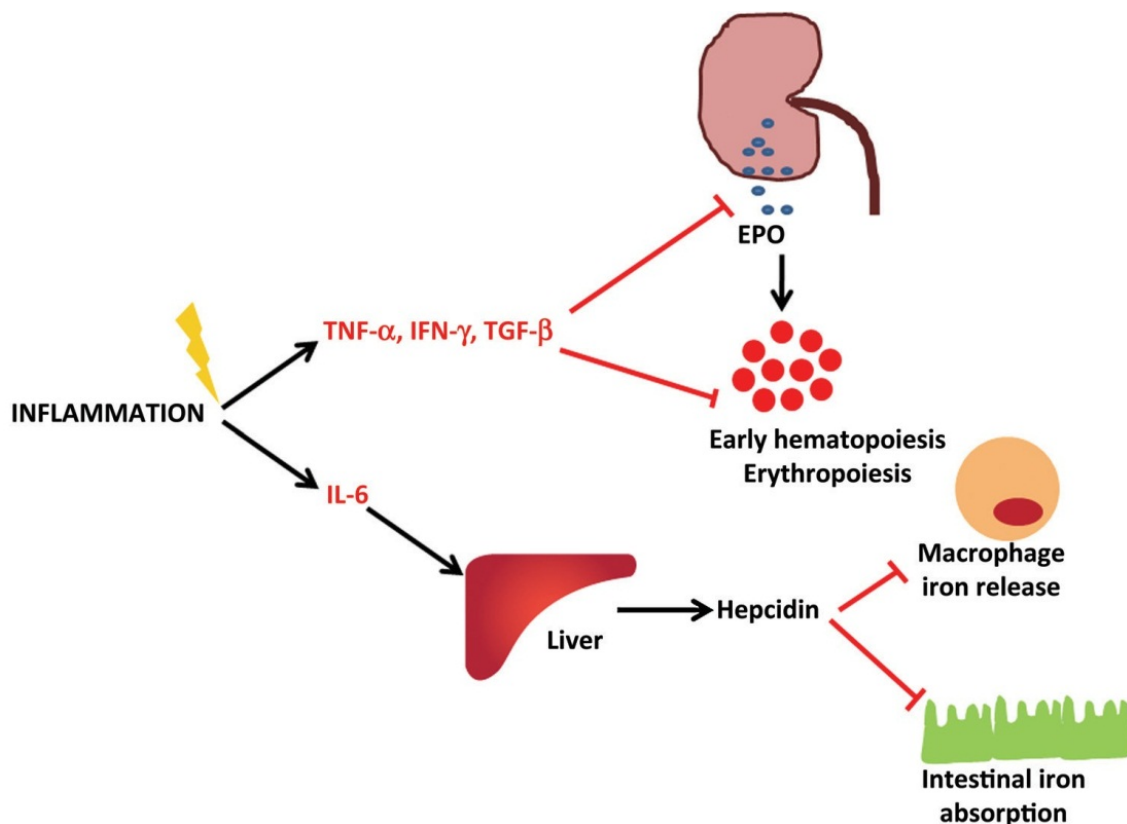
3.1 Introduction

Chronic anaemia may occur in various inflammatory situations, malignancies and infectious diseases (table 7). Anaemia of chronic disease (ACD) is the second most prevalent cause of anaemia after iron deficiency anaemia (IDA). It has been associated with disease activity, fatigue and physical disability in patients with arthritis (Han et al. 2007). Its prevalence varies greatly among different rheumatic diseases, probably because of pathophysiological differences, comorbid aggravating factors, genetic predisposition and treatment effects. It ranges between 33 and 60% for RA and >50% for SLE (Wilson et al. 2004; Weiss and Schett 2013*; Keel and Abkowitz, 2009*).

Table 7 Anaemia associated with chronic diseases

Disease	Estimated prevalence (%)
Inflammatory diseases	8–71
Rheumatoid arthritis	
Systemic lupus erythematosus	
Vasculitis	
Sarcoidosis	
Inflammatory bowel disease	
Acute and chronic infections	18–95
Malignancies	30–77
Haematological	
Solid	
Chronic renal failure	23–50

Figure 7 Chronic inflammation leads to anaemia by the production of proinflammatory cytokines. Among these cytokines, tumour necrosis factor α (TNF α), interferon γ (IFN γ) and transforming growth factor β (TGF β) inhibit erythropoiesis and the release of erythropoietin (EPO) from the kidney. Interleukin 6 (IL-6) stimulates the production of hepcidin by hepatocytes, which leads to the inhibition of iron absorption and iron release by macrophages.



3.2 Pathophysiology of chronic anaemia

ACD is a multifactorial immune-driven process, characterised by changes in iron homeostasis, impaired erythroid progenitor proliferation, reduced biological activity of erythropoietin (EPO) and reduced erythrocyte life cycle (Weiss and Goodnough 2005*).

3.2.1 Effects of proinflammatory cytokines on early haematopoiesis and erythropoiesis

TNF α and transforming growth factor β (TGF β), in synergism with IFN γ , inhibit the proliferation of haematopoietic progenitor cells, the self-renewal capacity of multipotent stem cells and induce Fas/Fas ligand-dependent apoptosis (Figure 7). In RA, TNF α and IFN γ also inhibit burst-forming unit-erythroid (BFU-E) and colony-forming unit-erythroid (CFU-E) colony formation and their effect is negated by DMARD treatment (Doyle et al. 2009). Erythroid progenitors express various death receptors so their exposure to death receptor ligands, including TNF α , Fas ligand or TRAIL, during inflammation results in disturbed erythropoiesis. In inflammatory diseases, the extent of anaemia correlates with circulating proinflammatory cytokine levels.

Proinflammatory cytokines also inhibit erythropoiesis indirectly, by suppressing the synthesis of EPO protein and mRNA synthesis (figure 7). There is impaired response to EPO in ACD associated with RA and SLE, where anti-EPO autoantibodies may also play a role (Voulgari et al. 1999; Giannouli et al. 2006*; Theurl et al. 2006).

3.2.2 Effects of IL-6 on the hepcidin system and iron homoeostasis

Another important mechanism of ACD is the IL-6–hepcidin axis that is involved in iron homoeostasis. Hepcidin, also known as LEAP-1 (liver-expressed antimicrobial peptide), is a 20–25 amino acid antimicrobial peptide that regulates iron homoeostasis by binding to and blocking ferroportin, the main cellular iron export protein. Increased expression of hepcidin results in inhibition of ferroportin-mediated transfer of dietary iron from duodenal enterocytes to the circulation and blockage of iron export from macrophages to be used for erythropoiesis. The expression of hepcidin is induced by inflammatory mediators (mainly IL-1, IL-6 or IL-22). Other cytokines, such as TNF α and IFN γ have similar effects on a hepcidin-independent manner. Thus, the combined action of hepcidin and cytokines leads to hypoferraemia and restricted availability of iron for erythropoiesis, which is the consequence of reduced dietary iron absorption and iron retention in macrophages, the latter reflected by increased ferritin levels.

Among proinflammatory cytokines, IL-6 (but not TNF α) induces hepatic synthesis of hepcidin, while hypoxia and anaemia downregulate hepcidin release. (Nemeth et al. 2004; Singh et al. 2011; Weiss and Schett 2013*).

3.2.3 Iron deficiency

Even though in ACD there usually is abundance of iron supply (which, however, is pathologically unavailable for haemopoiesis), there are several occasions where actual iron deficiency may occur. Menstruation is the commonest cause for IDA in the general population and the majority of RA and SLE patients are women. Acute or chronic gastrointestinal blood loss may accompany rheumatic diseases on account of underlying disease (eg. bowel inflammation) or treatment side effects (eg. glucocorticoids, NSAIDs). Furthermore, diseases that are frequently encountered as comorbidities in rheumatic diseases, such as autoimmune gastritis, *Helicobacter pylori* infection and coeliac disease, may also contribute to IDA (Hershko et al. 2005). Finally, although a rare cause of significant IDA, decreased dietary iron intake should always be considered.

3.2.4 Other vitamin deficiencies

The development of anaemia attributable exclusively to vitamin B12 or folic acid deficiency is rare, but deficiency of these vitamins can contribute to an extent to the anaemia of the rheumatic patient. Pernicious anaemia, a common autoimmune cause for vitamin B12 deficiency, is frequent in several autoimmune rheumatic conditions. In a mixed rheumatic disease population study with a 35–49% prevalence of anaemia, up to 24% of patients had vitamin B12 deficiency, although not all had anaemia (Segal et al. 2004). Low levels of serum folic acid were rare in the same study, but they may be seen with DMARD treatment that antagonises

folic acid metabolism (MTX, sulfasalazine, azathioprine), especially if there is no folic acid supplementation used, and should always be in the differential diagnosis. The aforementioned DMARD agents can cause macrocytosis, even in the absence of anaemia. This may disguise the expected microcytosis of iron deficiency or the normal indices of anaemia of chronic disease.

3.2.5 Treatment related factors

Several antirheumatic and immunosuppressive drugs (MTX, azathioprine, leflunomide, cyclosporine, mycophenolate) and adjunct treatments (NSAIDs, proton pump inhibitors, urate lowering drugs) can negatively affect erythropoiesis and decrease red blood cell half-life. Some of the newer DMARDs, in particular the Janus Kinase (JAK) inhibitors, exert a direct negative effect on EPO through JAK2 inhibition, which is an essential downstream signal component of the EPO receptor and, thus, cause mild anaemia through this unique mechanism. However, this seems to have only weak effect on fatigue and quality of life (Schulze-Koops et al. 2017).

3.2.6 Disease related factors

Besides chronic inflammation, several other causes of anaemia can be encountered in rheumatic diseases. In SLE, haemolysis may develop in up to 10% of patients during the disease and is more frequent in African American ethnicity and with the use of azathioprine (Durán et al. 2008). Pure red cell aplasia can also be seen in SLE, driven by IgG autoantibodies, but also in parvovirus B19 infection which may present as symmetric polyarthrititis. Macrophage activation (haemophagocytic) syndrome, caused by uncontrolled activation and proliferation of macrophages and T-cells, may complicate JIA, AOSD and SLE and is a rare cause of anaemia.

3.3 Differential diagnosis of chronic anaemia

ACI is usually normocytic-normochromic (normal MCV and MCH) and less frequently hypochromic – microcytic. Serum iron concentration and transferrin saturation (percentage of transferrin loaded with iron) are low, but these also characterise IDA. The distinguishing features lie in the ferritin concentration (high in ACI, but low in IDA) and the circulating transferrin levels (low in ACI, normal to high in IDA). In the complicated occasion where there is ACI with concomitant iron deficiency, other parameters to distinguish the two types of anaemia include serum soluble transferrin receptor (sTfR) or, even more accurate, the ratio sTfR:log ferritin (table 8) (Skikne et al. 2011; Weiss and Schett 2013*).

Table 8 Differential diagnosis of chronic inflammatory anaemia

Iron biomarkers	Inflammatory anaemia	Iron-deficiency anaemia	Combination
Serum iron	↓	↓	↓
Transferrin	N or ↓	↑	↓
Transferrin saturation	↓	↓	↓
Soluble transferrin receptor (sTfR)	N	↑	N or ↑
Ferritin	N or ↑	↓	N or ↓
sTfR:log ferritin	<1	>2	

N: normal, log: logarithm.

3.3 Treatment

3.3.1 Treatment of the underlying inflammatory disease

In chronic inflammatory diseases, such as arthritis, the degree of anaemia correlates with disease activity. Therefore, the underlying condition should be treated and disease activity suppressed. Glucocorticoid treatment reverses ACI in patients with giant cell arteritis and polymyalgia rheumatica. TNF α inhibitors improve anaemia in patients with RA. For example, administration of infliximab resulted in increasing haemoglobin and decreasing IL-6 levels. Infliximab also restored impaired erythropoiesis. Anti-TNF therapy improved postoperative recovery of haemoglobin in patients with RA. Etanercept and adalimumab also increased haemoglobin levels in RA or JIA. As IL-6 is a major stimulator of the hepcidin pathway and anaemia correlates with serum IL-6 levels, the blockade of IL-6 receptor by tocilizumab is also a feasible option for controlling chronic anaemia. Indeed, tocilizumab restored haemoglobin levels in RA and improved anaemia by downregulating hepcidin in Castleman's disease (Davis et al. 1997; Doyle et al. 2009; Isaacs et al. 2013; Song et al. 2013).

3.3.2 Treatment of anaemia

In severe life-threatening cases, blood transfusions should be carried out if necessary but only as emergency treatment.

As rheumatic diseases are most often associated with normocytic–normochromic anaemia and normal soluble transferrin receptor levels (table 7), iron supplementation is rarely needed. If iron deficiency is also present, intravenous iron treatment may be given in the form of iron gluconate or iron sucrose and is probably preferable to oral treatment, as iron enteric absorption is impaired in ACD. Intravenous iron supplementation is needed when transferrin saturation is <20% and ferritin <400 ng/mL. If ferritin is >800 ng/mL or transferrin saturation >50%, no iron supplementation is necessary.

As EPO stimulates erythroid colony growth, there have been few trials using recombinant human EPO to treat chronic anaemia. In a Cochrane meta-analysis, the data supporting the use of EPO-stimulating agents in

increasing haemoglobin and improving quality of life in RA were conflicting and the trials had high risk of bias (Martí-Carvajal et al. 2013).

SUMMARY POINTS

- ➔ Chronic anaemia is common in inflammatory diseases.
- ➔ Chronic inflammatory anaemia is usually normocytic--normochromic, rarely mildly microcytic--hypochromic.
- ➔ Proinflammatory cytokines inhibit early haematopoiesis and erythropoiesis, in part by suppressing the release of erythropoietin (EPO).
- ➔ Interleukin 6 induces hepcidin release by hepatocytes, leading to impaired iron absorption and release by macrophages.
- ➔ Inflammatory anaemia should be distinguished from iron-deficiency anaemia, but the two forms may be associated. Inflammatory anaemia is usually milder.
- ➔ Therapeutic strategies include control of the underlying disease and, if needed, iron and EPO supplementation.

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Systemic consequences of the inflammatory process

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IN-DEPTH DISCUSSION I

Cardiovascular disease risk in rheumatoid arthritis

Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in rheumatoid arthritis and it is mainly linked to accelerated atherosclerosis (1). Similar to the general population, increased CVD risk in RA has been associated with “traditional” risk factors, such as smoking, hypertension, dyslipidaemia, diabetes, obesity, physical inactivity) and “novel” risk factors, primarily systemic inflammation (increased high-sensitivity C-reactive protein (hsCRP)) and its sequelae, such as microalbuminuria and renal dysfunction (2). However, the excess CVD risk in RA is only partially explained by the traditional risk factors, which clearly suggests that systemic inflammation, genetic factors and antirheumatic treatment may contribute to it. Common inflammatory pathways for RA and atherosclerosis indicate a shared pathogenetic mechanism (3).

As many of these risk factors are modifiable (4), CVD risk management should be based on a determination of the CVD risk profile for the individual patient. The recent EULAR recommendations for CVD risk management in inflammatory arthritis advocate CVD risk assessment for all patients at least once every 5 years (or earlier if the risk is moderate-to-high) in order to implement lifestyle modification advice and CVD preventive treatment (5).

Primary CVD prevention

RA disease activity control remains the main focus for the rheumatologist and is a cornerstone for CVD risk reduction. Accumulated evidence clearly suggest that reducing the inflammatory burden lowers CVD morbidity and mortality. However, attention to classical CVD risk factors is also of paramount importance.

Patient education and lifestyle modification plays a significant role in CVD risk management in RA. All patients should be advised to quit smoking. Adherence to a healthy (e.g. Mediterranean) diet and weight control is also important. The role of structured exercise and prevention of physical inactivity has been proven and it should also be highlighted to RA patients. Treatment (to target) of arterial hypertension contributes in modifying a major CVD risk factor, which in RA has multiple possible causes and has been both under-recognised and undertreated. Indications for anti-hypertensive medication should follow the national guidelines. Lipid lowering treatment with statins has proven efficacious in reducing the overall atherosclerotic burden and improving CVD mortality in RA and is well-tolerated (5).

Cardiovascular risk prediction algorithms

Decision making for the use of cardio-protective medication should be backed by accurate CVD risk prediction. RA patients should be assigned to low, moderate, high and very high risk categories, using a calculator predicting their 10-year CVD mortality risk. For the general population, there are several such tools available, such as the Reynolds Risk Score (RRS)(6), Framingham Risk Score (FRS)(7) and the 2013 ACC/AHA guidelines

score (8), widely used in the US, the System for Cardiac Operative Risk Evaluation (SCORE) calculator(9), which is widely used in Europe, the QRISK2 calculator(10), which was developed and has been adopted in the UK. The RRS is the only score that includes a measure of inflammation (hsCRP), while only the QRISK2 incorporates RA as an independent risk factor (with a 1.4 multiplication).

However, none of these CVD risk assessment systems has been shown to perform well in patients with RA (11,12), possibly depicting the complex interplay of CVD pathogenesis in rheumatic disease (lipid paradox, presence of systemic inflammation, accelerated atherosclerosis). Thus, in 2009, EULAR recommended the implementation of a 1.5 multiplication factor on the SCORE algorithm in the presence of certain disease characteristics (13). Several other alternative approaches have also been advocated, e.g. to increase the age of an RA patient by 15 years or to add a multiplication factor of 1.4. In the light of the lack of appropriate evidence and also data showing increased CVD risk already in early RA, the 1.5 multiplication factor was retained in the recent updated EULAR recommendations, on this occasion independent of any disease characteristic criteria (5).

Solomon et al. (14) suggested an RA-specific CVD risk algorithm, the Expanded Risk Score for patients with RA (ERS-RA), which, besides traditional risk factors (age, gender, smoking status and presence or absence of hypertension, hyperlipidaemia and diabetes – captured from the physician's report for the diagnosis or the use of relevant medication), utilises measures for disease activity (Clinical Disease Activity Index, CDAI), function (modified Health Assessment Questionnaire, mHAQ), daily prednisolone use and RA disease duration (dichotomised at 10 years). This calculator performed well in a cohort from the CORRONA registry, but did not demonstrate any advantages to other calculators in other cohorts.

Comparison of the variables needed for each CVD risk algorithm is shown in table 1.

Recently, A Trans-Atlantic Cardiovascular Consortium for RA (ATACC-RA) was formed with the task to develop an RA specific CVD risk calculator by pooling resources from 13 centres worldwide. This effort has met significant challenges, because of differences in geographical and population characteristics, management strategies and, possibly, reducing prevalence of CVD in more recent cohorts due to improved disease control and lipid lowering treatments. Neither of the two developed models was demonstrated to have improved performance in RA patients compared to the general population calculators (15). Similarly, the RA specific calculators (QRISK2, SCORE with EULAR 1.5 multiplier, ERS-RA) did not improve CVD risk prediction in comparison with FRS and 2013 ACC/AHA models in a recent study and their clinical utility has become debatable (16).

The role of imaging in primary CVD prevention

Active screening for subclinical atherosclerosis may arguably be a good alternative to CVD risk prediction for primary CVD prevention (17). As both coronary and carotid atherosclerosis are frequent in RA patients, this approach might also be useful in this population. Available screening methods include measurements of coronary artery calcification, endothelial dysfunction and arterial stiffness, but carotid ultrasonography (cUS) looking for carotid plaques (CP) and measuring carotid intima media thickness (cIMT) is gaining ground. RA-specific factors, such as disease duration and activity (as measured by CDAI), have been positively correlated with CP larger size and higher vulnerability (18). The presence of CP has been linked to poor CVD-free survival and higher rate of ischemic heart disease (19), while severe cUS abnormalities (cIMT>0.9mm and/or CP) were observed in 63% of RA patients categorized in moderate CVD risk. A composite model of mSCORE (which includes the EULAR 1.5 multiplier) and severe cUS abnormalities was highly sensitive for high/very high CVD risk (20). EULAR recently recommended considering the use of cUS screening as part of CVD risk evaluation in RA (5). However, the clinical and cost-effectiveness of such a strategy remains to be proven in relevant trials.

Conclusion

Regardless of the difficulties in accurate CVD risk assessment, there is no doubt that adequate preventive management in RA is suboptimal, both in primary (patients in high CVD risk) and secondary (patients with already established CVD) prevention (21). In this context, there is a need to improve CV risk stratification and prediction, but also make sure that rheumatologists are educated with respect to screening and identifying high-risk patients. Educational programs for patients and allied health professionals on RA comorbidity management might be instrumental in facilitating the identification and management of CV risk factors by general practitioners, rheumatologists and cardiologists (22).

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Table 1. Cardiovascular risk production models in rheumatoid arthritis

Scores Exclusion factors	FRS Age >75, CVD/Diabetes	SCORE Age >65,CVD / Diabetes / TC ≥8 /LDL ≥6 / BP ≥180/110	RRS Age >80, CVD/Diabetes	QRISK2 Age ≥75, CVD/Diabetes	2013 ACC/AHA Age <40 & >80, CVD	ERS-RA Age <20 & >80, CVD
Age/gender	✓	✓	✓	✓	✓	✓
Postcode				✓		
Ethnicity				✓	✓	
BMI				✓		
Smoking	✓	✓	✓	✓	✓	✓
FHx CVD			✓	✓		
Diastolic BP	✓					
Systolic BP	✓	✓	✓	✓	✓	
Hyperlipidaemia					✓	✓
TC	✓	✓	✓	✓	✓	
HDL	✓	✓	✓	✓	✓	
BP treated?	✓			✓	✓	✓
RA				✓		
AF				✓		
CKD				✓		
hs-CRP			✓			
DM					✓	✓
Aspirin use					✓	
CDAI						✓
mHAQ						✓
Prednisolone						✓
RA ≥ 10 years						✓

FRS: Framingham Risk Score, SCORE: System for Cardiac Operative Risk Evaluation, RRS: Reynolds Risk Score, ERS-RA: Expanded Risk Score in Rheumatoid Arthritis. FHx CVD: Family history for premature CVD, BP: blood pressure, TC: total cholesterol, HDL: high density cholesterol, AF: atrial fibrillation, CKD: chronic kidney disease, hsCRP: high sensitivity C reactive protein, DM: diabetes mellitus, CDAI: Clinical Disease Activity Index, mHAQ: modified Health Assessment Questionnaire.

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Systemic consequences of the inflammatory process

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IN-DEPTH DISCUSSION II

Current therapies of AA amyloidosis secondary to inflammatory rheumatic diseases

Introduction

Systemic amyloidosis is caused by the misfolding and irreversible transition of amyloid precursor proteins to insoluble fibrils, which cause damage by deposition on various internal organs. Serum amyloid A (SAA) is the amyloid precursor characteristic for AA amyloidosis. High levels of circulating SAA are associated with inflammatory rheumatic diseases. In fact, rheumatoid arthritis (RA), ankylosing spondylitis (AS) and other arthritides account for 70% of all AA amyloidosis cases. The production of SAA is regulated by pro-inflammatory cytokines, such as tumour necrosis factor α (TNF- α), interleukin-1 (IL-1) and IL-6 [1-3].

In AA amyloidosis, amyloid deposition occurs primarily to the kidneys, liver, spleen and gastrointestinal (GI) tract. The predominant feature of amyloidosis at diagnosis is proteinuria and renal failure. Hepatic and splenic deposits rarely lead to clinical manifestations. GI features include malabsorption, pseudo-obstruction, diarrhoea or vomiting secondary to submucosal amyloid infiltration [1-5].

The survival of AA amyloidosis patients has increased from 24 months in 1991 [6] to 79 months by 2008 [7]. Also, recent data confirm both reducing incidence and improved survival in systemic amyloidosis [8, 9], suggesting improved management of inflammatory disease in the era of biologic drugs [10]. Overall, however early referral to a specialist and early treatment are necessary to improve prognosis. Reducing SAA concentrations to lower than 4mg/L has been associated with the best outcomes [10].

Treatment of AA amyloidosis by controlling the underlying disease

In AA amyloidosis secondary to arthritides and autoimmune diseases, the major goal of therapy is to control the underlying disease. Aiming at disease remission or low disease activity will decrease the risk of amyloid deposition and will eventually improve survival [1, 7]

In case reports, traditional disease modifying antirheumatic drugs (DMARDs), such as methotrexate, cyclophosphamide and leflunomide showed some efficacy to decrease circulating SAA levels, however, no large trials have been conducted [1, 2, 5, 7, 11]. High dose colchicine has proven effective in inducing remission in AA amyloidosis caused by Familial Mediterranean Fever [2], but results from its use in rheumatic disease related amyloidosis were not optimistic [12].

Biologic DMARDs have shown outstanding efficacy in arthritides and are also effective in controlling secondary renal and gastrointestinal AA amyloidosis [5, 13]. Among TNF- α inhibitors, etanercept and infliximab decreased proteinuria, improved renal function, reduced acute phase reactants and inhibited gastrointestinal amyloid deposition in arthritis patients [13, 14]. In one study, 15 patients with AA amyloidosis secondary to inflammatory arthritis were treated with infliximab (n=10), etanercept (n=4) or both (n=1). Anti-TNF therapy resulted in dramatic improvement in proteinuria in 3 patients, stabilized it in 5 patients, while amyloidosis

progressed in 7 patients [13]. In a cohort of 14 patients with secondary AA amyloidosis, etanercept treatment resulted in clinical improvement of proteinuria and diarrhoea and reduction of SAA levels [15].

Among other biologics, IL-1 inhibition (mainly through the IL-1 receptor antagonist anakinra) has been introduced to the treatment of AA amyloidosis secondary to auto inflammatory syndromes. These periodic fever syndromes include TNF receptor-associated (TRAPS) and cryopirin-associated periodic syndrome (CAPS), as well as FMF, Muckle-Wells syndrome and familial cold auto inflammatory syndrome (FCAS) [5]. Anakinra has also been proven efficacious in the empirical treatment of AA amyloidosis of uncertain aetiology [16]. Canakinumab, an anti-IL1 β IgG1/k monoclonal antibody, led to clinical and laboratory improvement in similar cases of AA amyloidosis [17].

The IL-6 pathway is also involved in the regulation of SAA production [1] and thus its inhibition was expected to provide significant benefit. The anti-IL-6 receptor antibody tocilizumab successfully controlled AA amyloidosis in patients with RA, juvenile idiopathic arthritis (JIA) and adult onset Still's disease, as well as in non-RA patients (FMF). Tocilizumab improved proteinuria, as well as gastrointestinal amyloid deposition and diarrhoea [2, 5, 18-20]. It may have better results compared to TNF-inhibitors as suggested by a retrospective study looking into disease remission and drug survival but this requires confirmation [21].

There are limited data on the effects of abatacept and rituximab in AA amyloidosis.

Inhibition of fibrillogenesis

Glucosaminoglycan (GAG) chains are universal constituents of amyloid deposits. Thus, inhibition of proteoglycan assembly may block amyloid fibrillogenesis. Indeed, some carbohydrate analogues of N-acetyl glucosamine inhibit the binding between heparan sulfate or the heparin sulfate proteoglycan perlecan and amyloid fibril proteins. In preclinical studies, orally administered low molecular weight anionic sulfonate or sulfated compounds inhibited the development of experimental murine AA amyloidosis. One of these GAG mimetic agents, eprodisate has been introduced to human trials [21, 22]. In a phase II/III clinical trial, the effects of eprodisate were compared to those of placebo in 183 patients with systemic AA amyloidosis. Although the specified primary end point for efficacy was not achieved, eprodisate significantly slowed the progression of renal disease in comparison to placebo. Thus, inhibition of interactions between GAGs and amyloid fibrils by using small molecule GAG mimetics remains a promising therapeutic approach in all types of amyloidosis [1, 2, 22].

Induction of amyloid deposit regression

Although direct induction of amyloid deposit regression has not yet been feasible, there have been attempts to target the serum amyloid P (SAP) component. The non-fibrillar SAP is universally present in amyloid

deposits, persists within these deposits for prolonged periods and it can be identified by SAP scintigraphy [1,5]. Small molecular compounds, as well as antibodies inhibiting the binding of SAP to amyloid fibrils are under investigation. For example, administration of an anti-human-SAP antibody to mice with amyloid deposits containing human SAP triggered a potent, complement-dependent, macrophage-derived giant cell reaction that removed massive visceral amyloid deposits without adverse effects [24]. The antibody has been tested on humans in a proof-of-concept study with promising results [25]. Finally, blocking SAA-transcribing mRNA with antisense oligonucleotides reduced SAA and tissue amyloid burden in murine models [26].

Conclusion

In AA amyloidosis secondary to inflammatory rheumatic diseases, our primary goal is to control the underlying disease. Traditional DMARDs have limited efficacy in AA amyloidosis as no large trials have been conducted with these compounds. The efficacy of TNF inhibitor biologics, primarily etanercept and infliximab, has been increasingly investigated with good results. Anakinra may be administered to patients with amyloidosis secondary to periodic fever (auto-inflammatory) syndromes. IL-6 inhibition by tocilizumab seems to offer significant benefits in controlling SAA production and disease activity. Other mechanisms to reverse amyloidosis include the inhibition of fibrillogenesis by GAG mimetics, such as eprodisate. Small molecule inhibitors of and antibodies to SAP may induce the regression of amyloid deposits.

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Rheumatic manifestations of systemic diseases / miscellaneous rheumatic diseases

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Part I: Hereditary hemochromatosis

LEARNING OBJECTIVES

- Outline the epidemiology of hereditary haemochromatosis (HH)
- Describe known genetic defects (HFE and non HFE) and their relative frequencies in HH
- Describe the pathogenesis of HH at the tissue, cellular and receptor levels
- Describe the musculoskeletal manifestations of HH
- Describe the other organ-specific manifestations
- Describe and evaluate methods of diagnosing HH, including serological markers of iron stores and genotype testing
- Describe the indications for and management of therapeutic and maintenance phlebotomies in HH
- Describe factors related to prognosis in HH

I. INTRODUCTION.

Haemochromatosis, first described by the French physician Armand Trousseau in 1713, is a hereditary multi-organ disorder due to mutations in genes that control iron metabolism leading to iron overload (Pietrangelo, 2010*). It is characterized by increased iron accumulation in many organs including the liver, heart, joints and endocrine organs. The most severe features of the disease are liver cirrhosis and hepatocarcinoma, diabetes and heart failure. As severe organ failure can be prevented by phlebotomy starting before irreversible damage has occurred, hereditary haemochromatosis (HH) must be recognised early. Since arthralgia, together with fatigue, is one of the earliest features of HH, rheumatologists have an important role to play in the early diagnosis of the disease. Family screening is also very important for its early recognition and treatment. The most common genotype (> 95%) is homozygosity for the p.Cys282Tyr mutation of the HFE gene (MIM 235200) (Feder et al, 1996*). Several other mutations have been described (Brissot and Loréal, 2016*).

II. EPIDEMIOLOGY.

HH is the most common inherited genetic disease in European populations. Classic HH, linked to the HFE gene, is transmitted as an autosomal recessive trait. Population screening has shown that the prevalence of the HFE genotype varies among ethnic groups. In white populations in the USA and Western Europe, the frequency of homozygotes is approximately 4 per 1000 (0.44%), and the frequency of heterozygotes is approximately 100 per 1000 (9.6%) (Adams et al, 2005). The highest reported prevalence of C282Y homozygosity is in Ireland (Gleeson et al, 2004). Lower prevalences are estimated for other ethnic groups. In Native Americans, the frequency of homozygotes is approximately 0.11%, in Mexican Americans 0.027%, in non-Hispanic black people 0.014%, in

Pacific Islanders 0.012% and in Asians 0.00004% (Adams et al, 2005). Such distribution is consistent with a predominantly northern European origin of the mutation (Powell et al, 2016*). It should be stressed that the phenotype penetrance of the C282Y genotype is low, making population screening unsuitable. Longitudinal studies have shown that only 38–50% of homozygous individuals develop raised iron parameters, and only 10–33% eventually develop haemochromatosis-associated morbidity (Whitlock et al, 2006). Because of iron loss through menstrual bleeding and childbirth, the rate of iron accumulation is lower in premenopausal women and clinical penetrance is lower in women. A cohort study showed that at least 28% of male C282Y homozygotes compared with 1% of female C282Y homozygotes developed iron overload-related disease (Allen et al, 2008). Genetic polymorphism, environmental factors such as alcohol misuse, liver steatosis and coexisting viral infection, also seem to modify the risk of developing clinically overt liver disease (van Boven et al, 2011*; Brissot and Loréal, 2016*).

III. GENETICS.

Five genes have a key role in iron metabolism: ferroportin, hepcidin, haemojuveline, caeruleoplasmine and transferrin. The gene defect first described in 1996 as a cause of HH is a G>A mis-sense mutation leading to substitution of tyrosine for cysteine at the 282 amino acid position (C282Y) of the protein product of the HFE gene, located on the short arm of chromosome 6 (Feder et al, 1996*). Another mutation in which aspartic acid is substituted for histidine at position 63 (H63D) His63Asp has also been associated with haemochromatosis. Phenotypic HH may arise when both alleles of chromosome 6 have the C282Y mutation in an homozygous state. In the other cases, iron overload is very rare or there is another associated gene mutation. A C282Y homozygous state has been found in 70–100% of patients with phenotypic HH; approximately 10% are compound heterozygotes (Feder et al, 1996*; Brissot and Loréal, 2016*), but in the population at large, documented iron overload disease has been found to be rare in C282Y/H63D heterozygotes (Gurrin et al, 2009). A small number of patients are either heterozygous for C282Y or homozygous for H63D, but these genotypes do not appear to confer an increased risk of iron overload (Brissot and Loréal, 2016*). Although more than 95% of HH in the white population are associated with HFE gene mutations, other genes have been linked to much rarer forms of the disease, in particular in southern European and non-Caucasian populations (table 1) (Brissot and Loréal, 2016*).

Table 1: Genetic, clinical and laboratory features, and pathogenesis of the various types of hereditary haemochromatosis (HH)

HH type	Gene	inheritance	Typical features	Laboratory findings	Pathogenesis
1	HFE	Autosomal recessive	Caucasian, male, 40-50 years old. Fatigue, arthralgia, liver damage with predominant hepatocyte iron loading. Diabetes, endocrine dysfunction, cardiomyopathy, dark skin	Increased serum ferritin and transferrin saturation	Decreased hepcidin, due to impaired regulation and leading to increased intestinal iron absorption and release of iron from reticuloendothelial cells
2A	Hemojuvelin (HJV)	Autosomal recessive	Caucasian or non-Caucasian, Male or female, 20-40 years old, As for HFE; cardiomyopathy and endocrine disorders are more frequent	Increased serum ferritin and transferrin saturation	Decreased hepcidin, due to loss of regulation, leading to increased intestinal iron absorption and release of iron from reticuloendothelial cells
2B	Hepcidin (HAMP)	Autosomal recessive	Caucasian or non-Caucasian, Male or female, 15-20 years old, As for HFE; cardiomyopathy and endocrine disorders are more frequent	Increased serum ferritin and transferrin saturation	No active hepcidin leading to maximal intestinal iron absorption and release of iron from reticuloendothelial cells
3	Transferrin Receptor 2 (TfR2)	Autosomal recessive	As for HFE	Increased serum ferritin; transferrin saturation may be normal	Decreased hepcidin, due to impaired regulation and leading to increased intestinal iron absorption and release of iron from reticuloendothelial cells
4	Ferroportin (Fpn)	Autosomal dominant	Caucasian or non-Caucasian, Male or female, 10-80 years old, As for HFE, generally milder; liver iron loading frequently predominates to Kupffer cells	Increased serum ferritin and transferrin saturation	Reduced ferroportin iron transport ability, leading to hepcidin resistance and accumulation of iron in reticuloendothelial cells

IV. PATHOGENESIS.

IV.1 Iron Metabolism

Iron is involved in basic cellular functions such as DNA synthesis, cellular respiration and oxygen transport and is mandatory for erythropoiesis (Brissot and Loréal, 2016* Powell et al , 2016*) . The only iron source is alimentary, absorbed in duodenum.. Two-thirds of iron is incorporated into haemoglobin, and the remainder is found in muscle myoglobin, enzymes and cytochromes. Macrophages are involved by recycling iron from erythrocytes. Less than 1% circulates in plasma bound to transferrin. Excess free iron, however, damages tissue by catalysing the production of free-radical oxygen species that attack cell membranes, proteins and DNA.

The master regulator of iron metabolism is the protein hepcidin, a polypeptide hormone which is produced by the liver (Pietrangelo, 2010*; Ganz, 2011*). The plasma hepcidin level is regulated by various stimuli: hypoxia, anaemia and iron deficiency all inhibit hepcidin synthesis. In contrast, hepcidin secretion is induced by infections and inflammation, through inflammatory cytokines, including IL-6. Hepcidin is involved in the pathogenesis of anaemia and hypoferrremia of inflammation (Ganz, 2011*).

Hepcidin acts in connection with ferroportin (FPN), a transmembrane protein that exports iron from the cells. FPN is expressed by cells involved in iron metabolism, including duodenal enterocytes, hepatocytes and reticuloendothelial macrophages. Following interaction with hepcidin, FPN is internalised and degraded, and transfer of iron from the cell into the plasma compartment is impaired (Ganz, 2011*; Brissot and Loréal, 2016*).

IV.2 Mechanisms of HHs

Mutations of the FPN gene are involved in type 4 HFE, linked to an increased iron transport from enterocytes and macrophages into the blood. The other types of HFE are linked to a decrease in hepcidin production (table 1). Type 2B is due to a mutation of the gene coding for hepcidin and results in a very severe form of HH. Type 2A may be explained by the role of haemojuvelin (HJV) in hepcidin secretion control by the BMP-SMAD signalling pathway. BMP6 is held to play an important part in this control, as *bmp6*-null mice exhibit reduced hepcidin expression and tissue iron overload, that is, a haemochromatosis-like phenotype (Andriopoulos et al, 2009; Meynard et al, 2009). In mice, interaction between BMP6 and HJV increases hepcidin expression and reduces levels of iron (Andriopoulos et al, 2009). The human mutation could impair HJV binding to BMP6. Type 3 HH is related to mutations of the *TfR2* gene. *TfR2* is a homolog of *TfR1*, the receptor essential for the uptake of iron transferrin by erythrocytes and expressed in most cells. *TfR2* is primarily expressed in the liver and plays a role in transferrin-induced hepcidin expression. Loss of function is associated with haemochromatosis (Fleming et al,

2002). Interaction between HFE and Tfr2 has been shown to be required for hepcidin induction, explaining the fact that a defect in Tfr2 or HFE could result in decreased hepcidin synthesis (Gao et al, 2009).

V. CLINICAL FEATURES.

V.1 General Presentation.

The natural history of HH evolves through a series of stages. During their first 20 years of life, patients with HH may undergo clinically insignificant iron accumulation, with 0–5 g of parenchymal iron storage. In their 20s to 40s, patients may evolve to a stage of iron overload, but without symptomatic disease, with 10–20 g of parenchymal iron storage. Finally, by the age of 40, patients may progress to a stage of iron overload with parenchymal organ damage, with more than 20 g of iron storage in the liver, heart and endocrine tissue (Adams et al, 1997). In men, HFE HH rarely becomes symptomatic before the fourth or fifth decade of life except in juvenile HH. In women, menstruation, pregnancy and lactation delay iron accumulation by approximately 10 years and symptomatic HH usually presents after the menopause.

Due to increasingly early diagnosis, the classic triad of HH –diabetes, bronze pigmentation of the skin and cirrhosis-is now rare and not representative of the majority of HH patients at diagnosis. Early disease manifestations are often non-specific and the most frequently experienced symptoms are fatigue and joint pain (Brissot et al, 2011). However, symptoms are progressive and if not treated, patients may develop end-organ dysfunction (table 2) (McDonnell et al, 1999*;Brissot et al, 2011).

Table 2. Frequency of signs and symptoms in hereditary haemochromatosis

Sign or symptom	Frequency (%)
At diagnosis	
Fatigue	74
Arthralgia	56
Loss of libido	30
Skin bronzing	25
Current symptoms with phlebotomy treatment	
Fatigue	60
Joint pain	50
Skin hyperpigmentation	12
Diabetes mellitus	48
Loss of libido	23
Liver problems	10
Electrocardiographic abnormalities	12

Adapted from Brissot et al, Transfusion 2011

Most HH is now diagnosed when elevated serum ferritin levels are found on routine laboratory screening or when targeted screening is performed because of familial HH.

V.2 Arthropathy

Joint complaints are one of the most frequent symptoms of HH (De Seze et al, 1972; Pawlotsky et al, 1999; Brissot et al, 2011; Guggenbuhl et al, 2011; Carroll et al, 2012). They occur in 33–70% of patients and are often the first manifestation of disease. Affected patients may present with arthralgia or an arthropathy which usually resembles non-inflammatory osteoarthritis (OA) and calcium pyrophosphate dihydrate deposition (CPPD) disease. Presentation is therefore often non-specific and because of the practical consequences of early diagnosis (to prevent life threatening complications of the disease), rheumatologists should very much remain alerted by a younger age for classical osteoarthritis or CPPD disease. In a recent study, diagnosis was made only 9 years after the onset of joint complaints and the mean age of onset was 45.8 ± 13.2 years (Sahinbegovic et al, 2010*). Therefore, articular features appear frequently at a younger age than in OA or CPPD disease; their occurrence in a person below the age of 55–60 years should prompt strong suspicion of HH. Involvement of the second and third metacarpophalangeal (MCP) joints, with bony enlargement rather than swelling due to synovitis, is seen in one third of HH patients (Valenti et al, 2008) and is very suggestive of HH. Arthropathy in HH may also display the full spectrum of CPPD disease, with acute calcium pyrophosphate crystal arthritis ('pseudogout'), chondrocalcinosis and chronic arthropathy. Joint inflammation is typically minimal, but acute attacks of inflammation with bilateral destruction of the MCP joints may occur. Acute attacks of synovitis probably result from calcium pyrophosphate crystal deposition.

Reduced flexion at the MCP joints has been noted, but ulnar deviation, a common finding in rheumatoid arthritis (RA), has not been reported in HH. Radiographs differ from those in RA and typically exhibit joint space narrowing, fine subchondral bone sclerosis underlining bone contours, epiphyseal small cysts and frequent osteophytosis with no marginal erosion. This radiological picture is very suggestive of HH when it develops at the second and third MCP joints, associated with large hook-like osteophytes of the proximal radial side of MCP joints (figures 1 and 2). Chondrocalcinosis is seen in 10–30% of patients (figures 1 and 3) and the aetiological work-up of CPPD disease should include a search for HH. HH arthropathy is usually polyarticular and may involve many joints, in particular the knees and hips. HH should particularly be looked for when OA features are present in joints rarely affected by primary OA, including the wrist, the glenohumeral joint with no rotator cuff rupture, and the ankle. Non-traumatic OA of the ankle is clearly one of the presenting features of HH (Jacki et al, 1999; Schmid et al, 2003; Carroll, 2006; Carroll et al, 2012). Hip involvement does not differ from regular OA but is been found to be more frequent and more severe. The rate of total joint prosthesis (most frequently of the hip, followed by the knee) appears to be five- to nine fold higher than in the general population, particularly with HFE C282 homozygosity associated with an increased risk of both single and bilateral total hip replacement (Richette et al, 2010b; Sahinbegovic et al, 2010*; Wang et al, 2012) and prostheses are indicated at a younger age. HH has also been reported as a cause of aseptic necrosis of the femoral head (Rollot et al, 2005).

Arthropathy may significantly affect the quality of life in patients with HH, even more so than diabetes or cirrhosis .

Figure 1. Anteroposterior view of the hand of a patient with haemochromatosis with severe joint space narrowing, most marked at the metacarpophalangeal (MCP) joints. A small amount of chondrocalcinosis can be seen at the second MCP joint (arrow).



Figure 2. Metacarpophalangeal (MCP) joint involvement in hereditary haemochromatosis. Note the presence of joint space narrowing, fine subchondral bone sclerosis, containing small cysts, and large osteophytes. Erosion of the MCP joints can also be seen, a rare finding in hereditary haemochromatosis.



Figure 3 Anteroposterior view of the knee showing chondrocalcinosis

A direct role of iron in the arthropathy has never been clearly established even if many elements go in this direction. Pathological studies demonstrate the deposition of iron in the synovium and cartilage, which could play a pathogenic role (Schumacher, 1972). Free iron can generate free radicals able to induce lipid peroxidation and collagen cleavage, promoting immune complex formation, and can favour deposition of calcium pyrophosphate crystals by inhibition of the membrane-bound alkaline phosphatase. A correlation between the extent of iron deposition, as measured by ferritinaemia, and the presence or severity of the arthropathy has been observed by some authors, in particular when ferritinaemia exceeded 1000 µg/L (Pawlotsky et al, 1999; Valenti et al, 2008), but appears to be inconsistent across studies. Moreover, arthropathy generally does not respond to iron removal (McDonnell et al, 1999*; Sahinbegovic et al, 2010*), in contrast with the visceral localisations of HH, and can even arise during the initial phase of phlebotomy (Brissot et al, 2011). A recent study has even observed that phlebotomy was followed by an increase in the serum levels of CTXII, a marker of cartilage collagen degradation, and suggests that cartilage is sensitive to iron excess in patients with HH (Richette et al, 2010a).

V.3 Osteoporosis

Despite the decrease in hypogonadism, due to earlier diagnosis and treatment, osteoporosis, defined as a T score of <2.5 or lower, is still seen in roughly one third of patients with HH (Guggenbuhl et al, 2005; Valenti et al, 2009). The incidence of fractures is uncertain. Hypogonadism and liver cirrhosis have become rare. A Genetic hemochromatosis animal models have shown that excess iron has a direct impact on osteoblast function, with decreased bone formation, alterations in bone mass and microarchitecture, (de Vernejoul et al, 1984; Guggenbuhl et al, 2011; Doyard et al; PLoS One 2016) and on apatite crystal growth (Guggenbuhl et al, 2008)

V. 4 Hepatic Manifestations

Historically, more than 95% of symptomatic patients with HH had hepatomegaly, elevated liver enzymes or cirrhosis, owing to progressive iron deposition in the liver (Fracanzani et al, 1995; McDonnell et al, 1999*). Cirrhosis and cirrhosis-associated complications like oesophageal varices and variceal haemorrhage, account for approximately 89% of HH-related deaths (Niedermaier et al, 1996*). If treated with phlebotomy in the pre-cirrhotic stage, individuals with HH have now normal life expectancy (Bardou-Jacquet E et al, 2015). Iron overload in HH may potentiate the development of alcoholic liver disease and also hepatic fibrosis in patients with hepatitis C virus infection (Elmberg et al, 2003). One of the most serious complications of hepatic iron overload was the occurrence of hepatocellular carcinoma (HCC) (Thorburn et al, 2002). HCC accounted for approximately 30% of all deaths in HH (McDonnell et al, 1999*). The risk of HCC in patients with HH is increased approximately 20-fold (95% CI 16 to 22) compared with the general population (EASL European Association for the Study of the Liver, 2010*). The risk was highest in men, smokers and heavy alcohol users, and was not increased among first-degree relatives (Elmberg et al, 2003). Overall, patients with HH and cirrhosis have an estimated 5% annual risk for HCC. The risk for HCC continues to be a threat even after adequate phlebotomy. HCC is rare in non-cirrhotic HH.

Liver histology using the Perls stain is a way to document iron overload but its indication for diagnostic purposes has considerably decreased since the availability of the HFE genotyping test. It is still indicated in assessment of extensive bridging fibrosis and as a prognosis indicator, when liver cirrhosis is suspected, in particular in the case of hepatomegaly, high serum aspartate aminotransferase or elevation of ferritin above 1000 µg/L. Biological markers of hepatic fibrosis such as serum hyaluronic acid, and ultrasound elastography may become an alternative approach to liver biopsy for the diagnosis of advanced fibrosis (EASL, 2010*).

V.5 Diabetes Mellitus

Diabetes mellitus (DM), as a result of progressive iron deposition in the pancreas has become rare as it is effectively prevented by phlebotomy. Most patients with DM secondary to HH also have liver disease or skin hyperpigmentation (Salonen et al, 2000).

V.6 Cardiac Manifestations

In the past, approximately 15% of patients with HH presented with cardiac disease. Excess iron deposition within the myocardium may lead to a mixed dilated-restrictive or dilated cardiomyopathy, characterised by the development of heart failure and conduction disturbances, such as atrial fibrillation or the sick sinus syndrome. Electrocardiographic abnormalities include a decrease in QRS amplitude and T-wave flattening or inversion. Cardiac iron deposits produce a diagnostic pattern on cardiovascular MRI in which the myocardium has very low signal intensity. Treatment with phlebotomy has been associated with reversal of the left ventricular dysfunction, but in subjects with advanced disease, damage may be irreversible (Rivers et al, 1987).

V. 7 Hypogonadism

Hypogonadism with loss of libido has become rare. Repeated phlebotomy to remove excess tissue iron deposits may reverse the hypogonadism in men under the age of 40 years (McDermott and Walsh, 2005).

V.8 Hypothyroidism

Hypothyroidism in HH may be due to excess iron deposition in the thyroid gland, causing fibrosis and the development of antithyroid antibodies (Edwards et al, 1983). Affected individuals typically require lifelong supplementation therapy.

V.9 Dermatological Manifestations

Skin hyperpigmentation in HH reflects a combination of increased melanin and iron deposition around sweat glands (melanoderma) (McDonnel et al, 1999*). When severe, it has a grey or brownish colour, with slate-grey patches in the oral mucosa. Generalised hyperpigmentation usually occurs but can be limited to the face, neck, extensor aspects of the lower forearms, dorsum of the hands, lower legs, genital region and scars. Skin atrophy, flattening of the nails and loss of body hair are also common

V.10 Susceptibility to Infections

Susceptibility to specific infections has been described in patients with HH. Iron overload of macrophages can diminish phagocytosis of *Listeria*, while high serum iron levels may increase bacterial virulence (van Asbeck et al, 1982). *Yersinia enterocolitica* and *Vibrio vulnificus* are both siderophoric (iron-loving) and may pose an increased risk of infection in patients with HH (Carniel et al, 1987). *V. vulnificus* occurs in uncooked seafood (Bullen et al, 1991).

VI. Diagnosis

When the disorder is suspected, the first step towards diagnosis is to demonstrate iron overload. HH is then further diagnosed by genotyping the HFE gene. The main difficulty is to suspect the disorder when facing early, frequently non-specific symptoms, for example fatigue or arthralgia. Screening of first-degree relatives of HH patients is very important for early diagnosis (see in-depth discussion). As serological testing for iron markers has become widely available, the majority of patients with HH are now identified while still asymptomatic and without evidence of hepatic fibrosis or cirrhosis.

VI. 1 Serological Markers of Iron Overload.

Most of HH are characterized by increase of the transferrin saturation and increase of ferritin.

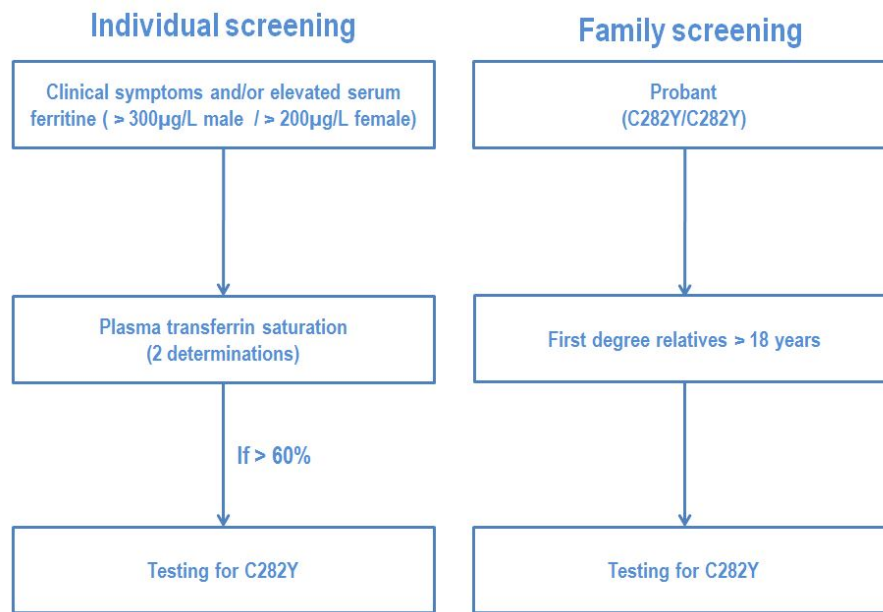
Transferrin saturation, obtained by dividing the serum iron by the total iron binding capacity, is the proportion of the iron transport protein transferrin that is saturated with iron. Overnight fasting avoids circadian and postprandial variations and eliminates 80% of false-positive transferrin saturation results. In HH, transferrin saturation is generally increased during the day as a result of innately low hepcidin. Expert consensus considers 45% to be the upper limit of normal in the non-fasting situation, in the absence of inflammation. For many years, transferrin saturation was endorsed as an ideal test for the diagnosis of haemochromatosis, because most C282Y homozygotes with iron overload have high transferrin saturation (>45% in women and >50% in men). The unsaturated iron-binding capacity is a one-step test that costs less than the transferrin saturation test and has similar sensitivity and specificity. However, much biological variation exists within individuals for both tests, including large numbers of false positives and the inability to detect some C282Y homozygotes with a high ferritin level.

Serum ferritin estimates the total body iron stores. A ferritin value greater than 300 µg/L in men and greater than 200 µg/L in women provides additional support for iron overload. Serum ferritin levels may be influenced by inflammatory conditions, chronic hepatitis C, alcohol-induced liver disease and neoplastic diseases. However, serum ferritin combined with transferrin saturation has a negative predictive value of 97%. In confirmed HH, serum ferritin levels >1000 ng/mL may accurately predict the degree of hepatic fibrosis (cirrhosis). A fasting transferrin saturation of less than 45% with a normal serum ferritin requires no further evaluation.

Ferritin but not transferrin saturation can be increased in diseases other than HFE haemochromatosis, including inflammation, chronic alcohol consumption, liver cell necrosis, metabolic syndrome, non-alcoholic steatohepatitis, Gaucher disease, refractory haemolytic anaemia. These conditions should be excluded before HFE genetic testing (EASL, 2010*; van Boven et al, 2011*).

VI.2 Genotype Testing

Patients with elevated transferrin saturation and serum ferritin levels, not explained by other disease, require further genotypic testing. The presence of the HFE mutations C282Y and H63D can be detected by polymerase chain reaction using whole blood samples (Feder et al, 1996*). Individuals with serum indicators of iron overload who are homozygous for the C282Y mutation require phlebotomy therapy and screening of first-degree relatives for HH. According to recent guidelines, C282Y/H63D compound heterozygotes and H63D homozygotes should be further investigated for other causes of hyperferritinaemia because of the relative rarity of HH in these patients (EASL, 2010*).

Table 3. Flowchart genetic screening haemochromatosis.

Adapted from Brissot and Loréal, J Hepatology 2016; Powell et al, Lancet 2016

VI.3 Other Diagnosis Tests

Since the availability of the HFE genotyping test, liver biopsy, which allows demonstration of iron overload of the liver, for the diagnosis of HH has become very rare. Non-invasive MRI quantification of iron liver load is used in clinical practice. Liver biopsy is restricted to patients with no clear explanation for the iron overload and those with high risk of cirrhosis (hepatomegaly, transaminases increase or ferritin > 1000). Quantitative phlebotomy may be also used to quantify iron overload by determining the number of phlebotomies required to induce iron deficiency (EASL, 2010*).

VII. Treatment

The current standard of care is phlebotomy that is considered effective with benefits in terms of morbidity and long-term survival (Niedermaier et al, 1996*; McDonnell et al, 1999*). It prevents the occurrence of life threatening complications such as diabetes, cirrhosis and hepatocellular carcinoma, heart failure. Phlebotomy lessens some clinical manifestations and organ damage (malaise, fatigue, abdominal pain, skin pigmentation). Diabetic patients may require less insulin. Regression of hepatic fibrosis can be observed in some patients, the best results occurring when fibrosis is mild (European Association for the Study of the Liver, 2010*). Iron-related joint disease and other manifestations as cardiac conduction abnormalities do not consistently respond to phlebotomy (Bardou-Jacquet et al; 2017). Therefore, early identification and treatment of those at risk is required. A European consensus-based recommendation (EASL, 2010*) is to start phlebotomy when serum ferritin levels rise above local reference values (usually 300 µg/L in men and 200 µg/L in women). However, as

not all patients with raised serum ferritin show further increases, a watchful approach for asymptomatic patients with a moderate increase in serum ferritin levels, with phlebotomy only when ferritinaemia increases progressively, might be an alternative. No special dietary restrictions are recommended

VII.1 Phlebotomy

Phlebotomy is used to reduce levels of excess iron by removing red blood cells and to maintain this state of iron balance over a patient's lifetime. In the induction-phase, the aim of bloodletting is to decrease serum ferritin levels to 50 µg/L or less. Weekly removal of one unit (without exceeding 7 ml/kg) of blood, which contains approximately 200–250 mg of iron, usually allows the target SF level to be reached within 1–2 years. In the maintenance-phase, the frequency of maintenance phlebotomies varies among individuals. On average, three to four phlebotomies per year for men, and one to two phlebotomies per year for women should keep the SF levels at 50 µg/L or less. Each venesection should be preceded by measurement of the haematocrit. The haematocrit should have returned to within 10 points of, or be no lower than 20% below, its starting value. Transferrin saturation may remain elevated until iron stores are depleted and worse outcomes are associated with persistent increases in transferrin saturation during maintenance therapy (Bardou-Jacquet et al; 2017). Adequate hydration before and after treatment and avoidance of vigorous physical activity for 24 h after phlebotomy are recommended (EASL, 2010*). SF levels of less than 25 ng/mL indicate iron deficiency and require temporary cessation of phlebotomy. Iron deficiency anaemia should be avoided. Side effects as tiredness are frequently reported. Rapid mobilisation of iron may increase the risk of cardiac dysrhythmias and cardiomyopathy. Iron supplements and supplemental vitamin C should be avoided by patients undergoing phlebotomy, as vitamin C may accelerate the mobilisation of iron. (Brissot et al, 2011).

VII.2 Alternatives Therapies

Chelation therapy is restricted to a minority of patients with contraindications for venesection including severe anaemia, cardiac failure, poor tolerance or problems with venous access. A daily 2 g subcutaneous dose of deferoxamine infused over 8 h has been shown to be effective (Barton, 2007). An oral iron chelator has also been developed and is starting to be tested in HH. In the future, promising potential therapies include mini hepcidin and BMP6 agonists.

VII.3 Liver Transplantation

End-stage liver disease in HH can be treated with liver transplantation but survival is reduced compared with transplantation in patients without HH, especially when HCC is present. Survival at 1, 3 and 5 years after

transplantation was 72%, 62% and 55%, respectively. Death was secondary to perioperative cardiac or infection-related complications (Crawford et al, 2004).

VIII. Prognosis

The degree of iron overload has a direct impact on the life expectancy of an individual with HH. Major causes of death are decompensated cirrhosis, HCC, DM and cardiomyopathy (Niederau et al, 1996*). These occur at frequencies which are 10–120-fold higher than in an age-matched and sex-matched population without HH. Cardiac dysrhythmias and cardiomyopathies are the most common causes of sudden death in patients with HH. Survival in HH patients in whom treatment is initiated before the development of cirrhosis or diabetes, is similar to that in the general population. Reversibility of changes following adequate iron removal is more likely early in the course of the disease, but can occur even in patients with cirrhosis and varices.

SUMMARY POINTS

- Hereditary haemochromatosis (HH) is the most common identified genetic disease in the white population. In Caucasians, it is most often due to homozygous C282Y HFE gene mutation (> 90 %) with an increased intestinal iron absorption; other genetic mutations more rare have been described.
- The clinical manifestations of HH are related to excessive iron accumulation in tissues, especially the liver, heart, joints and endocrine organs, usually manifesting in adults in their 40s and 50s.
- Phenotypic HH may arise when both alleles of chromosome 6 possess the C282Y mutation (homozygous state) or with the C282Y mutation on one chromosome and H63D on the other (compound heterozygous state).
- Early disease manifestations are non-specific and may include fatigue, arthralgias, weight loss, abdominal pain and loss of libido.
- Patient's quality of life is often altered by the rheumatological complications of HH, particularly joint symptoms and sometimes osteoporosis. Arthropathy is frequently an early feature of HH and it is important it is recognised to allow early treatment and improved prognosis. It may resemble non-inflammatory osteoarthritis involving the second and third metacarpophalangeal and other joints. HH is a cause of calcium pyrophosphate dihydrate deposition (CPPD) disease. Arthropathy in HH is severe, impairs the quality of life and is frequently the indication for total hip arthroplasty.
- Cirrhosis and cirrhosis-associated complications such as oesophageal varices and variceal haemorrhage account for approximately 89% of HH-related deaths. Early treatment can avoid this serious outcome.
- The risk of hepatocellular carcinoma (HCC) in patients with HH is increased approximately 20-fold.
- Diabetes mellitus caused by progressive iron deposition in the pancreas is a feature of HH which can be prevented by early treatment.
- Cardiac dysrhythmias and cardiomyopathies are the most common cause of sudden death in iron overload states.
- Initial screening of individuals with suspected iron overload and those over the age of 20 years who are first-degree relatives of known cases of HH should be done by measurement of transferrin saturation after an overnight fast. Simultaneous serum ferritin determination increases the predictive accuracy for the diagnosis of iron overload.
- Genotyping to detect HFE mutations should be performed for individuals who have abnormal iron studies and for first-degree relatives of identified HH homozygotes.
- Liver biopsy is now rarely indicated for the purpose of diagnosis. Initiation of phlebotomy therapy before cirrhosis or diabetes develops significantly reduce the morbidity and mortality of HH.
- If tolerated, therapeutic phlebotomy should be continued until serum ferritin falls below 50 µg/L. Maintenance phlebotomies should keep the serum ferritin concentration at 50 µg/L or less, and should be continued for life.

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Part II: Gaucher's disease

LEARNING OBJECTIVES

- Outline the pathophysiology of Gaucher's disease
- Describe the different clinical types of Gaucher's disease
- Describe the skeletal involvement in Gaucher's disease
- Describe the radiological findings in Gaucher's disease
- Describe treatment options in Gaucher's disease

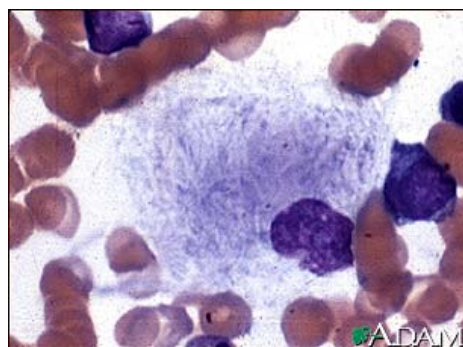
I INTRODUCTION

Gaucher's disease GD is a rare inborn error of metabolism with few rheumatological manifestations. (Grabowski et al, 2015*). As the risk of skeletal disease with irreversible complications is reduced with early initiation of enzyme replacement therapy, rheumatologists should be alert to splenomegaly or hepatomegaly of unknown cause in the presence of bone disease and/or unexplained pain and should include GD in the differential diagnosis.

II PATHOPHYSIOLOGY

GD was first described by Philippe CE Gaucher in 1882 as 'epithelioma of the spleen', in a patient with massive hepatosplenomegaly and haematological features suggestive of leukaemia. GD is a lysosomal glycolipid storage disease due to mutations of both alleles of the acid β -glucosidase gene on chromosome 1 (long arm at position 22 1q22) leading to decreased activity of the lysosomal enzyme, acid β -glucosidase in cells (especially macrophages) of the reticuloendothelial system. Glucocerebrosidase normally catabolises glucocerebroside derived from the degradation of membranes, into ceramide and glucose. Glucocerebroside accumulation within the lysosomes of macrophages ('Gaucher cells') (figure 1) in the spleen, liver, bone marrow and bone leads to organomegaly, bone disease, cytopenia and chronic macrophage activation with inflammasome activation (Grabowski et al, 2015*; Mucci et al, 2015; Migdalska-Richards et al 2016). An animal model with conditional GBA1 deletion in mice shows a defect in osteoblast differentiation and function with an increase of bone resorption (Mistry et al, 2010*). Bone marrow fibrosis may cause localised loss of haematopoiesis, while thrombocytopenia results from decreased platelet production and splenic sequestration.

Figure 1. Light microscopy aspect of a Gaucher cell with characteristic 'wrinkled tissue paper' appearance of the cytoplasm



GD is the most common inherited glycolipid storage disease, with a worldwide incidence of approximately 1 in 57 000 births, and about 10 000 patients world-wide. More than 400 discrete mutant alleles have been identified in the β -glucocerebrosidase gene (GBA1). Three different clinical types can be distinguished. Type 1 (GD1), the adult non-neuropathic form, is the most frequent type and occurs predominantly in populations of European Ancestry and Ashkenazi Jews. More than 95% of GD patients have GD1. Type 2 Gaucher's disease, the infantile

acute neuropathic form and type 3, the juvenile subacute neuropathic form, are much less common and occur predominantly in non-Jewish patients (Grabowski et al, 2015*) .

III. CLINICAL FEATURES

GD is characterized by complex multiorgan involvement with non-specific symptoms. The most commonly reported signs and symptoms at diagnosis are splenomegaly, hepatomegaly followed by bone manifestations. We will focus on GD1.

Table 1. Key features of the three types of Gaucher disease.

Key features	Type 1 « non neuronopathic »	Type 2 «acute neuronopathic»	Type 3 «subacute neuronopathic»
Incidence	1:40000–1:60000 1:850 in Ashkenazi Jews	<1:100000	<1:50000 to <1:100000
Transmission	Autosomal recessive	Autosomal recessive	Autosomal recessive
Ethnic predilection	Pan ethnic/Ashkenazi Jews	Pan ethnic	Pan ethnic/Norrbottnian Sweden
Peak age at onset	Any age (birth to old age)	Infancy	Childhood/adolescence
Hepatosplenomegaly	+ → +++	+ → ++	+ → ++++
Haematological symptoms	+ → +++	+++	+ → +++
Skeletal involvement	+ → +++	Absent	++ → ++++
Neurodegeneration	Absent	+++	+ → +++ (progressive)
Age at death	Childhood/adulthood	Median 9 months	Childhood/adulthood

GD1 is heterogeneous in age at presentation, clinical expression, disease severity and progression. Two-thirds of patients are diagnosed by 20 years of age. However, some may present as infants, while others remain asymptomatic throughout life. The principal presenting feature is painless splenomegaly. Hypersplenism with thrombocytopenia, anaemia and leukopenia occurs frequently, but splenic infarction or rupture is rare. Hepatomegaly usually occurs later in the course of the disease. Hepatic fibrosis is common, but liver failure and portal hypertension are rare. Patients often also present with lymphadenopathy.

Skeletal involvement affects more than 80% of patients, often with high morbidity and a major impact on quality of life. Before any treatment, 63% of patients complain of bone pain in the back, hips, legs, and shoulders. Fractures occur most frequently in the vertebral spine spontaneously or with minimal trauma (36.4% of all fractures), followed by the lower extremities (Javier et al 2011; Grabowski et al, 2015*). Neurologic compression and thoracic hyperkyphosis have been reported as being consequences of severe or multiple vertebral fractures.

Failure of bone modelling during growth is the most characteristic skeletal abnormality, present in about 80% of GD1 adults. The so-called Erlenmeyer flask deformity (expansion of the contours of long tubular bones with loss of the normal concavity of the bony outline) is very suggestive of GD1, though not pathognomonic. Osteonecrosis and bony infarctions are the most common bone complications in GD1 and the most frequent cause of chronic pain and limitation of function (Khan et al, 2012*). Both are the consequences of sudden ischemia in an infiltrated bone area and result in acute-onset episodes (bone crisis). All bones may be involved, including flat bones. Symptoms include acute pain, tenderness, and fever, similar to the symptoms of osteomyelitis or septic arthritis. Epiphyseal osteonecrosis frequently occurs at multiple sites and affects the femoral heads, humeral heads. Symptomatic bone involvement becomes less common after splenectomy. Bone marrow encroachment and fibrosis may result in localised loss of haematopoiesis. However, the degree of anaemia and thrombocytopenia is more often related to splenic sequestration and depends on whether or not the patient has had splenectomy.

Other infrequent manifestations include interstitial lung disease due to infiltration of Gaucher cells into the interstitial and alveolar spaces, and pulmonary hypertension due to infiltration and occlusion of pulmonary capillaries. Patients with Gaucher's disease appear to have an increased risk of haematological malignancies and multiple myeloma. Gaucher's disease has also been associated with Parkinsonism (Grabowski et al, 2015*; Migdalska-Richards et al, 2016).

Pregnancy in GD1 usually has a good outcome. The most common serious complication is postpartum bleeding. Children with GD1 may have growth retardation and delayed onset of puberty.

The clinical course of GD1 is usually progressive but varies from rapid progression in severely affected children to a more insidious course in asymptomatic adults. Morbidity and mortality in symptomatic patients results from the sequelae of severe bone disease, bleeding complications, infections, liver failure or severe pulmonary disease (Weinreb et al, 2013*).

IV. DIAGNOSIS

IV.1 Laboratory and Radiological Findings

Typical laboratory findings are thrombocytopenia and anaemia, especially in patients with splenomegaly. Liver enzymes may be mildly elevated in patients with hepatomegaly. Biochemical markers reflecting overloading of activated macrophages, such as plasma tartrate-resistant acid phosphatase, angiotensin-converting enzyme, ferritin, chitotriosidase, and recently glucosylsphingosine are useful for evaluating disease activity and monitoring response to therapy (van Dussen et al, 2011; Rolfs et al, 2013).

Radiologic bone manifestations are found in more than 95% of patients with features and frequency depending on the imaging method used. Radiographs may show increased symmetrical radiolucency and cortical scalloping

with thinning of the axial skeleton and proximal long bones, prominent in the distal portion of the femur and tibia.

Plain X-rays may also show fractures and lytic lesions. The vertebral bodies may show identical deformities as seen in sickle cell anaemia, with step-like depressions of the superior and inferior margins, called 'H vertebra'. The extent and severity of the disease vary and are poorly evaluated by radiography, computed tomography (CT), or bone scintigraphy. Magnetic resonance imaging (MRI) has been shown to be the most sensitive technique for detecting early bone marrow changes and for assessing the extent and severity of marrow involvement. Computed tomography, MRI or abdominal sonography of the liver and spleen may demonstrate hepatosplenomegaly and can be used to assess response to therapy (Grabowski et al, 2015*). A decrease in bone mineral density by Dual-energy X-ray absorptiometry is reported (osteopenia in 42% of cases) and is correlated with the severity of skeletal involvement.

Figure 2. Typical features of ischemic bone complications in GD: radiograph of the left femoral diaphysis of a 52-year-old man showing osteopenia, osteolytic lesions, cortical thinning, and scalloping



IV.2 Diagnosing Gaucher's Disease

The most appropriate and less invasive diagnostic test for detecting GD1 is demonstrating decreased or absent acid β -glucosidase activity in leucocytes and/or by molecular analysis of the GBA1 gene instead of the bone marrow biopsy often made for patients being evaluated for splenomegaly, anaemia and/or thrombocytopenia. Mutation analysis may further help to predict clinical findings and to identify affected but undiagnosed family

members or heterozygote carriers (Grabowski et al, 2015*). Recently, an easy screening evaluation of GBA activity in dried blood spots has become available.

V TREATMENT

Treatment goals in Gaucher's disease are increasing survival, prevention of irreversible damage, elimination of symptoms, and improvement of overall health and quality of life (Weinreb et al, 2013*; Zimran et al, 2015*; Zimran et al, 2016*). Therapeutic goals for skeletal involvement are to lessen or eliminate bone pain within 1 to 2 years, prevent bone crises, prevent osteonecrosis and subchondral joint collapse and improve BMD (Pastores et al, 2004*).

V.1 Enzyme Replacement Therapy ERT

Venous infusions of ERT are used for more than two decades (Weinreb et al, 2013*). Three forms of macrophage-targeted glucocerebrosidase are now available: recombinant glucocerebrosidase produced by DNA technology (imiglucerase, Cerezyme), human glucocerebrosidase produced in a human cell line with gene activation technology (velaglucerase alfa, VPRIV), and a carrot cell-expressed human recombinant β -glucocerebrosidase (taliglucerase alfa, Elelyso) (Weinreb et al, 2013*; Zimran et al, 2015*; Zimran et al, 2016*).

ERT usually results in improvements in all clinical and laboratory parameters of GD1. Currently recommended therapeutic regimens start with 2-hour intravenous infusions of 60 IU/kg every 2 weeks. Glucocerebrosidase infusions have a good control over haematological and visceral parameters (hepatosplenomegaly) within 12 to 20 weeks, although a bone response requires a longer period with an increase in BMD and a significant positive impact on quality of life (Sims et al ;2008). MRI scores and recently whole-body magnetic resonance imaging MRI have been proposed for evaluating the therapeutic bone response.

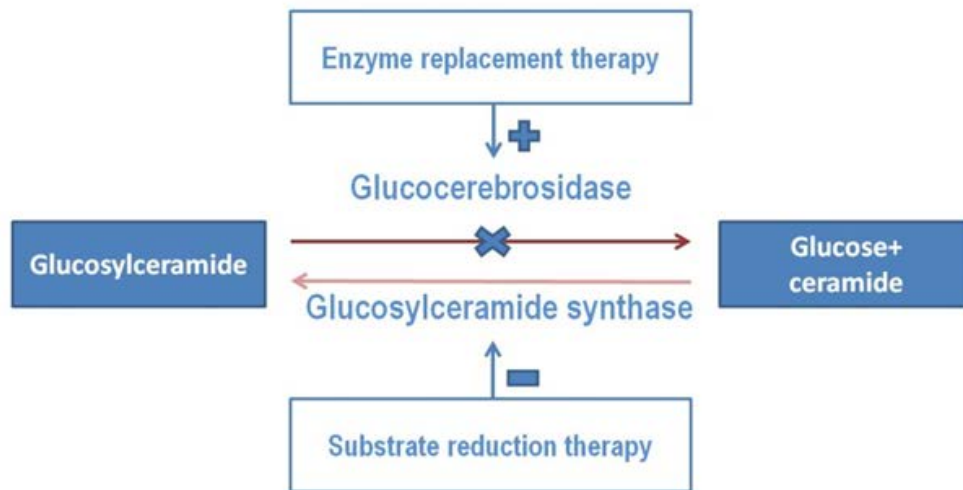
ERT may be less effective in patients with neuropathic GD. The recombinant enzyme does not cross the blood–brain barrier and is therefore likely to have only a limited impact on neurological involvement.

V.2 Substrate Reduction Therapy

Substrate reduction therapy (Figure 3) is an alternative treatment in patients with GD1. Miglustat (Zavesca) is an oral iminosugar that decreases substrate synthesis (Pastores et al; 2007). It is approved for patients with mild to moderate GD1 who are intolerant of imiglucerase or unwilling to take ERT. Eliglustat (Cerdelga) is an oral ceramide analogue that inhibits glucosylceramide synthase, the enzyme responsible for biosynthesis of glucosylceramide which accumulate in GD, thus reducing glucosylceramide accumulation (Belmatoug et al; 2017). Eliglustat is approved as a first line treatment for adults (> 18 years) with GD1 who are CYP2D6 extensive,

intermediate or poor metabolizers. Miglustat does cross the blood–brain barrier and may therefore have potential benefit in neuropathic GD (Pastores et al, 2007*).

Figure 3: Mechanisms of action of treatment in Gaucher disease



V.3 Symptomatic Treatments

Antiresorptive therapy with high-dose alendronate in addition to ERT increases BMD at 24 months without radiologic modification of focal lesions (Wenstrup et al; 2004). The effect on the risk for fractures is unknown. As vitamin D deficiency seems to be frequent in patients with GD1, optimization of vitamin D levels is recommended. Osteonecrosis often require surgery earlier than in the general population but improved surgical techniques have increased the probability of good results and decreased the postoperative complications that were reported in historical series (Khan et al; 2012).

**SUMMARY POINTS**

- Gaucher's disease GD is a rare autosomal recessive lysosomal glycolipid storage disease in which gene mutations on chromosome 1q22 lead to decreased activity of the enzyme glucocerebrosidase in cells (especially macrophages) of the reticuloendothelial system.
- Clinical manifestations develop as glucocerebroside and other glycolipids accumulate within the lysosomes of macrophages ('Gaucher cells') in the spleen, liver, bone marrow and bone.
- Type 1 GD, the adult non-neuropathic form, is the most common clinical type. Type 2, the infantile acute neuropathic form and type 3, the juvenile subacute neuropathic form, are much less common.
- The principal presenting feature in GD1 is often painless splenomegaly, with thrombocytopenia, anaemia and leucopenia.
- Skeletal disease affects more than 80% of GD1 patients with a major impact on quality of life. Osteopenia and osteolytic lesions can cause pathological fractures of the long bones, vertebral compression. Osteonecrosis and bony infarctions are the most common bone complications, the most frequent cause of chronic pain and limitation of function.
- MRI is the most sensitive technique for detecting early bone marrow changes and for assessing the extent and severity of marrow involvement. The most appropriate and least invasive diagnostic test for detecting GD1 is demonstrating decreased or absent acid β -glucosidase activity in leucocytes and/or by molecular analysis of the GBA1 gene
- GD1 must be treated early with enzyme replacement therapy or substrate reduction therapy to prevent irreversible severe bone complications. Bone disease remains a major therapeutic issue in GD1.

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Part III: Histiocytosis

LEARNING OBJECTIVES

- Outline the pathophysiology of Langerhans cell histiocytosis (LCH) and importance of the BRAF mutation
- Describe the most frequent localisation of LCH
- Describe some clinical features of LCH, especially bone and joint involvement
- Describe the clinical workup of suspected LCH
- Describe some treatment strategies in LCH
- Describe the differences in clinical presentation between childhood LCH and adult LCH

I INTRODUCTION

There is some confusion over the terminology of histiocytosis. Despite proposals clarifying classification and terminology, different terminologies and interpretations are still used in the literature. In this review we will focus on bone and joint manifestations of Langerhans Cell histiocytosis (LCH). We will not discuss other forms of Histiocytosis such as Erdheim Chester Disease, Rosai Dorfman Disease or Juvenile Xanthogranuloma.

II PATHOPHYSIOLOGY

Histiocytosis is the name given to abnormal proliferation of histiocytes. The Langerhans cell derives from bone marrow dendritic cells and is capable of migrating to the skin, spleen and lymph nodes. It is an antigen-presenting cell and is positive for CD1a and CD207. On electron microscopy, pentalaminar Birbeck granules are easily recognised. In LCH, the abnormal cells are immature, poorly antigen presenting, and proliferating at a moderate rate. The disease is defined through a clonal (but not malignant) proliferation of Langerhans cells in various abnormal locations. Histologic findings may show various involvements of other cells such as macrophages, eosinophiles, or multinucleated giant cells. It has been unclear for many years whether immunologic or infection events are responsible for the disease. The main recent finding is the involvement of the oncogene BRAF : the mutation V600E has been found in 86.8% of multisystem forms with risk organ involvement, 68.6% of multisystem forms without risk organ involvement and 43.9% of single system patients (Héritier et al, 2016*; Badalian-Very et al, 2010).

III EPIDEMIOLOGY

LCH is a rare condition, and mostly (80% of cases) affects children. Yearly incidence rates are estimated at approximately 4.6 to 8.9 per million children, under 15 years (Guyot-Goubin et al, 2008; Stalemark et al, 2008, Ribeiro et al, 2015). The incidence of adult LCH is estimated to be less than 1 per million. It appears that LCH can present at any age during adulthood, and has usually a single system presentation (68% single system presentation versus 31% multisystem presentation). Located forms are observed more frequently in males, while generalised forms are found equally in males and females. Paediatric histiocytosis has a more severe phenotype (Minkov et al, 2005).

IV CLINICAL MANIFESTATIONS

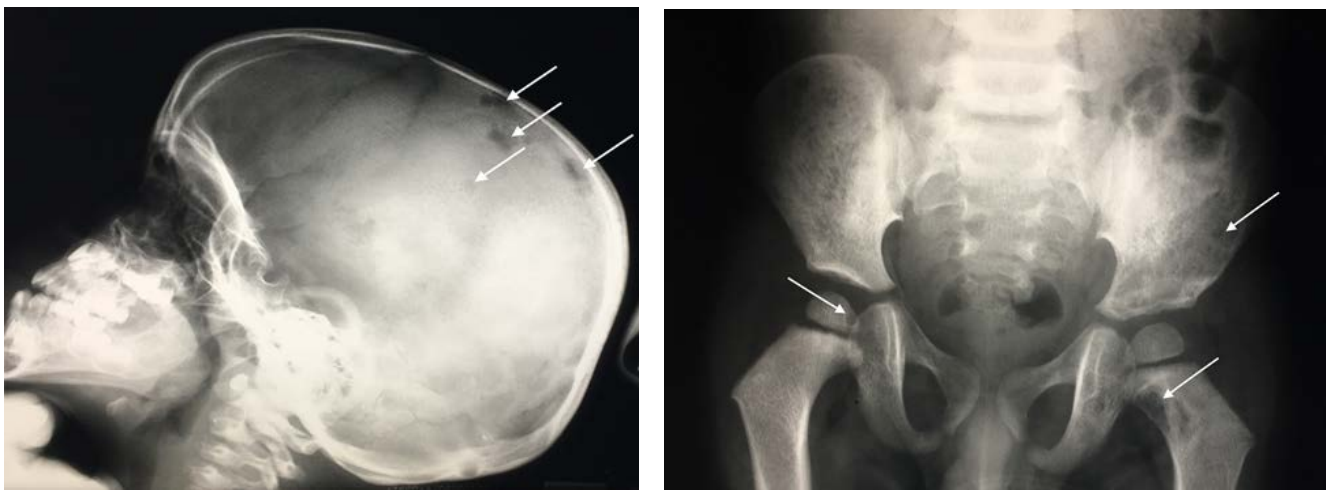
The clinical manifestations are very diverse, and LCH has been described in almost every organ (Haupt et al, 2013*). Systemic signs such as fever and weight loss may also be presenting features, but are usually lacking. A considerable delay between the first onset of symptoms and the final diagnosis is common.

IV-1 Classical Presentation

IV-1-1 Skeletal disease

The classic single presentation is bone disease with osteolytic lesions without periosteal reaction, single or multiple, located in the skull, vertebra, jaw, ribs, flat bones (pelvis , scapula), and proximal portions of the long bones (figures 1 and 2). Classically hands and feet are spared. Localised pain may be present along with discrete local swelling but asymptomatic lesions are possible. Other clinical manifestations may be pathological fractures or osteoarthritis of the adjacent bones. In children, growth retardation can be a revealing symptom.

Figures 1 and 2. Osteolytic lesions in the skull, the pelvis and femoral neck of a 3-year-old child with Langerhans cell histiocytosis



IV-1-2 Skin and mucosa

Skin involvement is often mistaken for seborrheic dermatitis, but various forms of red papular rash have been described, with polymorphic presentation. Face, neck torso and groin are the main sites. It may include hypopigmented macules and eczema. Dermatological manifestation is often the first sign of underlying disease.

IV-1-3 Pituitary gland

Pituitary involvement causes diabetes insipidus through posterior pituitary involvement. Anterior pituitary deficit can be associated. When cranio-facial bones are affected, the risk of pituitary involvement increases.

IV-2 Other Manifestations

Many other clinical manifestations can occur, such as cytopenias due to bone marrow involvement, lungs manifestations with reticulo-nodular lung disease or lung cysts, or Lymphadenopathy. Other organs involved are the thymus, thyroid, spleen, liver, gastro-intestinal tract (sclerosing cholangitis) or the central nervous system

(CNS) with neurodegenerative syndromes. Systemic signs such as fever and weight loss have also been described.

IV-3 Clinical Classification (Girschikofsky and al, 2013*)

IV-3-1 Single system disease (SS-LCH)

When only one organ is involved, for example, when exclusive manifestations occur in the bone compartment. However, a single system LCH can have multifocal lesions within the bone.

IV-3-2 Multi system disease (MS-LCH)

When two or more organs/systems are involved. The classical presentation is the triad with bone, pituitary and skin lesions.

IV-3-3 Risk lesions

Risk lesions occur when risk organs/systems are involved, they are associated with poor prognosis (Haupt et al, 2013*, Girschikofsky et al, 2013*), including the spleen, the liver, the hematopoietic system (bone marrow) and central nervous system. Some “special” sites have to be considered as risk lesions because of high risk of functional impairment caused by neurological compression, including vertebral lesions, craniofacial bone lesions (mastoid, sphenoid, temporal bone) or orbital lesions.

IV-4 Differential Diagnosis

In these patients, it is important for the rheumatologist to consider the differential diagnosis of the most frequent osteolytic lesions, especially when lesions are unifocal. Malignancies include metastasis, osteoblastoma, chondroblastoma, or myeloma. Benign lesions include fibrous dysplasia, enchondroma, giant cell tumour, non-ossifying fibroma, bone cyst, hyperparathyroidism, or infection. Biopsy is the only certain procedure to rule out these differentials.

V DIAGNOSIS

V-1 Biopsy

The definitive diagnosis of LCH requires histological confirmation (Haupt et al, 2013*). Biopsy of the most accessible lesion should be performed whenever Histiocytosis is suspected on clinical, biological and/or radiological findings. Biopsy fragments should include immunophenotypic markings for CD1a and CD207, also

known as langerin (Girschikofsky et al, 2013*). Electron microscopy, for Birbeck granules identification, is no longer necessary for diagnosis (Haupt et al, 2013*).

V-2 Disease Severity Assessment

V-2-1 Skeletal involvement

Diagnosis and follow up include skeletal radiography and skeletal scintigram (bone scan).

V-2-2 Risk lesions assessment

Laboratory tests of the blood should include a complete blood count as well as screening for haematopoietic, liver, spleen and renal function. The clinical workup of suspected cases of LCH should include a chest X-ray and a survey of the skeleton; technetium bone scintigraphy is useful as a screening tool and can be completed with X-rays and computerised tomography. In cases with suspected CNS involvement, gadolinium-enhanced MRI scans are warranted. The usefulness of FDG-PET scan has still to be determined, but seems promising for follow up and for monitoring disease activity (Phillips et al, 2009).

V-3 BRAF Mutation

If LCH is confirmed, based on histological findings, screening for the BRAF gain of function mutation V600E should be discussed in specialized centres (through immunohistochemistry or molecular diagnostic methods), especially with young patients who have a multi system, severe or recurrent form, and resistant to treatment.

VI TREATMENT

Specific treatment depends on clinical presentation (SS-LCH or MS-LCH), or involvement of risk organs.

Although LCH is a rare condition, some studies have thoroughly investigated potential treatments. For obvious reasons formal treatment studies are not frequent in LCH, especially in adult forms . However, recent progress has been made and specific treatments emerge (table 1).

VI-1 SS-LCH with single bone compartment involvement.

No specific treatment is mandatory, but follow-up is necessary. Systematic radical curettage is not recommended. Spontaneous regression is possible. Bone curettage is generally sufficient when performed. Sometime the bone lesions heal after the biopsy or after corticosteroid injections. Preventive orthopaedic surgery is sometimes proposed because of fracture risk.

Systemic chemotherapy (corticosteroid/vinblastine) is only proposed when there is are severe multifocal bone lesions or “risk lesions” such as cranio-facial bone lesions or vertebral lesions with fracture risk.

Bone resorption inhibitors such as bisphosphonates (Morimoto et al, 2011) or denosumab (Makras et al 2017*) have shown interesting results, mostly on pain and should be considered when the bone disease is severe or associated with fracture/fracture risk. The effect on extra skeletal symptoms is not well known.

VI-2 SS-LCH concerning other single systems, without risk organ involvement

Studies indicate that in cases without risk organ involvement, prognosis (survival) is favourable, independent of the treatment strategy. Treatment is specific for the type of organ/system involved.

VI-3 MS-LCH or SS-LCH with risk organ involvement

Treatment should be initiated in specialized centres. Treatment is systemic and consists of chemotherapy. First line of treatment includes vinblastine and corticosteroid in paediatric cases. Children undergo 6 weeks to a year of treatment (Haupt et al 2013*, Gadner et al, 2011*). Treatments are summarized in Table 1.

The recent discovery of the BRAF mutation, as in Erdheim Chester disease, offers new promising therapeutic options: targeting the RAS pathway with BRAF inhibitors such as vemurafenib showing some efficacy in preliminary studies (Haroche et al, 2013; Charles et al, 2014).

Table 1. Summary of the treatments according to clinical presentation.

<i>Disease presentation</i>	<i>Treatment</i>
<ul style="list-style-type: none"> SS-LCH with bone impairment 	<ul style="list-style-type: none"> - Abstention to treat if unifocal / asymptomatic lesion. - Bone curettage and/or orthopaedic surgery if the lesion is at risk or symptomatic. - Corticosteroid injection if lesion is symptomatic. - Systemic chemotherapy is recommended only if there is a severe multifocal bone involvement, or risk lesions for nervous system. - Focal radiotherapy if lesions are difficult of access for other therapeutic options.
<ul style="list-style-type: none"> Other SS-LCH presentations without risk organ involvement 	<ul style="list-style-type: none"> - Symptomatic and specific of the organ affected.
<ul style="list-style-type: none"> SS-LCH with risk organ involvement MS-LCH 	<ul style="list-style-type: none"> - First line chemotherapy: vinblastine + corticosteroid (Haupt et al 2013*, Gadner et al, 2011*). - Second line chemotherapy: cladribine, cytarabine, hematopoietic stem cell Transplantation (Steiner et al, 2005). In adults: etoposide. - Radiotherapy (Kriz et al, 2013) has shown some efficacy but should be avoided in children, because of long-term adverse effects.

Adapted from Steiner et al, 2005;Gadner et al, 2011; Haupt et al 2013; ;Kriz et al, 2013 ;Morimoto et al, Cancer 2006;107:613**

VI PROGNOSIS

Prognosis is highly variable and depends on the age at onset, and the number and degree of dysfunction of affected organs. Five year relative survival is estimated at 90%, 79% survival under 1 year but 97% survival between 1 and 4 years of age, and 100% after 5 years. Patients with LCH with a low risk profile often achieve remission without long term sequelae. Patients with risk organ involvement are at considerable risk for long term complications. In 20% of cases, growth and development are impaired. In over 10% of cases, neurological problems can be expected due to vertebral compression. Moreover, in 20% of cases, symptomatic lesions of long bones are to be expected. Histiocytosis can be definitively cured due to natural evolution of the disease or secondary to treatment. However reactivations are possible in 25% to 45% of MS-LCH (Morimoto et al, 2006*; Cantu et al, 2012*). When multiple organs are involved, there is a lack of response to treatment, and a higher mortality. Finally, malignancy is found more frequently in patients surviving LCH, specifically acute myeloid leukaemia, lymphoblastic lymphoma, lymphoblastic leukaemia or Langerhans Cell sarcoma (Gadner et al, 2001*; Morimoto et al, 2006*; Girschikofsky et al, 2013*).

SUMMARY POINTS

- The Langerhans cell derives from bone marrow dendritic cells and is capable of migrating to the skin and lymph nodes. It is an antigen-presenting cell.
- In Langerhans cell histiocytosis (LCH), the abnormal cells are immature, poorly antigen presenting, and proliferating at a moderate rate. Recent studies have shown the importance of gain-of-function mutations of the BRAF oncogene.
- LCH may present as a single system disease, the most frequent site being an unifocal or multifocal lytic bone lesion.
- Involvement of risk organs (liver, spleen, lungs, bone marrow, endocrine organs, gastrointestinal organs and central nervous system) is associated with a poor prognosis.
- The clinical workup of LCH should include a chest X-ray and a survey of the skeleton: technetium bone scintigraphy screening, completed with X-rays and CT.
- The diagnosis of LCH needs histological confirmation with immunophenotypic marking.
- In cases without risk organ involvement, prognosis (survival) is favourable, independent of the treatment strategy, while risk organ involvement is associated with lack of response, and a higher mortality rate.
- Patients with risk organ involvement are at considerable risk for long term complications.
- LCH is rare in children and is extremely rare in adults.

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Part IV: Endocrine diseases

LEARNING OBJECTIVES

- Describe the musculoskeletal features associated with diabetes mellitus (DM)
- Describe the musculoskeletal features associated with thyroid disease
- Describe the management of musculoskeletal features of endocrine disease

I. DIABETES MELLITUS

Diabetes mellitus (DM) is a systemic disease with widespread involvement of different organs. A variety of musculoskeletal conditions have been associated with DM. These conditions are important to recognize because many of them respond to treatment, preventing pain and disability and improving quality of life.

The prevalence of musculoskeletal conditions in patients with DM varies depending upon the definitions used and the study population with DM, which may range from a primary care cohort to patients with severe DM in a specialized academic centre. In contrast to the studied microvascular and macrovascular complications, characterization of the musculoskeletal features associated with DM is derived mainly from observational studies. The pathogenetic mechanism for many of these conditions remained to be elucidated; their association with DM is based largely on epidemiologic data (Crispin JC, 2003; *Lebiedz-Odrobina D 2010,)

I.1 Upper Extremity Manifestations of DM

I.1.1 Carpal tunnel Syndrome

Carpal tunnel syndrome (CTS) is an entrapment neuropathy caused by compression of the median nerve within the carpal tunnel. CTS presents with pain and paraesthesia of the thumb, index and middle fingers and of the radial aspect of the ring finger. Symptoms may be reproduced by percussion of the median nerve at the wrist (Tinel's test) or on wrist dorsiflexion (Phalen's Test). DM is a known risk factor of CTS. DM has been reported in 6 to 17 % in all cases of CTS, and CTS might be more common in those with pre-diabetes (Gulliford MC, 2006). CTS is associated with duration of DM but not with the degree of underlying metabolic control. CTS is more frequent in DM patients with neuropathy. The physiopathology is not fully understood and includes several mechanisms such as increased pressure in the tunnel, median nerve microcirculation injury, median nerve connective tissue compression, and synovial tissue hypertrophy. Local corticosteroid injection and splinting may be beneficial in management though surgery is often required (*Lebiedz-Odrobina et al, 2010).

I.1.2 Flexor tenosynovitis

Flexor tenosynovitis (Trigger finger) is characterized by palpable nodule formation and thickening localized to the flexor tendon or sheath and by the presence of 'locking' phenomena. The ring finger, middle finger and thumb are most often affected and the condition may be bilateral. Flexor tenosynovitis is described up to 12% of diabetic patients (*Cagliero et al, 2002), is more common in type II DM and is associated with duration of the disease but does not seem dependent on glycaemic control. Multiple digit involvement is frequent. Local corticosteroid injection may be beneficial though surgery is often required (Lebiedz-Odrobina D, 2010).

I.1.3 Dupuytren's disease

Dupuytren's disease (DD) is characterized by fibrosis of the palmar fascia, with subsequent nodule formation and contracture of the palmar fascia leading to flexion contracture of the digits. DD is more prevalent in diabetic patients affecting between 16 and 42%, with prevalence increasing with age and duration of diabetes. DD is equally frequent in type I and type II diabetes (Rodrigues et al, 2015). DD is painless and usually not very disabling. Among diabetics, DD most often involves the middle and ring fingers rather than the ring and little finger, as in non-diabetics (*Cagliero E, 2002). Intra-lesional corticosteroid injection and surgery followed by physiotherapy have shown some efficacy. However, recurrence rates are high. Recently, injecting the palmar fascia with collagenase from *Clostridium histolyticum* has been developed as a nonsurgical treatment of DD (Hurst, 2009).

1.1.4 Shoulder pain

Two types of shoulder problems occurs in diabetic patients: Adhesive capsulitis (also known as frozen shoulder) and calcific tendinitis. Adhesive capsulitis has been reported to be twice as frequent in diabetic patients: the prevalence is 10,3% in type I diabetics and 20,4% in type II diabetics. It presents as a painful progressive restriction of range of shoulder motion. Its natural history may be divided into 3 phases: pain, stiffness and recovery. The duration of the symptoms may last an average of 30 months. Increased age and, longer duration of diabetes are associated with capsulitis (Crispin JC, 2003; *Lebiedz-Odrobina D 2010). Analgesics, physical therapy are the first-line of treatment. Intra-articular corticosteroid injections are helpful to obtain short-term pain relief (Roh et al, 2012). Although diabetic patients benefit from arthroscopic release, results from surgery are not as good as in non-diabetic patients, with only 71% of diabetics recovering full range of shoulder movement compared with 90% of non-diabetics in one prospective study (Mehta SS 2014). Calcific tendinitis is a painful condition most commonly affecting the shoulder in which calcium hydroxyapatite crystals deposit predominantly in periarticular areas. The incidence of calcific tendinitis is 31,8% in patients with DM, compared with 10% of non-diabetic patients. Calcific tendinitis may coexist with adhesive capsulitis of the shoulder. Analgesics, physical therapy and intra-articular corticosteroid injections are the standard treatment (Crispin JC, 2003; *Lebiedz-Odrobina D 2010).

1.1.5 Limited joint mobility

Limited joint mobility (LJM), also known as diabetic cheiroarthropathy, is common in patients with DM. It is characterized by limitation of joint movements most marked in the small joints of the hands. It may affect other joints including the metatarsophalangeal and the subtalar joints. Thickening and waxiness of the skin in extremities are also common (diabetic sclerodactyly but the face is spared and there are no telangiectasias). The prevalence of limited joint mobility in DM ranges from 8 to 58% (Gerrits et al, 2015). It occurs in both type I and type II diabetes. The risk increases with increasing glycated haemoglobin (HbA1c) and the duration of DM. There are conflicting data concerning the possible association of limited joint mobility with both

microvascular and other complications of DM. Limited joint mobility is a painless condition and is probably caused by an advanced glycosylation end product on collagen. Patients present generally when stiffness or contractures lead to decreased grip strength and declining dexterity with hand function. Two clinical tests are helpful for diagnosis: the “prayer sign” which is the ability to flatten the hands together as in prayer (figure 1) and the “table top sign” the ability to flatten the palm against the surface of a table. Physiotherapy is the mainstay of therapy (*Lebiedz-Odrobina D 2010).

Figure 1: Positive “prayer sign” test due to limited joint mobility in a diabetic patient



I.2 Lower Extremity Manifestations of DM

I.2.1 Muscle infarction (diabetic myonecrosis)

Spontaneous infarction of muscle is a rare condition which usually affects patients with longstanding and poorly controlled DM. It occurs in both type I and type II diabetes, and the majority of patients have multiple microvascular complications including retinopathy neuropathy and nephropathy. It presents with an acute onset of muscle pain and swelling. There is usually no history of trauma. The swelling may be mildly to extremely tender. The vastus lateralis, thigh adductors, and biceps femoris muscles are most frequently involved but calf or the deltoid muscles may be involved as well. Creatine Kinase levels may be normal or increased. MRI appears to be the most useful diagnostic technique. Differentiation from soft tissue infection and pyomyositis may be difficult and therefore muscle biopsy for bacterial analysis is often performed. Treatment of muscle infarction is symptomatic and includes rest and anti-inflammatory therapy, surgery is not recommended (*Lebiedz-Odrobina D 2010, Trujillo-Santos AJ 2003).

1.2.2 Diabetic amyotrophy (also known as Bruns-Garland syndrome)

Diabetic amyotrophy typically occurs in patients with type II DM that has been recently diagnosed. It is not associated with duration of diabetes. The clinical manifestations include asymmetric focal onset of leg pain which is usually severe, followed by weakness involving the proximal leg, with associated autonomic failure and weight loss. Progression occurs during months and is followed by partial to full recovery in most patients. The diagnosis is based mainly upon the presence of suggestive clinical manifestations in patients with known or newly diagnosed diabetes mellitus. The diagnosis is confirmed with electro diagnostic studies which show axonal degeneration, contrasting with normal spine imaging, with no compression signs. Diabetic amyotrophy is not a pure plexopathy because it also affects the lumbosacral nerve roots and lower extremity peripheral nerves. Occasionally it also affects cervical nerve roots, or upper extremity nerves. The most likely cause is ischemic injury from a non-systemic micro vasculitis causing ischemia in the lumbosacral plexus (Bhanushali et al, 2008). Recovery is rarely complete even if there is a natural improvement of muscle weakness. Ambulatory aids and wheelchair may be needed. Symptomatic treatment including analgesics, narcotics and agents for neuropathic pain may be beneficial (Barohn RJ, 1991). Immunotherapy such as corticosteroids or intra venous immunoglobulins are sometimes discussed, however there is no proof of their efficacy and steroids may aggravate diabetes (Chan et al, 2012).

1.2.3 Neuropathic arthropathy (also known as Charcot osteoarthropathy or Charcot's Joint)

Neuropathic arthropathy is a progressive, degenerative arthropathy associated with various diseases in which severe neuropathy occur. In patients with DM, the loss of sensation may result in a chronic, progressive and destructive arthropathy. DM is the disease most commonly associated with neuropathic arthropathy. The prevalence of neuropathic arthropathy has been reported to be 0.15%. The joints most commonly involved include the ankle, tarso-metatarsal, metatarsophalangeal and toe interphalangeal joints. The pathogenesis remains uncertain though is likely to be due to a combination of mechanical micro traumatisms, bone fragility caused by hyper-resorption, obesity, neuropathic and vascular factors (*Lebiedz-Odrobina D 2010; Papanas et al, 2013).

The diagnosis requires a high index of clinical suspicion. In earlier stages x-rays are normal, while in advanced disease the radiographic features are usually marked (figure 2). Scintigraphic studies and MRI are useful. The diagnosis should always be considered in any patient with diabetes who presents with a unilateral warm, swollen, erythematous foot in the context of peripheral neuropathy and with longstanding diabetes (Lebiedz-Odrobina D 2010). Treatment of neuropathic arthropathy requires a multidisciplinary approach. In early stages immobilization with a cast is recommended. The role of bisphosphonates in management remains unclear (Jude EB, 2001; Parakinen et al, 2013). Surgical correction should be avoided.

Figure 2: Advanced stage of a bilateral Charcot's joints in diabetes: sclerosis and fragmentation is seen



I.3 Spine Manifestations of DM

I.3.1 Diffuse idiopathic skeletal hyperostosis (Forestier Rotes disease)

Diffuse idiopathic skeletal hyperostosis (DISH) is characterized by the calcification and ossification of ligaments and entheses. It affects the axial and appendicular skeleton. The aetiology of DISH is unknown. DISH has been observed more often in diabetics, particularly among patients with type II DM with an estimated prevalence of 13% to 40%. Most patients are asymptomatic; occasionally patients complain of stiffness. Analgesics and exercise have been used to treat patients with DISH (*Lebiedz-Odrobina D 2010).

I.3.2 Osteoporosis

The association between DM and osteoporosis is controversial. Patients with DM have a low turnover in bone formation and to a lesser degree bone resorption. Bone mineral density as measured by DXA is lower in patients with type I diabetes and normal or increased in patients with type II diabetes.(*Shah et al, 2017). One of the reasons seems to be the anabolic effects of insulin, on the bone, thus stimulating osteoblasts. Fracture risk is increased in both groups, although it is not clear whether comorbidities are partially responsible for

increased fracture risk, such as neuropathy, retinopathy, nephropathy or other cardiovascular complications (*de Liefde et al, 2005; *Vestergaard, 2007). There are no specific treatment guidelines for diabetic patients and general guidelines should be followed.

II. THYROID DISEASE

Disorders of the thyroid gland may present with a variety of musculoskeletal symptoms. Conversely, rheumatic diseases may be associated with autoimmune thyroid disease or the presence of antibodies (*Anwar 2010).

II.1 Hypothyroidism

II.1.1 Carpal tunnel syndrome

Unilateral or bilateral carpal tunnel syndrome (CTS) has been reported in hypothyroidism. The mechanism is thought to be due to accumulation of glycosaminoglycans within the carpal tunnel area. CTS is a common entrapment neuropathy with an estimated prevalence of 3.8% in the general population. Electro diagnostic studies are the gold standard for diagnosing CTS. CTS generally improves with thyroid hormone replacement. Local corticosteroid injection and splinting may be beneficial though surgery is often required.

II.1.2 Hypothyroid myopathy

Muscle symptoms may manifest in 25% to 79% of adult patients with hypothyroidism. Symptoms reported by patients include myalgia, cramps, stiffness, fatigability and weakness. It is more common if hypothyroidism is severe or with a prolonged evolution. Symptoms may mimic common rheumatic diseases such as polymyalgia rheumatic and fibromyalgia (*Anwar, 2010). Serum muscle enzymes are frequently mildly elevated in patients with hypothyroid myopathy including creatine-phosphokinase. The physiopathologic mechanism involves an increase in glucoaminoglycan deposition in muscle fibres, sometimes responsible for a pseudohypertrophy. Calves and forearms are the most frequently affected. There are numerous reports in the literature of polymyositis like illnesses associated with hypothyroidism. Diagnosis is supported by electromyography studies which helps to differentiate thyroid myopathy from other myopathies. Muscle biopsy is not usually indicated. There is a favourable prognosis with hormone replacement, although clinical and biological improvement can take several months to be observed.

II-1-3 Bone metabolism.

In paediatric patients, cases of growth retardation are possible. In adults, if hypothyroidism is severe, bone turnover is decreased, but bone mineral density measures may be decreased or normal or increased. Increased fracture risk is suspected in hypothyroid patients, even in case of subclinical hypothyroidism (Yang et al, 2017).

II.2 Hyperthyroidism

Hyperthyroidism may be due to several causes, including autoimmune, drug induced or iatrogenic disease. Grave's disease is the most common cause of autoimmune hyperthyroidism worldwide (*Anwar 2010).

II.2.1 Myopathy

Hyperthyroid myopathy has a similar presentation as hypothyroidism: proximal weakness, myalgia and fatigability. In contrast with hypothyroidism, serum CK levels are normal; furthermore myopathic changes on EMG are rare. Muscle biopsy is not necessary to confirm the diagnosis except if an associated auto-immune disease is suspected with inflammatory myopathy. Two unusual manifestations of hyperthyroidism (commoner in the past) were associated with rheumatic complaints: pretibial myxoedema and thyroid acropachy. Pretibial myxoedema is asymptomatic and is manifested as skin induration over the pretibial area. Thyroid acropachy is characterized by clubbing of the finger and toes. Both conditions are associated with thyroid ophthalmopathy (*Anwar 2010).

II.2.2 Bone metabolism

Patients with untreated hyperthyroidism have an increase bone turnover and net loss of bone mass. In a meta-analysis the risk of fracture was increased in patients with hyperthyroidism (Vestergaard P, 2003). Hyperthyroidism is a classical cause for secondary osteoporosis, and should be considered in every osteoporotic patient. Hypercalcemia and hypercalciuria may also be present. Bone involvement is reversible, when patients regain normal thyroid function, bone mineral density increases to normal values, although the process may take more than a year.

II.2.3 Other

Auto-antibodies are the hallmark of autoimmune disease and patients suffering from Hashimoto's Disease or Graves' Disease are at higher risk to develop other auto-immune mediated diseases. Some of these associated auto-immune diseases, such as lupus, rheumatoid arthritis, celiac disease, and myasthenia are responsible for musculoskeletal involvement and must not be mistaken for an atypical manifestation of thyroid disease. (*Anwar et al, 2010; Boellaeert et al, 2010)

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Rheumatic manifestations of systemic diseases / miscellaneous rheumatic diseases

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A previous version was co-authored by Melania Martínez-Morillo, Thomas Bardin, Mart van de Laar, Harald Vonkeman, Barry Bresnihan, Thomas Barding, Claire Brière

IN-DEPTH DISCUSSION I

Gaucher's disease

INTRODUCTION

Gaucher disease (GD) is the most common lysosomal storage disease. It is caused by deficiency of glucocerebrosidase, which results in abnormal accumulation of glycolipids within cellular lysosomes. As the risk of skeletal disease with irreversible complications is reduced with early initiation of enzyme replacement therapy, rheumatologists should be alerted to splenomegaly or hepatomegaly of unknown cause in presence of bone disease and/or unexplained.

GD is an autosomal recessive disorder in which gene mutations on chromosome 1q22 lead to decreased activity of the hydrolytic enzyme glucocerebrosidase in all cells of the body. Three different clinical types can be distinguished, the adult non-neuropathic form (Type 1) is the most common type and occurs predominantly in Ashkenazi Jews. More than 95% of GD patients have type 1 disease.

Table I: Epidemiology of Gaucher disease

Peak age	Any age from birth to old age
Gender distribution	1:1
Prevalence	1/57000 births, more common in Ashkenazi Jews
Transmission	Autosomal recessive

CLINICAL MANIFESTATIONS OF TYPE 1 GAUCHER DISEASE

Symptomatic patients have mainly visceral involvement, bone disease and bleeding. Splenomegaly and hypersplenism leads to cytopenias. Bone marrow infiltration leads to osteopenia, fractures and bone pain.

The major clinical manifestations are depicted in table II.

Table II

Clinical Manifestation	Frequency at presentation (%)
Splenomegaly	85
Hepatomegaly	63
Thrombocytopenia	68
Anaemia	34
Bleeding	Common
Osteopenia	55
Bone pain	33
Pathologic fractures	7
Bone crisis	7
Growth retardation	36

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of GD depends upon the presenting symptoms and signs. Splenomegaly and thrombocytopenia can result from many disorders, namely leukaemia, lymphoma, rheumatoid arthritis or other storage diseases such as Niemann-Pick. On the other hand osteopenia, pathologic fractures, osteonecrosis and bone pain are features of a variety of diseases.

Table 3: Differential diagnosis of radiologic features of type 1 Gaucher disease

Erlenmeyer flask deformity	Diffuse or localized osteopenia
Niemann-Pick disease	Osteoporosis (idiopathic, corticosteroid induced)
Pyle disease	Hyperparathyroidism
Fibrous dysplasia	Hemoglobinopathies
Hyperthyroidism	Neoplastic disorders (multiple myeloma)
Haemolytic anaemias (thalassemia)	
Leukaemia	
Osteopetrosis (Albers-Schönberg disease)	
Heavy metal poisoning	
Rachitism sequelae	
Fracture sequelae	
Osteosclerosis	Osteonecrosis
Osteosclerotic skeletal metastasis	Hemoglobinopathies (sickle cell anaemia)
Phacomatosis (tuberous sclerosis)	Hypercorticism
Osteopetrosis	Caisson disease
Mastocytosis	Collagen vascular disorders
Osteomyelofibrosis	Pancreatitis
Hodgkin's disease	
Hemoglobinopathies	

MANAGEMENT

The current recommendations for the initial evaluation of Type 1 GD have been elaborated by the Gaucher registry coordinators:

1. History and pedigree
2. Comprehensive physical examination

3. Quality of life questionnaire
4. β -Glucocerebrosidase activity and genotyping
5. Primary blood test: haemoglobin and platelets
6. Biochemical markers of the disease: chitotriosidase, angiotensin converting enzyme and plasma tartrate resistant acid phosphatase
7. Additional blood test: white cell count, haemostasis testing, serum immunoelectrophoresis, liver enzymes, calcium and phosphorus values
8. Assessment of visceral involvement: spleen and liver (MRI or CT)
9. Assessment of skeletal involvement
 - a. Radiographs of the femora and spine
 - b. MRI of the entire femora
 - c. Dual energy x-ray absorptiometry of the lumbar spine and femur
10. Assessment of cardio-pulmonary involvement: electrocardiogram, chest radiograph, Doppler echocardiogram for measurements of right ventricular systolic pressure.

THERAPEUTIC GOALS

Following a consensus conference, treatment goals in Gaucher's disease are increasing survival, prevention of irreversible damage, elimination of symptoms, and improvement of overall health and quality of life. The following goals for skeletal involvement are recommended:

- Lessen or eliminate bone pain within 1-2 years
- Prevent bone crisis
- Preventing osteonecrosis and subchondral joint collapse
- Improve bone mass

TREATMENT

As many therapies are now available, choosing the right one (ERT or SRT) is a new challenge.

Enzyme replacement therapy (ERT) has been used for more than two decades. Three forms of macrophage targeted glucocerebrosidase are now available (imiglucerase, velaglucerase alfa and taliglucerase alfa). Glucocerebrosidase infusions reverse the haematological complications and hepatosplenomegaly within 12-20 weeks although bone response requires a longer period. Bone pain, bone crisis and osteonecrosis are reduced. Low dose or intermittent dose regimens fail to achieve sustained improvement and treatment for 2-3 years is currently recommended.

Substrate reduction therapy (SRT) is an oral alternative treatment. Miglustat, an iminosugar that decreases substrate synthesis, is approved for patients with mild to moderate GD 1 who are intolerant of imiglucerase. Eliglustat, a ceramide analogue that inhibits glucosylceramide synthase, has been recently approved as a first line treatment for adults (> 18 years) with GD1 who are CYP2D6 extensive, intermediate or poor metabolizers. Substrate reduction therapy reduces hepatic and splenic volume, the incidence of bone pain and also increases platelet counts.

Symptomatic treatments with bone remodelling drugs (alendronate) and orthopaedic surgery are often required. Splenectomy is rarely considered now that enzyme therapy is available.

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IN-DEPTH DISCUSSION II

Screening for hereditary haemochromatosis

Introduction:

Hereditary haemochromatosis (HH) is defined as the phenotypic expression of iron overload due to mutations in the HFE gene on both copies of chromosome 6 (Pietrangelo, 2010). This leads to excessive absorption of iron from food. In Western Europe over 90% of patients with HH are homozygous for the C282Y mutation of the HFE gene and another 4% are compound heterozygotes (C282Y/H63D). There are other rarer forms of HH where patients have 'classical' clinical features of haemochromatosis but lack known mutations in the HFE gene.

Table 1: Reversibility of HH features by phlebotomy

Reversible manifestations
• Heart: cardiomyopathy, conduction disturbances
• Liver: elevated liver function tests, hepatomegaly
• Skin: bronzing (melanin deposition), grey pigmentation (iron deposition)
• Infection: <i>Vibrio vulnificus</i> , <i>Listeria monocytogenes</i> , <i>Pasteurella pseudotuberculosis</i>
Irreversible manifestations
• Liver: cirrhosis, hepatocellular carcinoma
• Pituitary gland: gonadotropin insufficiency leading to secondary hypogonadism*
• Pancreas: diabetes mellitus
• Thyroid gland: hypothyroidism
• Genitalia: primary hypogonadism
• Joints: arthropathy, CPP deposition

Without treatment, excessive iron storage cause hepatic cirrhosis and other serious conditions including diabetes, cardiomyopathy and arthritis. HH becomes symptomatic from the age of around 40 onwards. Routine bloodletting to maintain appropriate serum iron levels is a simple yet effective means by which to prevent these complications. However, in symptomatic HH patients bloodletting is not completely curative. Some symptoms are (partly) reversible, while others manifestations are irreversible (see table 1). Taking into account that mortality in HH is highly correlated with the presence of irreversible manifestations like diabetes and liver cirrhosis this pleads for prevention.

Prevention

Prevention of HH-related morbidity and mortality warrants an early diagnosis. Since people homozygous or compound heterozygotes for the HFE gene mutation comprise 90% or more of the HH patients, accounting for approximately 6‰ of the general population, population screening is an option. Even more, screening of the first degree relatives of a symptomatic HH patient is highly effective. However, the disease shows relatively low penetrance, and many homozygotes never develop clinical symptoms. So demonstration of genetic susceptibility for HH will alarm many people who are unaware of possible disease and some never will become symptomatic. Indeed in studies on population or family screening for HH the willingness to participate was

limited and anxiety increased. The acquaintance with the disease HH, probably explains the higher willingness for participation in family studies (over 50%) as compared to studies in the general population (approximately 25%). Although not intended, the knowledge of having the HFE gene mutation even in the absence of increased serum iron concentration might have negative consequences for employability as well as for insurability. Although the relevant legislation differs across countries, and in many parts of Europe discrimination based on available genetic data is prohibited, negative consequences cannot be excluded totally.

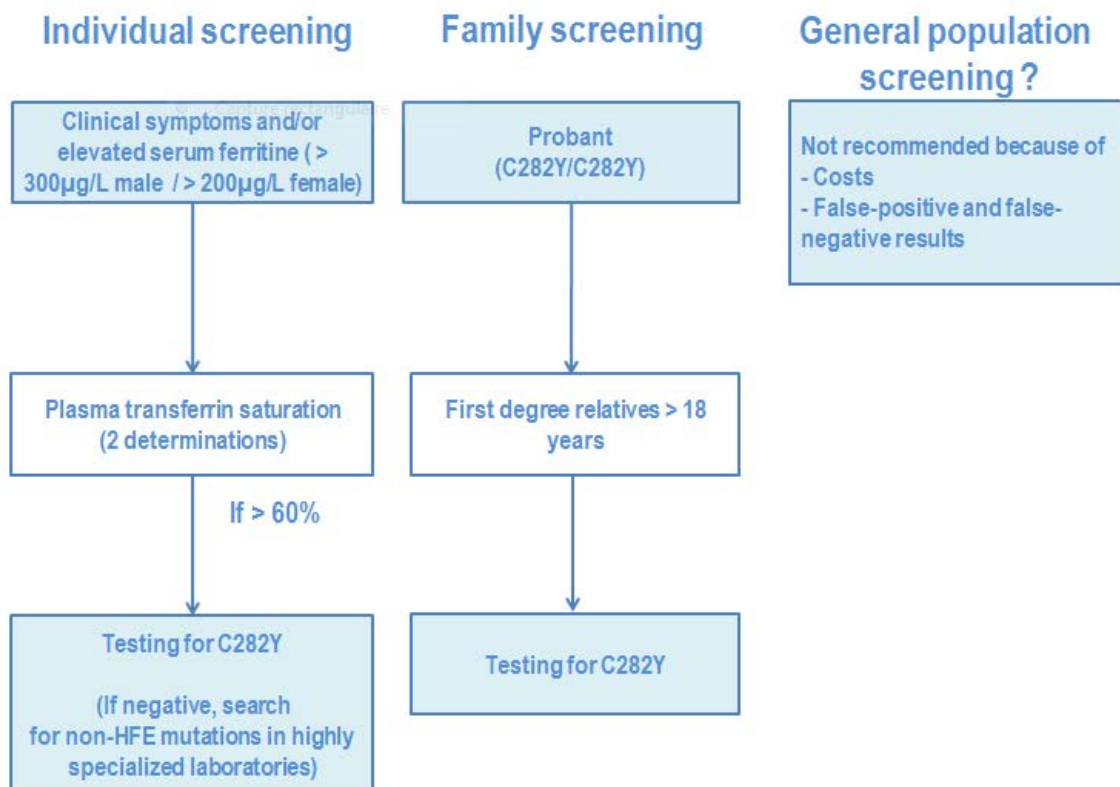
General population screening:

Population screening for HH has been recommended by some authors, due to the high prevalence of the mutant allele coupled with the low cost and high efficacy of early diagnosis and treatment compared with that for late-stage diagnosis. However, even for a simple genetic condition like HH, screening the general population is not straightforward. Since characterization of the HFE gene in 1996 (Feder et al, 1996), genetic testing has become available.

A person carrying two copies of the C282Y mutation or the compound heterozygote combination C282Y/H63D is at risk of developing iron overload and subsequent disease. However, like all diseases, HH is not only defined genetically and not every patient with the HFE mutation will develop the disease. At present it is difficult to predict if an individual patient with a HFE mutation will ever become symptomatic. The key factors in considering population screening are whether it will do more benefit than harm and whether it is cost-effective.

The present available genetic tests identify nearly 95% of patients with HH permitting early identification of those at risk for iron overload.

If the clinical penetrance is such that the majority of people who are C282Y homozygous eventually accumulate iron, the most logical approach will be to screen all adults by genetic testing and to follow those at risk by measuring ferritin or transferrin saturation at 3-yearly intervals (See fig 1). However, in non-northern European populations, HH is rare and the C282Y mutation is not associated with the disease so testing the general population would be inappropriate, and additional decisions may have to be made about selective testing. Moreover, even in the northern European population, the clinical penetrance is low, so a systematic genetic screening could lead to incorrect diagnosis in many people. This could be harmful and cause problems with obtaining medical insurance. The population genetic screening is therefore not recommended because it could lead to more harms than benefits (EASL, 2010; Whitlock et al, 2006; Powell et al, 2016; Brissot et Loréal, 2016). The alternative, regular testing of transferrin saturation or ferritin concentration, provides many false positive results as well as false negative results (subjects with mutation of the HFE gene who have not yet accumulated iron).

Figure 1: Algorithm genetic testing for HFE mutation.

Family screening

Screening first degree relatives of patients diagnosed with HH is another option.

The value of testing for the C282Y mutation in relatives remains unclear, because of the unknown risk of developing clinical disease in C282Y homozygotes. Disease penetrance in the absence of comorbid factors may be low, although the iron overload of first degree relatives with the genotype at risk may be predicted by the disease severity in the index patient (Powell et al, 2016; Brissot et Loréal, 2016). Moreover, the acceptability of the test is certainly better in relatives of an affected patient than in the population at large and the overall efficiency of the test to detect HH patients is much better in relatives than in the population at large, as C282Y homozygotes are much more frequent. The current standard of care is therefore to propose screening of first degree relatives for the C282Y mutation (EASL, 2010), by informing the affected patient of the availability of the test and asking him to inform his relatives. Because the first symptoms develop in adulthood, the choice of testing in children is usually postponed until they become adult and can decide for themselves (Brissot et Loréal, 2016; Porto et al 2016). For patients with two or more children, the most cost-effective approach may be to test the patient's spouse first, and to then test the children only if the spouse is heterozygous. For one child, direct testing is more cost-effective (El-Serag et al, 2000). C282Y homozygotes should undergo monitoring of their iron parameters (serum transferrin saturation and serum ferritin) and phlebotomy should be started if iron overload develops (fig 1). The value of testing for other mutations than C282Y is more

arguable, because the chance of finding the H63D mutation is high, as its population frequency is 20 %, and because documented iron overload in C282Y/H63D compound heterozygote is rare (Gurrin et al, 2009).

Conclusion

Early diagnosis of HH is of the outmost importance, since the prognosis of the disease is much improved by early treatment. The rheumatologist has here a key role to play as joint involvement is frequently an early feature of the disease. Once the diagnosis is made he has to inform his patient about the availability of family screening and the opportunity to prevent development of the disease in his family.

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Skin and auto-immune rheumatic diseases

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LEARNING OBJECTIVES

- Identify the different types of skin manifestations in lupus erythematosus
- Assess the risk of systemic involvement in the different variants of cutaneous lupus erythematosus
- Identify possible conditions associated with subacute cutaneous lupus erythematosus
- Initiate treatment of skin manifestations in patients with lupus erythematosus
- Identify thrombotic vascular skin lesions in patients with systemic lupus erythematosus
- Identify skin lesions in dermatomyositis
- Correlate some of the dermatomyositis skin manifestations to a specific antibody profile and/or systemic disorder
- Identify type of skin involvement in the different forms of scleroderma
- Identify skin manifestations found in systemic vasculitis
- Recognize the most frequent and the most typical skin lesions of the different systemic vasculitides
- Assess skin conditions associated with rheumatoid arthritis and Still's disease
- Identify the cutaneous side effects of antirheumatic drugs including biologics

This chapter focuses on cutaneous manifestations observed in autoimmune rheumatic diseases, particularly lupus erythematosus (LE), dermatomyositis (DM), scleroderma, the main systemic vasculitides and rheumatoid arthritis. Clinical correlation between these manifestations and internal organ involvement is highlighted. See box 1 for definitions of skin manifestations.

Box 1 Definitions

- Alopecia: absence of hair from a normally hairy area
- Aphtha: small superficial and painful white ulceration of the mucosa, single or multiple, round or oval, lasting 7 to 14 days and healing without scarring (syn.: canker sore)
- Atrophy: thinning of normal skin. It may affect the epidermis, dermis or subcutaneous tissues.
- Bulla: rounded protrusion due to accumulation of fluid within or beneath the epidermis (greater than 0.5 cm to 1 cm in diameter)
- Ecchymosis (bruise): area of cutaneous haemorrhage more than 2 mm in diameter; usually this term is employed when referring to large (> 2 cm) lesions.
- Erosion: superficial loss of epidermis, which heals without scarring. It commonly follows a blister.
- Erythema: redness of the skin produced by vascular congestion or increased numbers of capillaries
- Excoriation: linear erosion or ulcer produced by scratching
- Exfoliation: splitting off the epidermal keratin in scales
- Fibrosis: formation of excessive fibrous tissue; this is a pathological finding and its most common clinical consequence is induration of skin sometimes also referred to as sclerosis, though the usage of this latter term should also be restricted to pathology reports.
- Fissure: any linear gap or slit in the skin surface
- Keratoderma: horny thickening of the skin, usually referring to palms and/or soles
- Macule: circumscribed alteration in the colour of the skin. It can be any colour or shape.
- Milium: tiny white cyst in the epidermis containing keratin
- Nodule: solid mass in the skin, more than 1 cm in diameter. It may involve the epidermis and dermis, dermis and hypodermis, or hypodermis alone.
- Papule: circumscribed palpable elevation, less than 1 cm in diameter
- Petechia: punctate haemorrhagic spot, approximately 1–2 mm in diameter
- Plaque: elevated area of skin, 1 cm or more in diameter, usually flat. It may be formed by the extension or coalescence of papules.
- Purpura: haemorrhagic area in the skin. Purpura does not blanch when touched. Petechia and ecchymoses are variants of purpura.
- Pustule: vesicle filled with pus
- Scale: flat plate or flake of stratum corneum (adjectives: scaling and squamous, but the latter term is usually restricted to histopathological descriptions)
- Scar: replacement by atrophic and/or fibrous tissue of another tissue that has been destroyed by injury or disease
- Ulceration: loss of epidermis and dermis, often with loss of the underlying tissues; if chronic: ulcer
- Vesicle: small bulla, less than 0.5 to 1 cm in diameter
- Weal: circumscribed, often confluent papule or plaque because of dermal oedema, white or reddish, compressible and per definition transient

1 Skin manifestations in lupus erythematosus

Skin manifestations are a main feature of lupus erythematosus (Werth, 2007*). They are present in more than 80% of cases. The Systemic Lupus International Collaborating Clinics (SLICC), an international group focused on systemic lupus erythematosus (SLE) clinical research, revised the American College of Rheumatology (ACR) classification criteria for SLE in 2012 (Petri et al, 2012*; Yu et al, 2014*).

Notably, 4 of the 11 clinical criteria for SLICC are dermatological criteria:

1. Acute or subacute cutaneous lupus erythematosus; also included: bullous SLE, toxic epidermal necrolysis variant of SLE
2. Chronic lupus erythematosus (CLE): numerous clinical variants
3. Oral (or nasal) ulcers
4. Non-scarring alopecia

Skin lesions of patients with LE can be divided into 4 groups (Lipsker, 2010*): specific lesions of lupus erythematosus, lesions reflecting thrombotic vasculopathy/vasculitis, neutrophilic cutaneous lupus erythematosus and miscellaneous lesions associated with lupus erythematosus. Lupus erythematosus should be considered as a continuous spectrum of variants with single organ lesions such as cutaneous lesions at one end (but renal variants also exist) and serious multi-organ disease at the other.

A precise dermatological diagnosis is very important as skin features not only help to identify the disease, but can also in many cases bear prognostic signification and involve specific therapeutic interventions.

1.1 Specific lesions of lupus erythematosus

They allow establishing a diagnosis of LE even when the ACR/SLICC criteria are not met, by clinico-pathological correlation of the organ skin. This is possible because all these so-called *specific lesions* display a common histopathological finding, namely an *interface dermatitis*. The latter corresponds to a lymphocytic infiltrate in the upper dermis, at the dermal-epidermal junction, with vacuolization of keratinocytes, keratinocyte necrosis, pigment incontinence and epidermal atrophy. Definition of the type of specific lesion should take into account the appearance, the site and the course of the lesion, its histological findings as well as the associated systemic signs and immunological abnormalities. Specific lupus lesions were traditionally separated in three main entities, namely acute, subacute and chronic lupus erythematosus (Walling and Sontheimer, 2009*). However, this does not reflect the more complex reality and a comprehensive and practical classification based on clinico-pathological correlation on one hand, and highlighting the importance of thrombotic and neutrophilic lesions on the other, has been proposed (Lipsker, 2010*). This newer classification is now increasingly

accepted. This classification separates the specific lesions according to the main level of anatomical skin involvement: dermo-epidermal, dermal and hypodermal. For historical reasons, the three main types of dermo-epidermal CLE will be first reviewed in detail.

1.1.1 Acute cutaneous lupus erythematosus

1.1.1.1 Clinical features

A *congestive erythema*, often mildly raised, mostly without skin surface alteration, with ill-defined borders, is the primary lesion of acute CLE. Acute cutaneous lupus erythematosus (ACLE) has one of the following presentations: malar erythema (does not count as SLICC criteria if chronic lupus erythematosus is also present), maculo-papular rash (mainly on photo-exposed areas), bullous lesions, and a toxic epidermal necrolysis (TEN)-like lupus rash. In ACLE, the lesions tend to be transient, following sun exposure; itching does usually not occur but a burning sensation is sometimes reported. An erythematous slightly oedematous rash over the cheeks, sparing the nasolabial folds, and across the bridge of the nose (a malar or 'butterfly' rash) is the most typical eruption. This localised eruption may also affect the forehead, the peri-orbital area, the neck and the low neckline (figure 1). In contrast to discoid LE, atrophy and follicular plugging are absent.

Figure 1 Oedematous and erythematous 'butterfly' rash. Patient consent obtained.

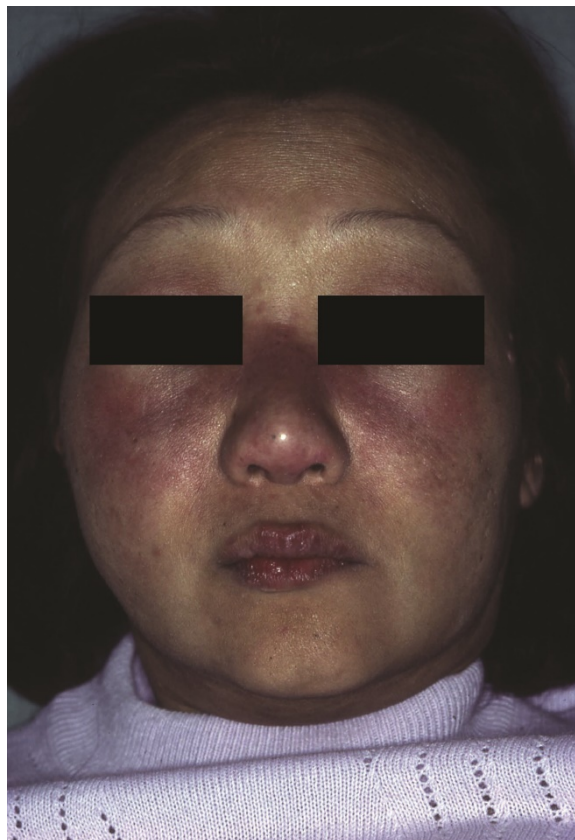


Figure 2 Macular lesions over the dorsum of the hands.



A more diffuse eruption can sometimes occur, mainly after sun exposure, with pruriginous maculo-papular lesions, especially above the waistline and resembling a drug reaction. Some scattered macular lesions can also be found over the dorsum of the hands (figure 2). Dermatomyositis (DM) should be excluded, but LE classically respects the articular surfaces of the back of the fingers, that are typically involved in dermatomyositis. Photosensitivity alone without skin lesions is no longer a diagnostic criterion for SLE because although it is present in about 60% of patients with SLE, it can be also found in normal subjects (20% of healthy people in Sweden), and it is difficult to establish a consensual definition.

Occasionally, *blistering* may complicate very acute forms, with bullous lesions predominating on erythematous skin (figure 3). This must be distinguished from bullous SLE, which is the consequence of a neutrophilic dermal infiltrate and not an interface dermatitis. Rarely, widespread erythema with a positive Nikolski sign (skin detachment on pressure) mimicking TEN is found in hypercube variants of LE. Erosive *oral lesions* are frequent, especially in case of renal involvement. The numerous types of bullous lesions and surface alterations in LE have been extensively reviewed by Merklen-Djafri et al. (2015*).

Figure 3 Bullous lesions in extremely acute lupus erythematosus.



All ACLE lesions heal without scarring, but sometimes with dyspigmentation.

1.1.1.2 Differential diagnosis

ACLE can be clinically confused with various facial dermatoses, especially rosacea (figure 4) characterised by telangiectases, with papules and pustules that are not found in ACLE, and with seborrheic dermatitis (figure 5) that mainly affects the naso-labial folds. Those 2 disorders are extremely common (2 to 3% of the general population). DM should be also considered in the differential diagnosis, but it is characterised by more intense purplish-red erythema and oedema of the upper eyelids, and DM lesions often itch. Both lupus erythematosus and DM can present with lesions on the dorsal aspect of the hands; in lupus erythematosus, the lesions mainly affect the inter-articular skin, while in DM they affect the skin over the joints.

Figure 4 Rosacea. Patient consent obtained.



Figure 5 Seborrheic dermatitis. Patient consent obtained.



Widespread eruption can resemble contact dermatitis, viral exanthema or a drug reaction.

1.1.2 Subacute cutaneous lupus erythematosus

1.1.2.1 Clinical features

Subacute cutaneous lupus erythematosus (SCLE) has two clinical subtypes: the maculo-papular lesions can present with 1) an annular shape or 2) a psoriasis-like pattern. In the first case, the lesions are polycyclic. Borders are erythemato-squamous and may show vesiculation and crusting. They surround a grey-white hypopigmented and teleangiectatic area (figure 6). In the psoriasis-like pattern, lesions are papulo-squamous (figure 7). Both manifestations can be seen in the same patient and the relevance of this distinction is thus low. SCLE lesions are superficial without prominent follicular plugging or hyperkeratosis. This type of cutaneous lupus is usually very photosensitive, with lesions confined to sun-exposed skin. However, the midfacial skin is usually spared, while the sides of the face, the V of the neck, the upper trunk, and extensor aspects of the upper extremities are commonly involved.

Figure 6 Subacute annular cutaneous lupus erythematosus lesions.



Figure 7 Subacute psoriasis-like cutaneous lupus erythematosus lesions.



Lesions can frequently leave pigmented or hypopigmented macules and telangiectases, but usually resolve without scarring, in contrast to the situation in discoid lupus erythematosus (DLE).

Oral erosive lesions are less frequent and do not correlate to any internal involvement.

1.1.2.2 Differential diagnosis

Differential diagnoses include dermatophytosis, nummular eczema, erythema multiforme, psoriasis, pityriasis rosea and drug eruption. Histological examination can easily distinguish SCLE from all these dermatoses except from drug eruption and a huge number of SCLE flares are triggered by drugs, especially calcium-channel inhibitors, proton-pump inhibitors, terbinafine and hydroxychlorothiazide.

1.1.2.3 Associations

- In approximately 80% of patients with SCLE, anti-Ro/SS-A antibodies are found on ELISA, immunoblot or more sensitive solid phase immunoassays.
- Newborns with neonatal lupus and many patients with inherited complement deficiencies have the same clinical SCLE features. Neonatal lupus erythematosus is a form of SCLE that occurs in newborns

whose mothers have anti-Ro/SS-A autoantibodies and usually manifests with erythematous annular patches, with the butterfly rash or with cardiac conduction abnormalities.

- SCLÉ is frequently (up to 50% of patients) associated with Sjögren's syndrome.
- Drug-induced lupus presents most frequently with SCLÉ lesions, therefore a careful drug history must always be performed (see 1.1.8).

1.1.3 Chronic lupus erythematosus

Discoid lupus erythematosus (DLE) is the most common type of chronic LE. Typical DLE (figure 8) demonstrates well-defined plaques with 4 primary lesions.

Two are features of active lesions:

- Erythema with well-demarcated borders and sometimes central telangiectasias;
- Adherent scales (keratosis) with follicular plugging, thus a rough surface on palpation.

Two others reflect damage:

- Atrophy, with a thinning of the skin that becomes fragile and translucent, and
- Pigmentary changes where hypo- and hyperpigmentation can coexist.

Lesions are often multiple and symmetrical. They are mainly localised on UV-exposed areas, especially over the bridge of the nose, the cheeks, the ears and the side of the neck. Even unexposed areas like the eyebrows, eyelids and scalp can be affected. Involvement of the scalp can be found in up to 60% of patients with DLE and are they are the only manifestation in 10% of cases, causing permanent cicatricial alopecia (figure 9). Lesions resolve leaving a sepia coloured hyperpigmentation.

DLE can be localised or disseminated. Localised DLE affects the head and the neck, whereas disseminated DLE extends to other areas of the body such as the trunk and the limbs, particularly the elbows and the dorsa of the hands and feet, especially in patients with complement deficiencies. Lesions of the palms and soles are erosive, painful and extremely disabling; they can evolve into a scleroderma-like atrophy of the digit. Nail changes are rare and occur with lichen-like dystrophies. Oral lesions have clinical and histological features hard to distinguish from lichen planus, i.e. white papules on a red atrophic background with irradiating white striae on the border.

Figure 8 Discoid lupus erythematosus.



Figure 9 Scarring alopecia in discoid lupus erythematosus.



Hypertrophic (or verrucous) DLE is an unusual variant characterised by thick scaling/keratosis over the discoid lesion or occurring at the periphery of the discoid lesion. The lesions are often located on the extensor arms, but the face and upper trunk may also be involved. Some variants are indistinguishable from inflammatory keratoacanthoma centrifugum marginatum.

1.1.4 Other forms of dermo-epidermal lupus (indeterminate lupus, chilblain lupus, bullous lupus)

1.1.4.1 Indeterminate lesions of lupus erythematosus (Sontheimer RD, 1997*)

This entity first described by Sontheimer corresponds to isolated erythematous plaques often located on the trunk, devoided of clinical characteristics of either ACL, SCLE or DLE (scaling, atrophy, follicular plugging), but with a typical histological aspect of interface dermatitis.

1.1.4.2 Chilblain lupus erythematosus

Chilblain LE (fig 10) can correspond to 2 situations. First, acral located LE lesions, with a typical interface dermatitis, but mimicking clinically chilblain. Second, chilblain lesions without interface dermatitis, where lesions can't be distinguished from idiopathic chilblain / perniosis (i.e. erythematous or purplish, infiltrated papules or plaques localized on fingers, toes, ears and nose). In this case, helpful clues to separate those 2 entities are: the persistence of the lesions during the warm season clinically and vacuolization of keratinocytes pathologically which, if present, are suggestive of chilblain LE while oedema, spongiosis and perieccrine infiltrate are more common in classic pernio. Chilblain LE is frequently associated with DLE lesions, and also with systemic signs of LE in approximately 20% of cases; it is difficult to treat and poorly responsive to antimalarials (Chasset et al, 2017). Confusion with “vasculitis” is frequently made by non-dermatologists.

Familial chilblain lupus is a monogenic form of cutaneous LE resulting from mutations of genes involved in the activation of type 1 interferon (*TREX1*, *SAMDH1*, *STING*), exemplifying the concept of interferonopathy.

Figure 10 Chilblain lupus erythematosus.



1.1.4.3 Bullous lupus erythematosus

Bullous LE is a rare auto-immune blistering disease affecting young adults and sometimes children with a known SLE. It is characterized by the presence of antibodies directed against collagen VII, an important component of the cutaneous basement membrane. Bullous LE manifests as tense vesicles or bullae on a normal or erythematous background, located on the trunk and extensor aspect of the limbs, without significant pruritus. Mucosa can be involved, especially the lip. Lesions spontaneously heal without scarring, but hyper- or hypopigmentation is generally present and may take months to resolve.

Bullous LE is a neutrophil-mediated form of cutaneous lupus and dapsone is the treatment of choice, not antimalarials.

1.1.5 Dermal lupus erythematosus

Dermal LE is a spectrum of lesions with consistent overlap that share clinical and histological characteristics, associated with a rather good prognosis as in DLE, even if rare aggressive systemic complications may occur. The spectrum of dermal lupus erythematosus encompasses a rather cellular form of dermal LE, with dense “sleeve-like” perivascular and periadnexal infiltrate, with no or slight mucin deposition (Jessner type) to a paucicellular form with substantial mucin deposition and no or slight infiltrate (papulonodular mucinosis type/cutaneous lupus mucinosis type).

1.1.5.1 Lupus tumidus (sometimes referred to as intermittent lupus erythematosus)

Lupus tumidus (figure 11) is characterised by sharply demarcated red-purple oedematous plaques in sun-exposed skin of the face and the upper trunk, without scale or follicular plugging. Those lesions are usually highly photosensitive. Healing occurs without scarring or alopecia.

Figure 11 Sharply demarcated red-purple oedematous plaques. Patient consent obtained.



1.1.5.2 Jessner's lymphocytic infiltrate of the skin

JLI is another variant of dermal LE which typically presents with multiple red papules and plaques with frequent annular or arciform configuration and/or arrangement, without scale or follicular plugging and less prominent oedema than lupus tumidus. Lesions are located on the head, neck and upper part of the thorax. Distinction with borreliac lymphocytoma may be difficult. It is often not possible to distinguish JLI from lupus tumidus.

1.1.5.3 Cutaneous lupus mucinoses (papulonodular mucinosis, reticulate erythema with mucinosis/REM)

Both entities are histologically characterized by abundant interstitial deposits of mucin, with a less prominent lymphocytic infiltrate (figure 12). Papulonodular mucinosis present with red firm nodules sometimes resulting in non-scarring alopecia on the scalp. REM present with reticulated pink to red macules or flat plaques on the chest with symmetrical distribution and midline involvement. For some authors, REM should not be considered as a variant of lupus erythematosus, but as a separate entity (Cinotti E et al, 2015*).

Figure 12 Papular mucinosis in systemic lupus erythematosus.



1.1.6 Hypodermal lupus (lupus panniculitis)

Lupus erythematosus profundus or lupus panniculitis (figure 13) is a rare hypodermic manifestation of LE. It appears as single or multiple indolent to sometimes painful subcutaneous plaques or nodules that may sometimes ulcerate, which evolve to a characteristic cupuliform depression resulting from secondary atrophy of the subcutaneous tissue (figure 14). The main localisations are the upper arms, the shoulder girdle, the breast in women, as well as the thighs and cheeks. In 70% of cases, lupus panniculitis is associated with DLE lesions, and systemic involvement may occur in approximately 40% of patients. Differential diagnoses include all other types of panniculitis and nodular vasculitis.

Figure 13 *Lupus panniculitis.*



Figure 14 *Atrophy in lupus panniculitis.*



1.1.7 Pathology

The various clinical cutaneous types of dermo-epidermal lupus erythematosus show a similar histological picture with interface dermatitis of the vacuolar type and a superficial and deep peri-vascular and peri-adnexal lymphocytic infiltrate in the dermis. Epidermal colloid bodies, corresponding to apoptotic keratinocytes, can be found, especially in SCLE. Interstitial mucin deposition is a good diagnostic clue. The level and intensity of

this infiltrate depend on the subtype, being more intense and deep in DLE than in ACLE. A progressive thickening of the basement membrane is present, which is best seen with a PAS stain.

In ACLE, there is a pronounced oedema of the superficial dermis with liquefying degeneration of the basal cell layer of the epidermis that may lead to blistering in very acute lesions. Hyperkeratosis is not prominent. The mononuclear infiltrate is moderate and often peri-vascular. ACLE can resemble DM on histological features and direct immunofluorescence can show deposits of IgM and C3 in both diseases, although the presence of immunoglobulins and complement at the dermo-epidermal junction in non-lesional skin is found only in ACLE.

In SCLE, epidermal colloid bodies are seen with slight hyperkeratosis and a moderate mononuclear lymphocytic infiltrate. Histological changes may be confused with those of drug eruption.

In DLE, marked orthokeratotic hyperkeratosis is present with plugging of the follicular ostia. A dense dermal lymphocytic infiltrate, particularly present around the appendages, can extend to the lower dermis and lead to skin atrophy. Usually there is less basal vacuolar change, dermal oedema and dermal mucin than in ACLE, and there is more lymphocytic infiltrate compared to ACLE.

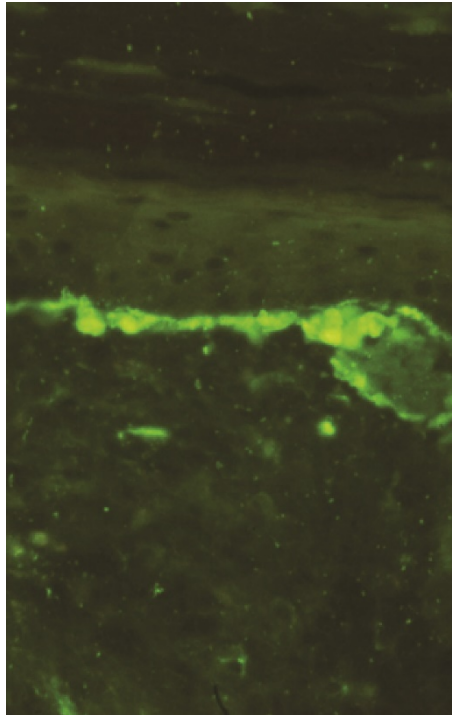
In bullous LE, biopsy from fresh vesicles typically shows junctional blistering associated with a neutrophil-predominant infiltrate in the dermis, without interface dermatitis but with sometimes mucin deposits as a useful clue to the diagnosis.

In dermal lupus (lupus tumidus being the most frequent variant), the epidermis is usually normal without interface dermatitis or if present, it is very mild. The lymphocytic infiltrate is found in the upper and lower dermis in a peri-vascular and peri-adnexal distribution with frequent dermal deposits of mucin.

In lupus panniculitis, the epidermis and dermis may or not have a DLE appearance, which is a help to the diagnosis if present. The hypodermis shows a striking lobular infiltrate of lymphocytes, plasma cells and histiocytes along with nuclear debris, fibrinoid deposits, mucin accumulation, hyalin necrosis of adipocytes and septa hyalinisation. Fibrosis and calcification can occur.

Direct immunofluorescence (DIF) shows linear or granular immunoglobulin (IgG, IgA or IgM) and/or complement (C1q, C3) deposits at the dermo-epidermal junction in 80–90% of cases of ACLE and DLE, 70% of cases of panniculitis and 60% of cases of SCLE (figure 15). In lupus tumidus, direct immunofluorescence may be negative. These deposits, however, are not specific to lupus erythematosus and can be found in DM, some cases of rosacea and on normal sun-exposed skin of 20% of the population (especially IgM). We thus do not use DIF in our routine daily practice because of this low positive predictive value, except for the diagnosis of bullous LE.

Figure 15 Positive direct immunofluorescence in lupus erythematosus.



1.1.8 Laboratory investigations

Lupus erythematosus is characterised by the presence of circulating antinuclear antibodies (ANA). These are rarely found in DLE, but are almost always present in ACLE and in SCLE.

In particular, anti-double strand DNA (dsDNA) antibodies are specific for lupus erythematosus and can also be found in early subclinical cases, antihistone antibodies are a sign of drug-induced lupus and usually disappear 1 year after the causative drug has been discontinued, while anti-La/SS-B and anti-Ro/SS-A antibodies are mostly related to SCLE and Sjögren's syndrome. Anti-collagen VII antibodies may be evidenced by specific ELISA or immunoblotting, with positive results in approximately 70% of patients with bullous LE.

Antiphospholipid antibodies are also frequently found in lupus (Frances et al, 2005*).

Low complement levels (C3, C4, CH50) may be associated with congenital deficiencies of certain fractions or related to consumption, the latter being suggestive of progression to systemic lupus erythematosus.

1.1.7 SLE and the different types of skin lupus

The relationships between the main types of skin lupus and SLE are summarised in table 1.

Table 1 Relationships between the main types of specific skin findings and systemic lupus erythematosus

Type of skin lupus	SLE association (%)	% Of different skin manifestations in SLE series
ACLE	90	60–80
SCLE	50	7–21
DLE	20	20
Panniculitis	40	2–3

ACLE, acute cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

All types of skin lupus can be associated with SLE to varying degrees (table 1). Thus, more than 90% of patients with ACLE have or will develop SLE, skin manifestations being inaugural in 50–60% of cases. Inversely, 60–80% of patients with SLE had or have ACLE lesions. These lesions very often develop together with systemic flares so that organ involvement must be searched for thoroughly.

According to the ACR/SLICC criteria, more than 50% of patients with SCLE have SLE. In fact, most patients with SCLE do not have severe systemic involvement that would justify treatment with systemic steroids or immunosuppressive treatment. Severe and life-threatening renal or neurological conditions can be found in only 10% of patients with SCLE. Inversely, 7–21% of patients with SLE have SCLE lesions.

Overall, 10–20% of patients with DLE have or will develop SLE and 15–30% of those who have SLE present DLE skin type lesions, which are inaugural in 5% of cases. Premenstrual or gestational flares as well as disseminated DLE might increase this risk.

About 40% of patients with lupus panniculitis could develop SLE. However, panniculitis is reported in less than 3% of patients with SLE.

1.1.8 Drug-induced lupus erythematosus

Similar to idiopathic lupus erythematosus, drug-induced lupus erythematosus (DILE) can manifest with ACLE, SCLE and DLE lesions; SCLE lesions are the most frequent. The drugs most often implicated in the development of ACLE-type lesions are hydralazine, procainamide, isoniazid and minocycline and the recently reported tumour necrosis factor (TNF)- α antagonists. Most cases of DILE induced by anti-TNF- α antagonists are caused by infliximab, followed by etanercept and adalimumab. Drugs associated with SCLE include calcium channel blockers, angiotensin-converting enzyme inhibitors, thiazide diuretics, terbinafine, carbamazepine, statins, proton pump inhibitors and TNF- α antagonists. Drug-induced DLE is very rarely described in the literature and usually associated with fluorouracil agents, methimazole or TNF- α antagonists. Moreover, anti-TNF- α antagonists frequently induce the production of ANA and anti-dsDNA autoantibodies without clinical signs of LE.

The typical laboratory profile of acute DILE consists of positive ANA and antihistone antibodies, the latter being regarded as the serum marker of this subset, whereas in drug-induced SCLE ANA and anti-Ro/SSA antibodies are present but antihistone antibodies are uncommon. In drug-induced DLE, ANA are usually negative. If DILE is clinically possible, drug discontinuation may help alleviate LE and also serve as a diagnostic test, whereby LE improvement would suggest the drug has a role. Most DILE cases spontaneously resolved within weeks of drug withdrawal, but autoantibodies could be present for months after treatment discontinuation.

1.1.9 Other associations

All cutaneous forms of lupus erythematosus can be associated with other autoimmune systemic diseases, but at unknown frequencies.

Some 3–50% of patients with SCLE develop Gougerot-Sjögren syndrome with an increased frequency in patients over 55 years of age. This association increases the risk of cutaneous vasculitis, central nervous system involvement and interstitial pulmonary syndrome. Annular eruptions reported in the Japanese literature to be associated with Gougerot-Sjögren syndrome and anti-SS-A, SS-B antibodies may resemble lupus tumidus lesions.

1.1.10 Treatment of lupus erythematosus lesions

European guidelines on the treatment of cutaneous lupus erythematosus have been recently published (Kuhn et al, 2017*), though the suggested strategy is not the one performed in most French reference centres. Sun protection is extremely important in all types of lupus. All patients should be advised to wear a broad-brimmed hat and avoid short-sleeved shirts and shorts. Moreover, sunscreen should be used permanently even when sun exposure is not expected. Patients should repeat sunscreen application every 2 hours when in the sun as the sun protection factor (SPF) does not take immersion or sweating into consideration. SPF 50 sunscreens and light reflecting sunscreens providing greater protection against UVA and UVB are more effective. However, it is also important to consider the risk of vitamin D deficiency in sun-avoiding patients, as sunlight is required for vitamin D synthesis. 25-Hydroxyvitamin D levels should be monitored and supplementation with vitamin D3, or cholecalciferol, is advised. Cessation of smoking is important, as cigarette smoking is an established risk factor of cutaneous lupus. Avoidance of mechanical stress (isomorphic trigger factors) should be recommended.

Topical treatment is frequently used as a first-line therapy in limited lesions (Walling and Sontheimer, 2009*), though it is rarely sufficient. It can be combined with antimalarials in case of partial response or diffuse lesions. High-potency steroid creams are effective, but should be avoided as long-term treatment of facial lesions.

Tacrolimus and pimecrolimus, two topical immunomodulators, are moderately effective in SCLE and lupus tumidus. Topical retinoids are of help in hyperkeratotic lesions.

Antimalarials are first-line treatment for cutaneous lupus erythematosus (Chang and Werth, 2011*).

Hydroxychloroquine (HCQ) and chloroquine sulfate (CQS) are most widely used. HCQ is often preferred to CQS since it is thought to cause less ocular toxicity and blood dosages to assess efficacy are more easily available. Efficacy assessment should be performed after 4 to 6 months of treatment, when clinical improvement is expected in more than 60% of patients (Chasset et al, 2017). The mechanism of action of oral antimalarials in skin lupus is not exactly known and probably includes photoprotection as well as anti-inflammatory and immunological effects. HCQ should be maintained during pregnancy where it prevents flares. As the most serious side effects are ocular manifestations and regular ophthalmological follow-up to detect toxicity before significant vision loss is essential. In the revised American recommendations on screening for CQS and HCQ retinopathy (Marmor et al, 2016*), the recommended dosage of HCQ to minimize ocular toxicity is ≤ 5.0 mg/kg real weight, and CQS ≤ 2.3 mg/kg real weight (which is inferior to the widely use dosing of 6.5 mg/kg for HCQ and 4 mg/kg for CQS). A baseline eye examination is required during the first year of treatment, with annual screening starting only after 5 years of treatment in the absence of major risk factors (box 2). The baseline screening should include automated visual fields and spectral-domain optical coherence tomography (SD-OCT). These examinations may be completed with tests not widely available such as multifocal electroretinogram and fundus autofluorescence. The frequency and type of eye examinations used in screening for retinopathy are determined by ophthalmologists and vary by country. HCQ and CQS should never be combined because of enhanced ophthalmological toxicity.

Box 2 Recommendations for ophthalmological screening of patients treated with antimalarials

Frequency of evaluation

First year of use: fundus examination, completed with visual fields and SD-OCT if abnormalities

Annually after 5 years in low-risk patients:

- daily dosage of HCQ ≤ 5.0 mg/kg real weight (≤ 2.3 mg/kg real weight if CQS)
- normal glomerular filtration rate
- no concomitant tamoxifen use
- no pre-existent macular disease

More frequent in patients with major risk (frequency to be determined by the ophthalmologist):

Examination by the ophthalmologist

Examination should include assessment of:

- automated visual fields (wider test patterns are needed for Asian patients);
- SD-OCT

SD-OCT: spectral-domain optical coherence, HCQ: hydroxychloroquine, CQS: chloroquine

Other side effects include pigmentation of the oral mucosa (figure 16), nails and legs, greying of the hair and, less commonly, aquagenic pruritus, urticaria, maculo-papular rash and vasculitis. If patients do not respond to

antimalarials, they may not have taken the medication as prescribed e.g. because of nausea or the bitter taste of antimalarials. Assessing blood levels of HCQ is very useful before concluding treatment ineffectiveness. Sun exposure, smoking and drug interactions may be associated with a lack of response. Exchanging HCQ for CQS or vice versa may improve the response. Adding quinacrine 100 to 200 mg/day to HCQ could also be another therapeutic option. However, about 15–20% of patients are refractory to antimalarials.

Figure 16 Palatal pigmentation in hydroxychloroquine treatment.



Thalidomide is used in some European countries, including France, as a second-line treatment at an initial dose of 100 mg/day followed by a minimal effective maintenance dose. Open studies show that the remission rate is above 70% after 3 months of treatment. However, the drug effect is only moribund. Strict contraceptive measures must be taken by fertile women starting therapy after a menstrual period, because of the drug's high teratogenicity. Procreation is not allowed, even in men. Thalidomide can also cause sleepiness, weight gain, amenorrhea, impotence, thrombotic complications, and mainly distal polyneuropathy with a risk of irreversible neurotoxicity. Therefore, a monthly neurological follow-up and a bi-annual electromyography are recommended, and thromboprophylaxis (i.e. low molecular weight heparin and/or aspirin) should systematically be discussed. Though not approved in this indication, low-dose (5 mg/d) lenalidomide is as efficient as thalidomide, but with a much better tolerance.

When skin lupus is resistant to antimalarials and there are contraindications for thalidomide, the therapeutic decision becomes more difficult. It is essential then to weigh the benefits and risks before choosing any further medication. Systemic glucocorticoids are usually not indicated in skin lupus. They are ineffective at low doses and their use is restricted due to known side effects at high doses impeding subsequently long-term treatment.

Dapsone at 100–150 mg/day may help some patients with cutaneous lupus erythematosus, and is the first-line drug in neutrophilic LE, including bullous SLE (see 1.3). Lower doses (<100 mg/day) may be sufficient in SCLE. Consequently, toxicity risks are diminished, particularly dose-dependent haemolysis and methaemoglobinemia. Concomitant intake of folic acid improves dapsone tolerance.

Sulfasalazine (1.5 or 2 g/day) has been reported to help in more than 50% of patients with DLE. However, multiple side effects were noted; some were particularly severe like hypersensitivity syndrome and lupus aggravation and its use is therefore no more recommended.

Immunosuppressors like azathioprine, methotrexate, mycophenolate mofetil, and rituximab have been prescribed in anecdotal cases with variable results, methotrexate and mycophenolate mofetil being those recommended as second- and third-line agents by recent European guidelines ((Kuhn et al, 2017*).

Intravenous immunoglobulins are expensive and irregularly effective.

Oral retinoids (mainly acitretin) are an alternative therapy in antimalarial-refractory DLE, especially the hyperkeratotic variant. As these agents are highly teratogenic, it is critical to ensure the use of effective contraception in women of childbearing potential, both during and after treatment (1 month for isotretinoin and 2 years for acitretin). Retinoids can also cause hyperlipidaemia and hepatotoxicity; therefore, careful monitoring of lipids and liver function tests is necessary during treatment.

Belimumab, a monoclonal human antibody that inhibits B lymphocyte stimulating protein (BLyS), is the first biologic agent approved for the treatment of SLE by the US Food and Drug Administration and the European Medicines Agency. Belimumab is recommended in combination with standard treatment in adult patients with SLE with high disease activity (defined, for example, by the presence of anti-native DNA antibodies and low complement) despite standard treatment (antimalarials, glucocorticoids and/or immunosuppressants) in the absence of kidney or central nervous system involvement or severe autoimmune thrombocytopenia. Although it has been demonstrated that this drug has some efficacy on cutaneous lupus erythematosus (unspecified skin rashes, alopecia and mucosal ulceration), belimumab is so far not recommended for the forms of lupus that are limited to the skin. The recommended dosage is 10 mg/kg intravenously on days 0, 14 and 28 and then every 4 weeks. Administration of belimumab may cause severe hypersensitivity infusion reactions. Therefore, belimumab should be administered in hospital and patients should remain under medical supervision for several hours after the first two infusions. Discontinuation of belimumab should be considered in the absence of disease control after 6 months of treatment. Belimumab has not been well studied in pregnancy or breastfeeding in humans, and should be not recommended in these cases.

A variety of other monoclonal antibodies including TNF- α blockers, epratuzumab (which blocks the CD22 antigen, an extracellular molecule that regulates B cell activation and interaction with T cells), tocilizumab (which blocks the IL-6 receptor), abatacept (which blocks the links between antigen-presenting cells and T cells) and atacicept (which blocks two B cell activating factors, BLyS and APRIL) have also been used in relatively small numbers of SLE patients with variable benefit. These biologics are not yet approved for the treatment of SLE and their efficacy on skin manifestations should be assessed. TNF- α blockers have been used

in some cases of CLE and SCLE with efficacy, but it should be noted that they can also induce a lupus-like syndrome as a side effect.

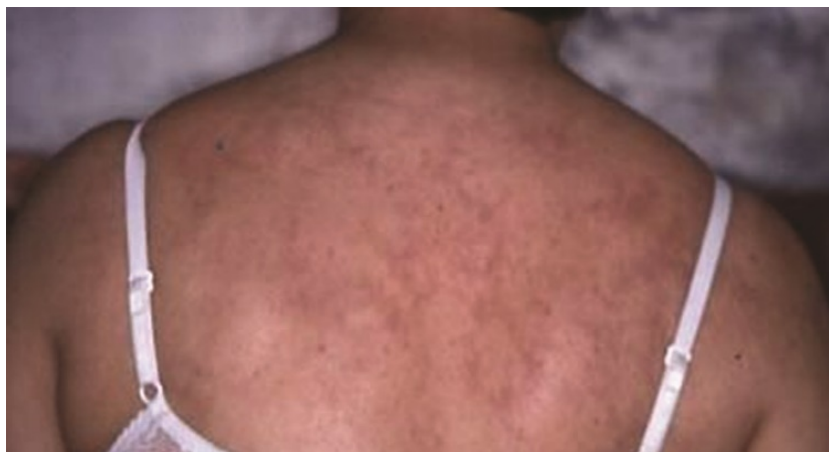
1.2 Lesions indicative of a thrombotic vasculopathy/vasculitis

The presence of vascular manifestations in lupus erythematosus may reflect distinct pathological processes. If genuine vasculitis can occur, mainly under the form of urticarial vasculitis (see 1.3), it is of uttermost importance to identify skin lesions reflecting an underlying thrombotic pathomechanisms, as it may be part of a potentially life-threatening thrombotic process necessitating anticoagulation, mainly –but not exclusively- in the context of the antiphospholipid antibodies syndrome.

1.2.1 Livedo

In SLE, livedo especially of the racemosa type (figure 17) is significantly associated with secondary antiphospholipid syndrome, thrombo-embolic arterial events (hypertension, cerebral ischaemic manifestations, and seizures) and thickened cardiac valves. It is less frequently reported when sole venous thrombosis occurs. Mottling is red, thin, particularly diffuse (trunk and limbs), not infiltrating, and looks like an incomplete net with an apparently branching configuration (livedo racemosa). It differs from the livedo associated with vasculitis which is infiltrated and mainly located on the legs. It also differs from cholesterol emboli livedo which is purplish, painful, and usually associated with skin necrosis. A skin biopsy taken from a livedoid area is frequently normal. If deep and wide-enough, it may show a proliferative endarteritis.

Figure 17 Livedo racemosa in systemic lupus erythematosus.



1.2.2 Lesions reflecting dermal micro-infarction (petechial purpura, 'atrophie blanche' and 'pseudo-Degos' papules, splinter haemorrhages of the nail)

Petechial purpura with variable necrosis is generally reflecting the thrombotic microangiopathy of lupus. It is observed on the tips of digits and toes, on the ankles and elbows.

'Atrophie blanche' and lesions similar to those of malignant atrophic papulosis (Degos' disease) (figure 18) are also usually subsequent to a thrombotic process and frequently seen in patients with positive antiphospholipid antibodies.

Figure 18 *Papule with depressed white centre and raised red border similar to malignant atrophic papulosis.*



The sudden onset of multiple splinter haemorrhages under the nails of several fingers in SLE patients is often concomitant with a systemic event like deep thrombosis or a systemic flare (figure 19). 'Haemorrhages' is an improperly used term because the pathological process usually consists of micro-thromboses; embolic or vasculitic aetiology is less common.

Figure 19 *Splinter haemorrhages of fingernails in systemic lupus erythematosus.*



1.2.3 Extensive skin necrosis and peripheral gangrenes

Extensive skin necrosis (figure 20) begins with widespread angular purpura of the limbs, the buttocks and the face (cheeks, ears and nose) that rapidly evolves into large areas of gangrene edged by a purpuric border. Biopsy of this area reveals thrombotic vessels. Anti-coagulation with heparin is the mainstay of treatment. Prostacyclin-derived vasodilators can be added. Plasmapheresis may be useful when life-threatening

complications of the antiphospholipid syndrome are present. Peripheral gangrene (mainly of digits) may be present.

Figure 20 Widespread purpura in systemic lupus erythematosus.



1.2.4 Anetoderma

The term anetoderma refers to circumscribed areas of slack skin associated with a loss of dermal substance on palpation and a loss of elastic tissue on histological examination (figure 21).

Lesions of variable number and size are mainly located on the neck, upper trunk and upper limbs. In lupus erythematosus, anetoderma is correlated with the presence of antiphospholipid antibodies and thus likely reflects underlying thrombosis.

Figure 21 Anetoderma in chronic lupus erythematosus.



1.2.5 Leg ulcers

Up to 3% of patients with SLE develop leg ulcers. Arterial and venous Doppler ultrasonography of the lower limbs must be performed and a skin biopsy of the ulcer border discussed, especially in the absence of macrovascular anomaly. The leg ulcer may be the result of either immune-complex-mediated vasculitis or,

more commonly, deep or superficial thrombosis. It is therefore more frequent in patients with antiphospholipid antibodies.

1.3 Neutrophilic cutaneous lupus erythematosus

A number of neutrophilic dermatoses may occur in patients with SLE, a general feature that is likely to reflect the involvement of auto-inflammatory processes in the pathogeny of lupus erythematosus. Identifying such conditions and underlying pathomechanisms is crucial, as immunosuppressive agents are usually not helpful and associated with overtreatment; instead anti-neutrophil drugs such as colchicine and dapsone are the treatment of choice. Bullous LE (already treated in 1.1.4.3) is a good example of this important distinction.

Besides bullous lesions, other skin signs that should suggest neutrophilic lupus erythematosus are urticarial lesions or pustular lesions.

1.3.1 Urticarial lesions (*urticarial vasculitis and neutrophilic urticarial dermatosis*)

The presence of urticarial lesions (figure 22) has been reported in 4–13% of patients with SLE, encompassing different nosological situations. Acute or chronic histamine-mediated idiopathic urticaria is possible in LE patients, sometimes drug-induced, responding well to anti-histamine H1 therapy. Urticarial lesions may also reflect small-vessel vasculitis, namely urticarial vasculitis, where authentic leucocytoclastic angiitis is present when histology is performed, generally accompanied by low complement levels and anti-C1q antibodies, as part of the McDuffie syndrome. Angioedema may be present in both histamine-mediated urticarial and urticarial vasculitis, however acquired C1 inhibitor deficiency or ACE-related angioedema should always be ruled out.

A distinctive picture of rose to red macules or slightly elevated papules with only minimal itching characterized histologically by an intense neutrophilic interstitial, perieccrine and perivascular infiltrate with leucocytoclasia but without fibrinoid necrosis of vessel walls has been termed 'Neutrophilic urticarial dermatosis'. This new entity first described in 2009 generally occurs in association with SLE (Gusdorf et al, 2014), but also with other systemic diseases such as Still's disease, Schnitzler syndrome or cryopyrin associated syndromes. The form associated with SLE may also rarely show an interface vacuolar alteration on histological examination.

Figure 22 *Urticaria in systemic lupus erythematosus.*



1.3.2 *Amicrobial pustulosis of skin folds*

Aseptic pustulosis of the folds is a well delineated clinical picture also belonging to the neutrophilic dermatoses spectrum. It has been reported in SLE and other autoimmune diseases. It manifests with aseptic pustules on an erythematous background of erosive evolution in the main skin folds, with highly suggestive scalp and external ear meatus involvement. Pustules are spongiform on histology. Oozing infections can complicate cruro-genital pustulosis (figure 23). Zinc deficiency was found in some cases. Systemic glucocorticoids are the most effective treatment, but colchicine and dapsone should be tried first. Anakinra and TNF alpha inhibitors may represent interesting alternatives in refractory cases or when steroids are contra-indicated, though a similar clinical picture can be induced by TNF inhibitors, as part of a so-called paradoxical reaction, in a few patients with inflammatory bowel disease or ankylosing spondylitis.

Figure 23 *Aseptic pustulosis of skin folds.*



1.4 Other miscellaneous lesions associated with lupus erythematosus

These skin manifestations represent a heterogeneous group of skin lesions found in patients with SLE, but devoid of well-identified significance.

1.4.1 Acral syndromes and other vascular signs

Raynaud's phenomenon, not so severe as in scleroderma, is present in 10–45% of patients with SLE and can occur a long time before other skin manifestations. Specific treatment such as calcium channel blockers and ACE inhibitors is rarely required.

Erythromelalgia (functional peripheral vascular disease associated with erythema, swelling and pain of the extremities) may be a presenting feature in SLE. Aspirin should be used as a first line treatment, and clonazepam has been reported as efficient in case reports; however, many patients will not be alleviated by treatment.

Palmar erythema and dilation of the nail fold capillaries frequently occur in SLE, resembling those seen in scleroderma and DM. Megacapillaries on capillaroscopy of the nail folds are found in 10% of SLE patients.

1.4.2 Diffuse non-scarring alopecia

Unlike in DLE where alopecia in involved areas is scarring and permanent, diffuse loss of hair occurs in SLE, especially in the active phase of the disease or, less frequently, 3 months later (figure 24). Hair recovers as the disease becomes inactive. Moreover, the hair is usually fine and growth slow, producing a band of short broken-off hair on the frontal margin (lupus hair).

Figure 24 Diffuse hair loss in systemic lupus erythematosus.



1.4.3 Calcinosis

Calcinosis in cutaneous LE is rare. Deposits can be palpable under lupus lesions or in normal skin. Mixed connective tissue disease and anti-RNP antibodies must be ruled out.

In conclusion, clinical analysis of skin manifestations in lupus erythematosus supported by histological examination facilitates a precise diagnosis, a very important step before initiating appropriate therapy. The practical classification presented here is synthesized in table 2.

Table 2 Skin manifestations in lupus erythematosus, with their significance (according to Lipsker, 2010)

Skin manifestations	Systemic involvement	Significance
Specific signs of LE		Allows to establish a diagnosis of LE ("specific" signs)
<i>Dermo-epidermal LE</i>		
- Acute	Frequent	
- Subacute	Less aggressive, anti-Ro +	
- Chronic discoid	Rare	
- Indeterminate	Possible	
- Bullous	Possible	
<i>Dermal LE</i>	Possible, but rare	
- Tumidus		
- Jessner's lymphocytic infiltrate of the skin		
- Lupic mucinoses		
<i>Hypodermal (subcutaneous) LE</i>	Possible	
- Panniculitis		
Signs indicative of a thrombotic vasculopathy	Present. Always search for underlying antiphospholipid syndrome	Important prognostic and therapeutic implications
- Dermal micro-infarctions		- Optimization of cardiovascular risk factors
- Peripheral gangrene, skin necrosis		- Discontinuation of oestroprogestative contraception
- Livedo reticularis		- Antiplatelet / anticoagulation therapy
- Acral non-infiltrated purpura		
- Anetoderma		
- Thrombophlebitis		
Neutrophilic LE	Present	Different pathophysiology implying different therapeutic approaches
- Bullous LE		
- Urticarial neutrophilic dermatosis		- Anti-neutrophil drugs (colchicine, dapsone)
- Urticarial vasculitis		
- Amicrobial pustulosis		
Miscellaneous	Present	Unknown
- Eruptive fibromas		

-
- Raynaud's phenomenon, erythromelalgia
 - Interstitial granulomatous dermatitis, rheumatoid nodules
 - Leukocytoclastic vasculitis
 - Non-scarring alopecia
 - Calcinosis
 - Histamine-mediated urticaria
 - ...
-

2 Skin manifestations in dermatomyositis

Skin signs in more than 50% of patients precede muscular manifestations by 3–6 months. They can be either typical or less characteristic and barely different from those seen in other autoimmune diseases, especially lupus erythematosus. DM skin features can be divided, as in LE, into three groups: specific DM lesions with interface dermatitis on histology, non-specific vascular lesions, and other non-DM-specific lesions.

2.1 DM-specific skin lesions

2.1.1 Clinical features

In 30–60% of cases, the face shows a purplish-pink oedema typically involving the upper eyelids and peri-orbital skin (figure 25). The violaceous lesions around the eyes reminded early clinicians of the colour of a heliotrope flower, and were thus referred to as heliotrope erythema. Heliotrope erythema can be found to a lesser extent on the cheeks, nose (sparing the tip and bridge), forehead, temples and ears. The peri-oral area and naso-labial folds are usually spared. Oedema is firm and of variable intensity. It can generate a burning sensation and even obscure the erythema, especially in African patients.

Figure 25 Heliotrope erythema. Patient consent obtained.



On the dorsum of the hands, small, erythematous, finely scaling papules/plaques occur as linear streaking over the extensor tendon sheaths with obvious reinforcement on the dorsal and lateral sides of metacarpophalangeal and interphalangeal joints (Gottron sign). Similar skin involvement can be seen on the outer aspects of the elbows, knees and, less commonly, the malleola.

Flat, infiltrated, purplish papules (Gottron papules) occur frequently with erythema (figure 26). They appear on the dorsum of finger joints and around the nails and are considered pathognomonic of DM. Sometimes, these papules become atrophic with pigmentary changes and telangiectases leading to poikiloderma. Erythema of the palmar folds of the fingers is a rare but very characteristic sign of DM, apparently related to mucin skin deposits.

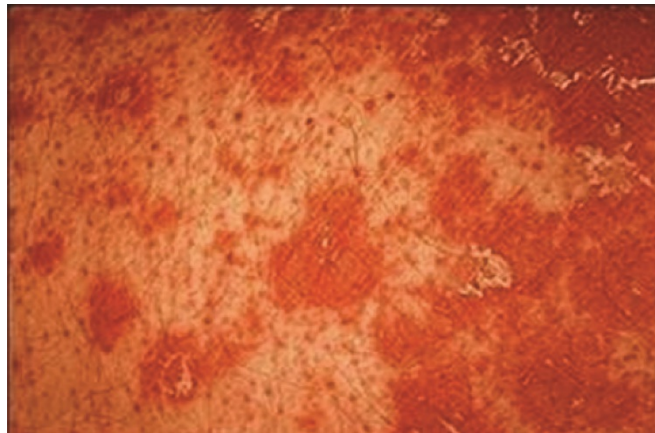
Widespread, symmetrical, purplish-red plaques are frequent in DM. They occur on the neck, limbs, anterior chest (often in a V sign) or on the back and shoulders (the shawl sign). They may be aggravated after exposure to the sun. When heliotrope erythema is missing, these diffuse lesions may resemble photodermatitis, contact dermatitis or LE. Moreover, the scaling aspect of some lesions may suggest the incorrect diagnosis of LE or seborrheic dermatitis. Linear erythematous streaks on the trunk and proximal extremities, known as flagellate erythema, are almost specific for DM (the only differential diagnoses being flagellate dermatitis consecutive to bleomycin administration or improperly cooked shiitake intake and fixed lesions observed in some patients with Still's disease). Bilateral, symmetrical, reticulate, sometimes poikilodermatous lesions of the lateral aspects of the thighs and hips (holster sign) are another sign suggesting DM.

Wong-type DM (figure 27) is characterised by follicular, erythematous and keratotic papules of the outer aspects of the limbs with palmar or less commonly diffuse keratoderma. It occurs more frequently in adults and children of Eurasian origin.

Figure 26 Gottron papules.



Figure 27 Follicular, erythematous and keratotic papules in Wong-type dermatomyositis.



Lateral and palmar areas of the fingers may become rough and cracked, with irregular dirty horizontal lines, resembling a mechanic's hand (figure 28). These mechanic's hands are found in the so-called anti-synthetase syndrome, which is serologically characterised by the presence of aminoacyl-tRNA synthetase autoantibodies and clinically by myositis, eczematous inflammatory skin changes as well as interstitial lung disease. In this type of DM, minimal muscle involvement should not lead to underestimation of disease severity since the risk of pulmonary fibrosis is high, and around 21% of patients die within 5 years.

Figure 28 Mechanic's hand.

The essential features of poikiloderma are atrophy, hyper or hypopigmentation and telangiectasia. The upper trunk (shoulders, upper back, and low neckline) and buttocks are frequently affected, in an asymmetrical pattern. Poikiloderma often follows the purplish plaques after a long natural course or treatment response. It can be, however, an inaugural manifestation of DM (poikilodermatomyositis) where differential diagnoses are radiodermatitis, T cell lymphoma (especially mycosis fungoides), LE or congenital forms of poikiloderma.

Scalp involvement is relatively common with diffuse erythematous-squamous lesions, poikiloderma and mild to moderate non-scarring alopecia.

Vesiculo-bullous, ulcerated or necrotic lesions can occur and point to a potential underlying malignancy. The histological picture variably associates vasculitis with severe interface dermatitis.

Erythroderma is the term applied to extended (> 90% of body surface) scaling, oedematous and persistent erythema with general malaise, thermoregulation abnormalities, and dermopathic lymph nodes. It is very uncommon in DM, so a relationship with poor prognosis or increased associated risk of an underlying malignancy cannot be established.

Panniculitis lesions are rare in DM. Deep, firm and painful nodules affect the arms, buttocks, thighs and abdomen. They can precede, accompany or follow initial signs of the disease. With interface vacuolar dermatitis, the subcutaneous fat shows a lobular lympho-plasmocytic infiltrate, sometimes with membranocystic changes.

Mucous membrane lesions such as bright red oral erythema and erosive genital lesions are rare.

2.1.2 Differential diagnosis

The cutaneous lesions of DM can be distinguished from those of lupus erythematosus by their characteristic violaceous colour and the tendency of lesions to be distributed around the eyes and on extensor surfaces. Moreover, the lesions on the backs of the hands are usually located over the joints in DM but in the spaces between the joints in lupus erythematosus.

Erythematous scaling plaques seen on the outer aspects of the elbows and knees can be misdiagnosed as psoriasis.

Clinically, Wong-type DM resembles pityriasis rubra pilaris but histological features are characteristic with follicular hyperkeratosis over a piloerector muscle myositis.

2.1.3 Pathology

DM lesion histology is not specific since some LE lesions demonstrate almost identical features: hyperkeratosis, epidermal atrophy, interface dermatitis with vacuolar changes in the basal cell layer, oedema of the superficial dermis, dilation of capillaries, pigmentary incontinence, and sometimes mucin deposits. The peri-vascular, inflammatory infiltrate consists of neutrophils and activated CD4 lymphocytes. Turgescient endothelial cells, vessel dilation and fibrin deposits in the vessel wall are frequently found. The presence of leucocytoclastic vasculitis might increase the risk of an associated malignancy. Positive direct immunofluorescence in affected skin is a statistically significant, distinctive criterion distinguishing between LE and DM: linear deposits of IgG or C3 at the dermo-epidermal junction are found in 90% of LE lesions but in only 10–20% of DM lesions.

2.1.4 Laboratory investigations

DM is characterised by myositis-specific autoantibodies (anti-Mi2, anti-MDA5, anti-RNA synthetase, anti-hPMS-1, anti-NXP2, anti-TIF-1 gamma, anti-SAE) and myositis-associated autoantibodies (anti-Ro/SSA, anti-PM/Scl, anti-Ku), the latter occurring also in autoimmune diseases without myositis and thus most frequently reflecting overlap syndrome. These antibodies are helpful as they are associated with distinctive clinical and evolutive features (Fujimoto et al. 2016*)

The anti-Mi2 antibodies are the most common myositis-specific autoantibodies found in these patients and are associated with an increased prevalence of cutaneous lesions and with a good response to therapy. The MDA-5 (melanoma differentiation-associated gene 5) antibodies, originally called CADM-140 (clinically amyopathic dermatomyositis antibody, 140 kD), are associated with amyopathic DM, pulmonary involvement and papules of the palms, digital ulcers and oral ulcerations or pain. Some 20% of patients have anti-RNA-synthetase antibodies, which include for example anti-Jo1, PL7 and PL12 antibodies and define the anti-synthetase syndrome, characterised by myositis, pulmonary fibrosis, Raynaud's phenomenon, non-erosive arthritis and mechanic's hand. Anti-synthetase syndrome may thus represent a distinct entity within the inflammatory myositis spectrum. The anti-TIF-1gamma and to a lesser extent anti-NXP2 antibodies (in adults) are clearly associated with an underlying malignancy, which should be actively monitored in this subgroup of patients for extended duration.

2.1.5 Treatment

No specific treatment is required for skin lesions since healing often occurs when myositis is treated, though this is not obligatory. Myositis and muscle enzymes often respond faster than the DM skin changes to high-dose or pulse treatment with glucocorticoids, immunosuppressants or intravenous immunoglobulins. However, affected skin should be treated in amyopathic DM and in isolated skin recurrences. Treatment is then similar to first-line treatment in LE, i.e. antimalarials, as skin signs alone do not justify the use of high-dose systemic steroids. Methotrexate and IgIV are alternatives.

Photoprotection is essential since the skin may be photosensitive. Daily use of topical steroids can help in limited moderate lesions (Callen and Wortmann, 2006*), but should be avoided on the face because of cutaneous atrophy and the risks of steroid-induced rosacea. Response after 6 weeks of tacrolimus 0.1% ointment or pimecrolimus 1% cream use is variable. HCQ is frequently prescribed as a first-line treatment (Quain and Werth, 2006*) at a dose of 200–400 mg/day with or without topical steroids; efficacy is variable. CQS was also used at a dose of 100–250 mg/day. When previous treatments fail, dapsone, mycophenolate mofetil, methotrexate and cyclophosphamide can be used. Thalidomide is not effective. High-dose intravenous immunoglobulins are frequently successful as second-line treatment especially when glucocorticoids are contraindicated, but their high cost may restrict their use.

2.2 Vascular lesions

Congestive well-demarcated erythema of finger or toe nail folds is characteristic. It is the result of vascular involvement and is often associated with thickened, haemorrhagic cuticles and macroscopic megacapillaries. The nail fold becomes painful when the cuticle is pressed or pushed back (manicurist sign).

Moderate Raynaud's phenomenon occurs in 10–15% of adult DM and is very rare in childhood DM. Onset may occur many years before cutaneous changes.

Cutaneous thrombosis and vasculitis are mainly reported in DM with an underlying malignancy or another associated autoimmune disease.

2.3 Other non-specific lesions

Pruritus and a burning skin sensation are frequent in DM. Secondary excoriations can also be found. Pruritus and a burning sensation may help distinguish DM from LE where it is rarely noted; it sometimes predicts the presence of an associated malignancy especially when very intense.

Photosensitivity occurs in 30% of cases necessitating sun protection.

Calcinosis represents a major clinical problem in DM and is more frequent in children (especially in association with anti-NXP2 antibodies) than in adults (30–70% vs 10%). It can affect the skin, aponeuroses and muscles. Common sites include the proximal joints of the limbs, axillary folds, and the hips and bony prominences of the elbows and knees. The notion that DM calcinosis spares distal finger joints and finger pads, which are frequently involved in systemic sclerosis, is most often but not always true. However, it can become a source of constant pain and discomfort. Early and intensive treatment of DM may partially prevent these calcifications. However, once calcinosis is present, treatment is disappointing. Colchicine (1 mg/day), warfarin, diltiazem, aluminium hydroxide, probenecid and alendronate have been used with anecdotal success. Surgery is the treatment of choice when feasible, especially in localised cutaneous calcifications.

2.4 DM sine myositis

DM sine myositis or amyopathic DM is defined as typical clinical and histological cutaneous DM lacking clinical or enzymatic muscle involvement even after 2 years of follow-up. A small subset of patients (2–18%) never develops myositis, despite having prominent cutaneous changes. The risk of underlying malignancy is similar to that in other types of DM. In some patients, myositis resolves with treatment but cutaneous disease persists as the most important feature. These cutaneous lesions are sometimes refractory to standard treatment such as topical glucocorticoids and HCQ. Topical calcineurin inhibitors are sometimes effective. Thalidomide is ineffective.

2.5 Childhood DM

Skin manifestations in childhood DM are similar to those in adults. Nevertheless, onset is insidious causing delay in diagnosis. They frequently begin with a persistent, telangiectatic, erythema around the nails.

Mucosal telangiectases of the anterior gingival fold and hypertrichosis, diffuse or localised especially under the patella, are rare but suggestive features of juvenile DM. Cutaneous vasculopathy is also more prominent, leading to skin necrosis and subsequent ulcers. Dystrophic calcinosis affecting inflammatory skin and underlying muscles may cause extreme pain, deep ulcers and musculo-tendinous retractions with severe and persistent impotence. Localised lipodystrophy with loss of masseter and limb subcutaneous fat has been reported. Generalised lipodystrophy can also occur and is associated in 50% of cases with hirsutism, acanthosis nigricans, insulin-dependent diabetes and hypertriglyceridaemia.

2.6 DM, auto-antibodies and cancer

Skin necrosis, cutaneous leucocytoclastic vasculitis, vesiculo-bullous lesions in non-traumatised areas and pruritus or a burning skin sensation occurring in older patients are cutaneous signs strongly suggesting malignancy. A strong association with specific autoantibodies (anti-TIF1-gamma and anti-NXP2) is observed. Inversely, in childhood DM (despite the presence of anti-NXP2), adult DM with anti-Mi-2 or anti-MDA-5, mixed

connective tissue diseases (anti-RNP, anti-PM-Scl, anti-Ku) and anti-synthetase syndrome (anti-Jo1 and other anti-synthetase), the risk of associated malignancy is extremely low; those patients have however a higher risk of potentially life-threatening interstitial lung disease

Breast, colon and lung carcinomas have been reported to be the most frequent tumours in DM; ovarian carcinoma has also been found much more frequently in women with DM than in the general population.

2.7 DM and other autoimmune diseases

It is important to look for dermatological signs of other connective tissue diseases in patients with DM because of the frequency of overlap syndromes. Mixed autoimmune diseases represent 10–20% of all inflammatory myositis, being more frequent in polymyositis (where skin is not affected) than in DM. The most common cutaneous findings are signs of overlap with scleroderma, especially CREST features (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasias), annular lesions suggestive of SCLE, and nodules suggestive of rheumatoid arthritis (RA). Other associated diseases include Sjögren syndrome and autoimmune thyroiditis. Cutaneous small vessel vasculitis can occur as an associated illness, especially in patients with juvenile DM.

2.8 DM and drugs

Many drug categories are known to induce myositis (fibrates, statins, anti-retroviral molecules, interferon, isoniazide, tamoxifen, chlorpromazin, antazolin, clemizol, phenylbutazone, D-penicillamine,...). However, published reports of genuine drug-induced DM, especially with statins, are scarce and have a low level of evidence, except for DM induced by immunological checkpoint inhibitors such as ipilimumab (anti-CTLA-4). D-penicillamine might induce DM or polymyositis in patients with rheumatoid arthritis. Hydroxyurea can produce, in 5% of treated patients, streaks of erythema over the hands similar to DM lesions but without muscle involvement. Moreover, patients taking hydroxyurea tend to have late onset (2 months) of DM. DM-like skin manifestations have also been reported with the following drugs: etoposide, cyclophosphamide, diclofenac and acetylsalicylic acid. The majority of cases of drug-induced DM improve after withdrawal of the medication thought to play a role.

3 Skin manifestations in systemic scleroderma

Skin manifestations in systemic scleroderma (SSc) are very important and can lead to diagnosis at first sight (Gabielli et al, 2009*). The 2013 ACR-EULAR diagnostic and classification criteria for SSc (Van den Hoogen et al, 2013*) determined that skin thickening of the fingers extending proximal to the metacarpophalangeal joints is sufficient for the patient to be classified as having SSc. If that sign is absent, seven additive items are considered, with varying weights for each: skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's

phenomenon and SSc-related autoantibodies. These criteria replace the previous criteria of LeRoy et al which emphasised the distinction between limited cutaneous scleroderma and diffuse cutaneous scleroderma. In limited cutaneous scleroderma (lcSSc), fibrosis is restricted to the hands, lower arms, neck and face. Raynaud's phenomenon is present for several years before fibrosis appears, pulmonary hypertension is notably frequent, and anticentromere antibodies occur in 50–90% of patients. Diffuse cutaneous scleroderma (dcSSc) is the more rapidly progressing subtype that affects larger areas of the skin and compromises one or several internal organs (pulmonary fibrosis as well as heart and kidney involvement).

In rare cases, patients with SSc have no obvious skin involvement. Patients with scleroderma and additional clinical signs of SLE, RA, polymyositis/dermatomyositis or Sjögren's syndrome are considered to have an overlap syndrome.

3.1 Vascular skin changes

Almost all patients have Raynaud's phenomenon, which generally precedes other manifestations. It is characterised by episodic vasospastic attacks that cause the blood vessels in the fingers and toes to constrict. It presents with three changes in skin colour. Pallor (in response to arteriole spasm) is followed by cyanosis (due to ischaemia) and then rubor (after arteriole reperfusion and dilation). Raynaud's phenomenon affects the fingers, toes, ears and nose. The duration of an attack varies from a minute to several hours/days. As the attack ends, finger and toe tips may throb and tingle.

Recurrent Raynaud's phenomenon is thought to be the direct consequence of structural changes in the vessels and perturbed control of vascular tone due to an imbalance between vasodilatory and vasoconstrictive mediators.

Unlike in rosacea, telangiectases in scleroderma are rounded or rectangular and affect not only the face, but also the trunk, the palms (figure 29) and the oral mucosa. They can be distinguished from Rendu-Osler disease lesions because the latter are papulous and not flat; moreover, bleeding never occurs. Facial abnormal telangiectases are one of the characteristic CREST signs. The term 'CREST syndrome' is becoming obsolete as it is not exclusive to a single subgroup of patients with the disease and does not sufficiently indicate the burden of internal organ involvement. Most patients with CREST syndrome are females with a long history of secondary Raynaud's syndrome before acroscleroderma develops. The prognosis of these patients is favourable if pulmonary hypertension does not occur. However, some scleroderma patients, frequently males, show disseminated telangiectases over the chest and trunk and develop severe lung disease and other organ manifestations associated with a poor outcome. Serologically, these patients are characterised by scleroderma-specific anti-nucleolar antibodies.

Figure 29 *Telangiectases on the skin of the hand.*



3.2 Fibrotic skin changes

Skin sclerosis first starts at the extremities (acroscleroderma), especially around the fingers and toes, which become initially oedematous with a characteristic puffy appearance, as in mixed connective tissue disease (Sharp's syndrome). Pads become smooth and lose fingerprints. Next, the skin becomes shiny and tight, binding to deeper structures mainly on the dorsum of phalanges. Movements are progressively limited, the joints are fixed in flexion, and fingers have a tapered appearance with difficulty obtaining full extension (sclerodactyly) (figure 30). Changes may extend proximally to involve the forearms and upper arms and can result in dermatogenic joint contractures, especially of the elbows and knees. Dermal sclerosis also leads to atrophy of appendages and subsequent decreased sweating and hair loss.

Figure 30 *Sclerodactyly.*



The face is frequently involved (figure 31). Sclerosis produces an abnormal tense feeling with an amimic facies. Forehead wrinkles disappear. Eyelids become retracted giving a particular look. The nose becomes small and pinched. The lips become thinner, and protrusion of the tongue is difficult. The mouth opening is constricted (microstomia), impairing proper dental hygiene, and marked radial peribuccal furrows appear. Resurfacing laser on the peri-oral skin is under evaluation. Filling with inert substances (collagen, proteoglycans and silicone) is not recommended.

Figure 31 Patient with systemic scleroderma with disappearance of forehead wrinkles, a tapered nose and perioral wrinkles. (Patient consent obtained.)



On the scalp, skin binds to the bone and alopecia may occur.

Oral mucosa can be affected with characteristic shortening of the tongue frenulum and widening of the periodontal membrane due to sclerosis, especially of the incisive alveolodental ligament. Bare teeth may follow gingival retraction. The mucosa is pale and dry.

The skin is tight, shiny, bound down, hard, and impairs breathing, and abdominal and joint movements.

3.2.1 Histological features

The diagnosis of skin sclerosis is clinical. Histology shows non-specific features that are similarly found in morphea. In the initial phase, deep dermis presents with an inflammatory infiltrate; lymphocytes, plasma cells and some mast cells accumulate around vessels and between homogenised collagen bundles dissociated by oedema. At a later stage, epidermal atrophy may occur with loss of the rete ridges. The dermis is markedly thickened with dense bundles of collagen. The elastic tissue is reduced and elastic fibres are horizontally flattened. Dermal appendages and vessels are progressively lost.

3.3 Other skin manifestations

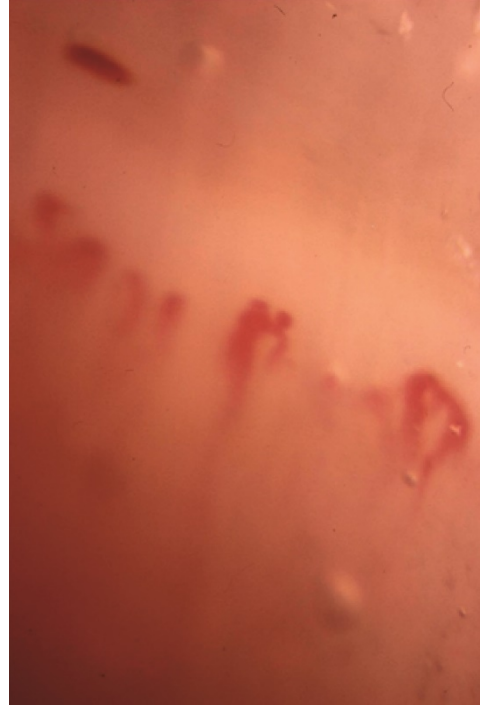
Fingers commonly show micro-ulcerations of the pads or the dorsum of the joints, pitted scars (figure 32), digital gangrene, and dystrophic slow-growing nails curving over atrophic phalanges; distal nail bed adherence

to the ventral surface of the nail plate (pterygium inversus unguis) is typical. Dilated capillaries and micro-thrombotic changes in the nail fold are similar to those observed in DM and can be verified by capillary microscopy (figure 33).

Figure 32 Ulcerations and pitted scars.



Figure 33 Megacapillaries on capillaroscopy.



Painful digital ulcers sometimes involving all fingertips are a major problem for scleroderma patients and greatly reduce their capacity to cope with the disease. They occur mostly in patients with diffuse skin involvement and multiple organ involvement, especially lung fibrosis and/or pulmonary arterial hypertension. Local dressings and systemic vasodilators (prostacyclin derivatives) are the mainstay of ulcer treatment. Bosentan, an endothelin receptor antagonist, has a proven but weak preventive effect on digital ulceration (30 to 50% reduction) without effect on ulcer healing. Preliminary studies suggested that the 5-phosphodiesterase inhibitor, sildenafil, may induce healing of digital ulcers in scleroderma patients, but a placebo-controlled study failed to confirm these results. These digital ulcerations need a multi-disciplinary approach with the prescription of different vasodilators (prostacyclin derivatives, bosentan, sildenafil, calcium channel blockers, ACE inhibitors and others) and physiotherapy.

Calcium deposits accumulate insidiously in the skin forming nodules that are mobile in relation to deep structures but tightly bound to overlying skin, giving a whitish appearance. They can be found on the hands (figure 34), forearms, wrists, elbows, shoulders and knees (figure 35). Nodules can grow considerably and resemble tumours. Complications include painful inflammatory flare, pseudo-dactylitis, and ulceration with discharge of chalky material. Large nodules are visible on soft tissue radiography.

Figure 34 Calcium deposits in scleroderma.**Figure 35 Calcific plaque in scleroderma.**

Pigmentary changes are frequent, especially on sclerotic skin. Diffuse hyperpigmentation associated with severe pruritus can be seen in rapidly progressive dcSSc with a poor prognosis. Diffuse or mottled hyperpigmentation may affect white skin, whereas peri-follicular hypo-pigmentation is commonly seen on dark skin (figure 36). On white skin, depigmentation with a relative sparing of the perifollicular areas is typical (“salt-and-pepper” appearance). Pruritus may be severe in early active scSSc and notably challenging to alleviate.

Figure 36 Depigmentation in scleroderma.

3.4 Laboratory investigations

Anti-centromere antibodies are more frequent in localised (65%) than in diffuse cutaneous SSc (30%), whereas anti-DNA topoisomerase I (anti-Scl 70) antibodies are more frequent in diffuse (40%) than in limited forms (20%). Other scleroderma-specific antibodies, found mostly in patients with overlap syndromes or with diffuse SSc and severe organ involvement, are frequently directed against nucleolar antigens such as fibrillarin.

3.5 Scleroderma and drugs

Systemic sclerosis-like syndrome may be induced by various drugs including bleomycin, taxane, pemetrexed, tryptophan, and rarely fosinopril. In drug-induced systemic sclerosis-like syndrome, ANA can be sometimes detected but usually there are no SS-specific antibodies. The characteristics of bleomycin-induced scleroderma are male predominance, a high incidence of limited-type cutaneous sclerosis and a low incidence of Raynaud's phenomenon, digital pitting scars, ANA and visceral involvement compared with idiopathic SS. Sclerosis and swelling of the hands and forearms usually resolve after the termination of bleomycin-containing chemotherapy, but sclerodactyly can persist in some cases. Bleomycin also has dose-related pulmonary toxicity that manifests as interstitial pneumonia and pulmonary fibrosis. Taxane-induced scleroderma is a clinical condition presenting with localised oedema evolving into skin sclerosis. Differently from classic SSc, taxane-induced scleroderma did not display the characteristic symptoms associated with SSc, such as Raynaud's phenomenon, nail fold changes, and pulmonary fibrosis. In SSc, skin sclerosis usually begins on the fingers and advances towards the centre of the body in a symmetrical pattern, whereas in most patients with taxane-induced scleroderma, lesions first arise on the legs. Scleroderma can develop during taxane chemotherapy or within 2 years after the termination of chemotherapy. L-tryptophan has also been reported to cause skin induration associated with myalgia and eosinophilia, but was banned by the US Food and Drug Administration in 1989.

4 Skin manifestations in systemic vasculitis

Skin manifestations are frequently observed in almost all types of systemic vasculitis (Fiorentino, 2003*). Some correspond to skin localisation of the systemic vasculitis, while others result from a different pathological process. As a biopsy of a dermatological lesion is easy to obtain, it is useful and important for confirming the diagnosis (Carlson et al, 2005*); however, it may not be of value in determining the particular type of vasculitis as clinical and pathological features of the skin are not specific to a given type. Indeed, medium- and large-sized vessels are not present in the skin.

4.1 Skin manifestations of vasculitis

4.1.1 Clinical features

Skin vasculitis presents as a spectrum of clinical lesions including erythema, purpura, papules, pustules, nodules, livedo, necrosis, ulcerations and bullae. These various lesions often co-occur giving the eruption a pleomorphic appearance.

Palpable purpura is unquestionably the most frequent manifestation (figure 37). Lesions usually begin as tiny red macules that later become papules and plaques ranging from several millimetres to several centimetres in width. Larger lesions are ecchymotic. The colour may change from red to purple to brownish-yellow as extravasated blood is progressively broken down. Palpable purpura is most common on the legs, ankles and feet, but other areas of the body can be affected.

Figure 37 Palpable purpura.



Urticarial vasculitis (also called anti c1q vasculitis) (figure 38) is characterised by *wheals* that persist for 2–3 days, unlike ordinary urticaria which is expected to clear within 24 h. Pruritus is less intense than in common urticaria. Lesions may become purpuric. They are mainly located on the trunk and the limbs. Elsewhere, other papules, which are not purpuric or urticarial, may also correspond to skin vasculitis, especially when found on the outer aspects of the limbs. Some papules appear red to purple, then become brown to yellow and follow a chronic evolution as in erythema elevatum diutinum (EED).

Figure 38 Urticarial vasculitis.



Pustular vasculitis (figure 39) is usually non-follicular, with underlying erythema. Other frequently observed pustules may result from secondary infection of necrotic lesions.

Figure 39 Pustular vasculitis.



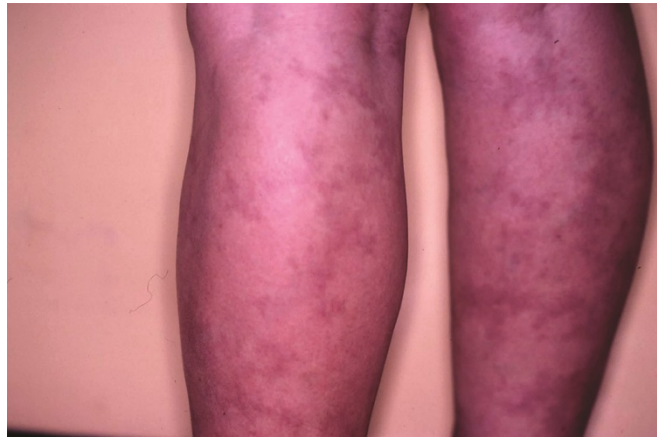
Nodules in vasculitis are typically inflammatory, tender, red and small (figure 40). They are mainly located on the lower limbs (legs, soles), where they can be surrounded by livedo reticularis/racemosa, but are also observed on other sites such as the dorsal aspect of the upper limbs or, rarely, the trunk. Nodules may also occur in groups along the course of superficial arteries.

Figure 40 Nodular vasculitis.



Livedo racemosa is a reddish-blue mottling of the skin in a 'fishnet' reticular pattern (figure 41). It is typically irregular with broken meshes. Some infiltrated areas are found on careful examination. When associated with vasculitis, livedo persists indefinitely with some fluctuations in intensity and extent as temperature varies.

Figure 41 Livedo in vasculitis.



Necrosis (figure 42) results from the obstruction of dermal vessels. Its extent and depth are highly variable depending on the extent and depth of the involved vessels. Localised necrotic lesions may develop into vesicles. Pustules may appear due to secondary infection. When necrosis is extensive, painful purpura is followed by a black necrotic plaque with an active purpuric border and bullous lesions. After removal of necrotic tissue, ulcers of various sizes develop.

4.1.2 Histopathology and clinico-pathological correlation

Leucocytoclastic vasculitis of the superficial dermal vessels is the pathological hallmark of palpable purpuric lesions. Post-capillary venules are preferentially involved. Leucocytoclastic vasculitis is characterised by vascular alterations and dermal cellular infiltrates.

Vascular alterations consist of endothelial cell swelling, necrosis with deposition of fibrinoid material into the vessel wall, and sometimes thrombosis. The fibrinoid material is predominantly made of fibrin but contains

also necrotic endothelial cells and deposits of immuno-reactants (immunoglobulins and/or complement proteins).

Dermal infiltrates vary in intensity. They are usually peri-vascular but at times widely dispersed. Neutrophils are the main cells and often the nucleus fragments (karyorrhexis or leucocytoclasia). In other cases or at a later stage, lymphocytes and monocytes may predominate.

In some patients, especially those with immune complex-mediated vasculitis and extensive complement activation, dermal small-vessel vasculitis generates focal dermal oedema with subsequent urticaria.

Nodular lesions of vasculitis results from inflammation of vessel walls at the dermo-hypodermal junction or in the subcutaneous fat. When arterioles are involved, pathological features are similar to those observed in cutaneous polyarteritis nodosa (PAN). Endothelial swelling and fibrinoid necrosis of the media are often severe with variable thrombosis. Invasion of the vessel wall with neutrophils usually occurs in the acute phase, although leucocytoclasia is less frequently observed. In other cases, the infiltrate can be initially granulomatous. In the healing phase, the vessel wall is invaded by granulation tissue and replaced by a fibrous scar. Continuous proliferation of capillaries occurs.

In summary, palpable purpura and papular lesions such as urticaria indicate a leucocytoclastic or lymphocytic vasculitis of the small vessels of the dermis. Nodules indicate a vasculitis of arterioles or vessels at the dermo-hypodermal junction or in the subcutaneous fat. Necrosis and livedo occur when either small and/or larger vessels are involved.

Figure 42 Necrosis in vasculitis.



4.1.3 Other skin manifestations associated with systemic vasculitis

4.1.3.1 Extravascular necrotising granuloma

Initially described by Churg and Strauss in 1951 as a manifestation of eosinophilic granulomatosis with polyangiitis (EGPA, formerly called allergic angiitis or Churg–Strauss syndrome), extravascular granuloma has also been described in many other types of systemic vasculitis and connective tissue diseases. Papular or nodular lesions vary in size from 2 mm to 2 cm or more, and in colour from red to purple. Central umbilication, crusting and/or ulceration are frequent. Rarely, other features are reported such as vesicles, pustules, arciform plaques or firm masses. Sites of involvement are the extensor aspects of the elbows, the fingers where there are usually multiple lesions (often symmetrical), and less frequently, the buttocks, scalp, knees, hands, dorsum of the feet, neck, forehead and ears.

Histological features include endothelial necrosis and oedema, fibrinoid necrosis of the collagen, and granulomas containing eosinophils, histiocytes and lymphocytes. The centre of the granuloma consists of basophilic (rather GPA) or eosinophilic (rather EGPA) fibrillar necrosis in which bands (sometimes linear) of destroyed tissue are interspersed with poly-morpho-nuclear leucocytes and leucocytoclastic debris. This necrotic area is surrounded by a granulomatous mass of histiocytes, often in a palisade array. A decrease in or absence of elastic fibres is observed in foci of degenerated collagen. No relationship is seen between the clinical appearance of lesions, the histological features, and the associated systemic disease. However, tissue eosinophilia is more frequently reported in patients with EGPA.

4.1.3.2 Panniculitis

Cutaneous eruption consists of recurrent crops of erythematous, oedematous and tender subcutaneous nodules or of a deep poorly limited infiltration. The nodules are 1–2 cm in diameter but may be much larger. Histologically, panniculitis is characterised by an inflammatory infiltrate composed of lymphocytes, plasma cells and histiocytes in adipose tissue. They can be classified as lobular or septal depending on whether the inflammatory infiltrate is more abundant in the lobules, the interlobular septa or around the vessels of the subcutaneous tissue septa. In lobular panniculitis, lesions are usually symmetrically distributed on the thighs and the posterior part of the lower legs. They usually regress spontaneously, leaving hypopigmented and atrophic scars due to fat necrosis. Occasionally, they may suppurate. In septal panniculitis (erythema nodosum), nodular lesions are primarily located over the anterior aspects of the lower limbs. They regress spontaneously without atrophic scarring and do not suppurate.

4.1.3.3 Pyoderma gangrenosum

Pyoderma gangrenosum (PG) lesions usually begin as deep-seated, painful nodules or as superficial haemorrhagic pustules, either de novo or after minimal trauma. They further break down and ulcerate,

discharging purulent and haemorrhagic exudates (figure 43). Ulcers can reach 10 cm or more in diameter, partially regress or remain indolent for a long period. The irregular edges are raised, red or purplish, undermined, soggy and often perforated. The most commonly affected sites are the lower extremities, buttocks and abdomen, but other areas of the body may be involved. Lesions are usually solitary but may arise in clusters, which then coalesce to form polycyclic irregular ulcerations. When healing occurs, an atrophic and often cribriform scar is left. PG lesions can be found alone or in association with a systemic disease (inflammatory bowel disease, rheumatoid arthritis, haematological disorder) or a systemic vasculitis, namely granulomatosis with polyangiitis (GPA), Takayasu arteritis or Behçet's disease. Infectious pyodermitis must always be ruled; substantial pain is a distinguishing feature.

Figure 43 *Pyoderma gangrenosum*.



The histological features, when a biopsy is performed, consist of a large, sterile abscess in which thrombosis of small and medium blood vessels, haemorrhage and necrosis are present. Neutrophils are numerous, but epithelioid, giant and mononuclear cells are also seen, especially in the more chronic forms. Leucocytoclastic or lymphocytic vasculitis may be observed, particularly in the active border of the lesion. These changes are not specific and may be observed within the main differential diagnosis, i.e. infectious ulcerations; besides pathergy is frequently observed with secondary exacerbation of the disease around the biopsy site. The diagnosis is therefore essentially based on clinical findings and negativity of microbiological swabs.

4.1.3.4 Granuloma

Granulomatous lesions without vasculitis or central necrosis may be observed in systemic vasculitis, especially granulomatous with polyangiitis (GPA, formerly Wegener's granulomatosis). The clinical aspect is highly variable, ranging from papules, nodules, subcutaneous infiltration and pseudo-tumour to chronic ulcers. Any site of the body may be involved: the breasts, scrotum, face, gums, etc. Other granulomatous diseases have to be considered in the differential diagnosis, such as sarcoidosis, metastatic Crohn's disease, mycobacterial infections, and foreign body granulomas.

4.1.3.5 Superficial thrombophlebitis

Thrombophlebitis of a superficial vein is sometimes clinically evident due to the presence of painful induration of the vein with redness and increased heat. In other cases, the clinical aspect is a linear or even non-specific red nodule and diagnosis is only confirmed by histological examination of a deep skin biopsy; ecodoppler investigations do not allow diagnosing nodular thrombophlebitis in most cases. Such lesions are essentially observed in thromboangiitis obliterans, Behçet's disease, Crohn's disease and relapsing polychondritis, but may also be observed in the context of an underlying malignancy (migratory thrombophlebitis, or Trousseau's syndrome).

4.1.3.6 Gangrene

Gangrene resulting from arterial occlusion may be observed in all types of vasculitis involving medium or large arteries. It is initially characterised by a sharply demarcated blue-black colour of the extremities. The main differential diagnoses are thrombosis, without inflammation of the vessel walls, and emboli. Angiography visualises occlusion or stenosis of arteries but does not help to differentiate these different pathological processes. The presence of other skin lesions with histologically proven vasculitis suggests vasculitis, although thrombosis, vasculitis and emboli may be concomitant as in atheromatous emboli.

4.1.3.7 Raynaud's phenomenon

Bilateral Raynaud's phenomenon may occur in 5–30% of a randomly selected population. It is classically associated with all types of vasculitis. However, its prevalence is unknown in many vasculitides and its diagnostic value is very low. In contrast, unilateral Raynaud's phenomenon suggests an obstructive arterial disease and, within the spectrum of vasculitides, is mainly observed in Takayasu's arteritis.

4.1.3.8 Interstitial granulomatous dermatitis

Interstitial granulomatous dermatitis (IGD) is an entity first described by AB Ackerman, and characterized histopathologically by a granulomatous inflammatory infiltrate centred on collagen bundles, with symmetrical, erythematous cords or plaques, mainly involving the lateral chest wall, abdomen and medial thighs clinically (figure 44). Other clinical findings present in 10% of patients include typical erythematous, asymptomatic, linear, palpable cord-like lesions on the lateral aspects of the trunk (the rope sign) (figure 45) and urticarial plaques. It is an uncommon disorder.

Figure 44 Plaques in interstitial granulomatous dermatitis.



Figure 45 The rope sign in interstitial granulomatous dermatitis.



Histopathologically, IGD is quite distinct and characterised by a dense, diffuse dermal inflammatory infiltrate composed primarily of histiocytes distributed interstitially and in a palisaded array. In the deep reticular dermis, small foci of degenerated collagen are enveloped by large numbers of neutrophils and/or eosinophils; this latter finding is the most characteristic.

IGD may be associated with various autoimmune vascular diseases (including RA, SLE, Still's disease, EGPA, thyroiditis and vitiligo), infections and drug intake. Although its cause remains unknown, its association with these conditions makes an immune complex-mediated pathogenesis likely.

4.2 Dermatological findings in the main systemic vasculitides (table 3)

Table 3 Skin signs in systemic vasculitis

Systemic vasculitis	Most frequent skin lesion	Most typical skin lesion
IgA vasculitis	Purpura, urticaria	Purpura, urticaria
Cryoglobulinaemic vasculitis	Purpura	Purpura with secondary pigmentation
Polyarteritis nodosa	Purpura	Nodules, livedo
Microscopic polyangiitis	Purpura, nodules	Purpura
Eosinophilic granulomatosis with polyangiitis	Purpura	Extravascular necrotising granuloma
Granulomatosis with polyangiitis	Purpura	Oral ulcers, gingival hyperplasia

4.2.1 IgA vasculitis

Purpuric lesions associated with arthritis, gastrointestinal symptoms and IgA nephritis are considered a distinct entity among the different types of angiitis and are called IgA vasculitis (figure 46). In the past, this entity was known as Henoch-Schönlein purpura, anaphylactoid purpura, allergic purpura and haemorrhagic capillary toxicosis. This type of vasculitis predominantly occurs in children, where it represents more than 90% of all types of vasculitis, although all ages can be affected. There is no seasonal pattern, but a higher incidence in winter and a lower incidence in summer have been recorded, probably in relation to infections that are possible triggers. This purpura is caused by deposition of immune complexes in the small vessels, and immune complex formation is induced by bacterial (*Streptococcus*, *Mycoplasma pneumonia*, etc.) or viral (Epstein-Barr virus, cytomegalovirus, etc.) infections, vaccines or drugs (penicillin, aspirin, etc.).

Figure 46 IgA vasculitis.



Some 70% of patients exhibit gastrointestinal discomfort or joint pain, especially of the large joints, and 40% of patients have glomerulonephritis with IgA deposition.

Skin lesions begin as a crop of red macules, some of which resolve in the early stage while others become papular, urticarial or purpuric. In some cases, the characteristic urticarial component of the rash is missing and purpura is the only sign. When inflammation and exudation are severe with involvement of all superficial vessels, haemorrhagic vesicles, bulla, necrosis and ulcers develop. The most common sites are the extensor aspects of the limbs, the buttocks, the back, and occasionally the face (peri-ocular haemorrhagic oedema). Rarely, oral mucosa is involved. Lesions occur in successive waves and then resolve spontaneously.

Infantile acute haemorrhagic oedema is considered by some to be a distinct clinical entity, especially because it has a better prognosis, but is thought by others to be a variant of IgA vasculitis. It is characterised by the following features: febrile onset in children below 2 years of age; oedema of the scalp, hands, feet and peri-orbital tissue preceding purpura; and lack of renal and gastrointestinal involvement. Recovery is expected within 3 weeks.

Oedema probably results from increased capillary permeability due to an underlying vasculitis.

On histology, early changes are essentially those of leucocytoclastic vasculitis with endothelial swelling, fibrinoid necrosis and extravasation of erythrocytes. In the later stages, mononuclear cells may predominate. The superficial dermal vessels are exclusively involved. The frequency of dermal IgA vessel deposits varies depending on the series. These IgA deposits are sometimes included in the diagnostic criteria of dermatology series and thus are present in 100% of cases. Inversely, these deposits are present in only 50% of patients of nephrology series where IgA nephropathy is present in 100% of cases. These dermal IgA deposits are not specific for IgA vasculitis; they may be encountered in many cutaneous vasculitides.

4.2.2 Cryoglobulinaemic vasculitis

Cryoglobulinaemia may be idiopathic or secondary to other systemic diseases such as infections, cancer or autoimmune disorders. The pathogenesis of this vasculitis is mediated by immune complexes formed by cryoglobulins, antibodies that precipitate at low temperatures. Only monoclonal antibodies are found in type I cryoglobulinaemia, monoclonal and polyclonal antibodies are found in type II, and polyclonal antibodies of different classes are found in type III. Type II and III are called 'mixed' cryoglobulinaemia.

As HCV infection is the main aetiology of mixed cryoglobulinaemia (especially type II), the influence of this infection on clinical presentation has been studied. Globally, the clinical and histological aspects of purpura are similar whether HCV infection is present or not.

Skin manifestations occur in 60–100% of patients with symptomatic cryoglobulinaemia. They are a frequent presenting complaint and often accompany arthralgia and fatigue. Renal and hepatic involvement is also frequent. The disease tends to wax and wane. Women outnumber men with a female:male sex ratio of 1.3:1. The average age of onset is 50 years. The interval between the first skin manifestation and diagnosis of

cryoglobulinaemia varies from 0 to 10 years. Palpable purpura of the lower extremities is the main manifestation, present in 92% of patients. Sometimes, purpuric lesions are masked by secondary diffuse pigmentation mimicking chronic venous insufficiency changes. Lesions are more commonly observed on the head and mucosal areas (ears, nose and mouth) in type I cryoglobulinaemia. Seasonal triggering of flares is frequently reported. Raynaud's phenomenon, acrocyanosis, livedo and cold urticaria are other possible manifestations during cold seasons. Post-inflammatory pigmentation is noted in 40% of patients and can retrospectively evoke the diagnosis. Infarction, haemorrhagic crusts and ulcers are present in 10–25% of patients. Widespread necrotic areas are relatively more common in type I cryoglobulinaemia.

Involvement of the skin is due to two major mechanisms: leukocytoclastic vasculitis (related to immune complex deposit) in type 2 cryoglobulinemia and/or occlusion of cutaneous vessels by precipitation of cryoglobulins in cold-exposed areas in type 1 cryoglobulinemia. Histology shows a leukocytoclastic vasculitis and rarely characteristic PAS-positive material in the vessel lumen, corresponding to the cryoprecipitate. Direct immunofluorescence studies have shown IgM, IgG and C3 deposits in some patients with acute vasculitis. In type I cryoglobulinaemia, thrombosis is the main histological feature, while signs of true vasculitis are usually lacking.

4.2.3 Polyarteritis nodosa

According to the names and definitions of vasculitis adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis, classic PAN is characterised by necrotising inflammation of medium-sized muscular arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules and it is not associated with anti-neutrophil cytoplasm antibodies (ANCA's).

The aetiology is unknown in most cases, while pathogenesis seems to be mediated by immune complexes. The triggering antigen could derive from viral infections such as hepatitis B or C.

Systemic PAN is very rare; its evolution is acute with skin manifestations different from those observed in cutaneous PAN. Skin lesions occur in 15–60% of patients with systemic PAN and are less frequently observed in patients above 65 years of age. Although this systemic disease mainly affects the medium arteries of the kidney, liver, heart and gastrointestinal tract, the most common cutaneous finding is palpable purpura corresponding to a small vessel vasculitis (which, *per definition*, should not occur, as it is the consequence of small vessel involvement). Nodules (8–27%), ulcerations and livedo of the racemosa type are less frequent. Other manifestations have been reported such as urticaria, transient erythema, superficial phlebitis, Raynaud's phenomenon, splinter haemorrhages and digital infarction.

The skin hallmarks of cutaneous PAN are nodules (Diaz-Perez et al, 2007*). These cutaneous or subcutaneous nodules appear in groups along the course of superficial arteries. They measure between 5 and 15 mm in

diameter and are mainly located on the lower legs, especially around the knees and on the feet. Livedo may precede, accompany or follow the onset of nodules. In *cutaneous PAN*, livedo of the racemosa type is typically located on the lower limbs, the dorsal aspects of the upper limbs, and rarely the trunk. The fishnet reticular pattern is irregular with broken meshes. On careful examination, some tender infiltrated areas are found. Painful ulcerations are frequently associated with tender and firm plaques resulting from coalescent nodules. These clinical features are characteristic of cutaneous PAN, which, by definition, only affects small arteries and arterioles of the skin and adjacent skeletal muscle, joints and peripheral nerves with consequent myalgia, arthralgia and pure sensitive neuropathy (mononeuritis multiplex). Cutaneous PAN is more chronic than systemic PAN and does not usually evolve into systemic PAN.

4.2.4 Microscopic polyangiitis

The microscopic form of PAN, now called microscopic polyangiitis (MPA), is defined as a systemic vasculitis of small blood vessels (i.e., capillaries, venules or arterioles) without granuloma. MPA is associated with segmental necrotising rapidly progressive glomerulonephritis and ANCA mainly of the myeloperoxidase type.

Dermatological manifestations occur in 30–58% of patients. Palpable purpura of the lower limbs is the most frequent. Other lesions have been reported such as mouth ulcers, vesicles, necrosis, ulcerations, nodules, splinter haemorrhages, livedo, urticaria and facial oedema. All these skin lesions rapidly disappear with treatment.

4.2.5 Eosinophilic granulomatosis with polyangiitis (EGPA)

In 1951, Churg and Strauss defined allergic granulomatosis as a distinct entity occurring in adults with asthma and associated with fever, eosinophilia, systemic vasculitis and extra-vascular granulomas (figure 47). Churg–Strauss syndrome is now known as eosinophilic granulomatosis with polyangiitis (EGPA).

Figure 47 Churg–Strauss granulomas.



The aetiology is unknown although some clinical (allergic respiratory disease) and biochemical (hypereosinophilia and sometimes total IgE elevation) features suggest that infectious or allergic factors such as *Aspergillus* can induce immune-complex or cell mediated reactions.

Usually the disease starts with allergic rhinitis, followed by asthma, hypereosinophilia, and chronic pneumonia or eosinophilic gastroenteritis. Skin lesions have been observed in 40–70% of cases depending on the series. They are rarely inaugural (6%). Palpable purpura on the lower extremities is the most frequent skin sign and is often necrotic. Cutaneous nodules or papules are also very frequent, and located on the lower limbs or on the extensor side of the elbows, fingers, scalp and breast. Lesions of the fingers are usually multiple, often symmetrical, and most commonly localised on both lateral sides of the distal interphalangeal joint. These nodules or papules of the upper limbs frequently have central crusting or ulceration. Their consistence is usually firm. A pustular or vesicular component is rarely noted. Various other dermatological lesions have been reported: maculo-papules resembling erythema multiforme, ulcerations, livedo reticularis, urticarial rash, nail fold infarction with splinter haemorrhages, and facial oedema.

The histological findings of skin lesions can be disappointing, typical granuloma and eosinophils being detected in less than half of patients. ANCA are present in almost half of patients and are usually p-ANCA. Skin lesions rapidly respond to systemic glucocorticoids, but additional immunosuppressive medications are often used to control the systemic disease.

4.2.6 Granulomatosis with polyangiitis (GPA)

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is characterised by involvement of the upper airway, lungs and kidneys, although all organs can be affected. Its pathogenesis mostly depends on the activation of cell mediated immunity, responsible for the formation of granulomas, and on c-ANCA production. Skin lesions occur in 14–77% of cases depending on the series. They are inaugural in about 10% of cases and are rarely isolated. Palpable purpura of the lower extremities is the most frequently observed lesion. Necrotic papules of the extensor aspects of the limbs are less frequent, but more suggestive of GPA. Exceptionally, skin features are similar to those in EED with IgA paraproteinaemia. Nodules are quite frequent, and mainly localised on the limbs. Extensive and painful cutaneous ulcerations may precede other systemic manifestations by weeks to years. These ulcers are sometimes described as 'PG-like lesions', especially when they follow localised trauma or the breakdown of painful nodules or pustules. However, they usually lack the typical raised, tender, undermined border of PG. Sometimes numerous, they are located on the limbs, trunk, face (pre-auricular area), breasts (mimicking adeno-carcinoma with possible nipple retraction and galactorrhoea) and perineum. Digital gangrene is occasionally reported. Florid xanthelasma is associated with long-standing granulomatous orbital and peri-orbital infiltration. In contrast to PAN, livedo reticularis is unusual in GPA.

The frequency of oral manifestations is difficult to estimate from literature series since they are often included in ear-nose-throat symptoms and not described separately. Oral ulcers are sometimes reported independently of other oral manifestations. They are undoubtedly frequent, and present in 10–50% of cases depending on the series. Unlike aphthae, they are persistent and not recurrent. Their number and localisation are highly variable. Gingival changes include gingival hyperplasia with a granular aspect, red to purple colour and many petechiae (figure 48). The entire peri-odontium and gingival mucosa may be involved, resulting in tooth mobility and loss of teeth. Significant but incomplete improvement is observed with empiric antimicrobial therapy. Genital ulcers are uncommon, although penile necrosis has previously been described.

Figure 48 *Gingival hyperplasia in GPA (ex-Wegener's granulomatosis).*



Except for xanthelasma, all clinical and histological types of skin lesions are associated with active systemic disease. They disappear in few weeks or months after treatment onset. They are reported in about 50% of relapses. Skin lesions may be associated with joint and kidney involvement.

Since 1966, limited and sub-acute forms of GPA without kidney involvement have been identified. In our experience, the most frequently observed skin lesions in these forms are nodules with granulomatous infiltration or granulomatous vasculitis on histology.

4.2.7 Behçet's disease

In 1937, a Turkish dermatologist, Hulusi Behçet, described an entity consisting of oral aphthosis, genital aphthosis and ocular inflammation. Since then, various other manifestations have been related to this disease, which is known as Behçet's disease. Skin lesions are frequent and helpful for the diagnosis.

Complex aphthosis is the mucosal hallmark of this disease (Rashtak and Pittelkow, 2008*). Oral aphthae occur as the first manifestation in 25–75% of cases (figure 49). They are usually indistinguishable from ordinary aphthae. They form a 1–3 cm, painful ulceration of variable depth with a yellow fibrinous base surrounded by erythema. Patients may have single or multiples ulcers spontaneously healing in 1–4 weeks without scarring. Ulcers may also be herpetiform with pinpoint lesions occurring in coalescing clusters. The usually affected sites

are the lips, gums, cheeks and tongue, and, less frequently, the pharynx and palate. The frequency of recurrences is highly variable. In the diagnostic criteria of the International Study Group on Behçet's Disease, at least three recurrences per year are required. Pathological features are usually non-specific with rarely a lymphocytic or leucocytoclastic vasculitis. Genital aphthae are present in 60–80% of cases (figure 50). They are similar to oral aphthae but do not usually recur as often. In men, they are mainly localised on the scrotum with a permanent residual scar useful to the diagnosis, more rarely on the sheath or the meatus. In women, the vulva is predominantly involved. Ocular or perineal aphthae are rarely reported.

Figure 49 Aphthae in Behçet's disease.



Figure 50 Genital aphthae in Behçet's disease.



Pseudo-folliculitis is the most frequent skin lesion, observed in 39–60% of cases (figure 51). It presents as non-follicular erythematous, sometimes purpuric, papules that become sterile pustules, and then resolve or ulcerate. They are mainly located on the trunk, lower limbs, buttocks and genitalia but may occur on other parts of the body like the palms and soles.

Figure 51 Pseudofolliculitis in Behçet's disease.



On histology, there is an amicrobial neutrophilic infiltration with a lymphocytic infiltrate and a variable leucocytoclastic vasculitis. Non-bacterial folliculitis can be histologically indistinguishable from a bacterial folliculitis.

Nodules are present in 30–40% of cases, sometimes resembling erythema nodosum, on the anterior aspects of the lower limbs. Histology shows a septal or lobular infiltration of the hypodermis consisting of lymphocytes, histiocytes and neutrophils associated with septal vasculitis. Sometimes these nodules correspond to a superficial thrombophlebitis.

In a few patients, tender erythematous papules and plaques resembling those of Sweet's disease may be present on the face and neck. PG-like lesions have also been reported in some cases. The association with gastrointestinal involvement raises the difficult problem of the differential diagnosis with inflammatory enterocolitis. Other manifestations have been occasionally described: livedo reticularis, purpuric lesions, and erythema multiforme-like lesions.

The pathergy test is an induced cutaneous reaction resembling pseudo-folliculitis. When the skin is pricked by a needle or injected with saline, an erythematous papule or pustule develops within 24–48 h. Pathergy is a characteristic response in Turkish, Israeli, French and Japanese patients but is uncommon in North American and British patients. The use of needles with a large diameter and a blunt point seems to increase the sensitivity of this test. On histology, a lymphocytic and neutrophilic dermal infiltration has been observed in the first 24 h. Vasculitis is rare. Immunoglobulin and/or complement deposits in vessel walls may be obvious using direct immunofluorescence techniques.

4.2.8 Takayasu's arteritis

Takayasu's arteritis is a rare chronic inflammatory arteriopathy of unknown origin that predominantly affects the aorta, its main branches and the pulmonary arteries (Pascual-López et al, 2004*). Two, sometimes overlapping, stages of this disease have been distinguished: a first systemic inflammatory stage followed by an occlusive stage characterised by inflammation of the media and adventitial layers of large vessel walls resulting in vascular stenosis and/or aneurysm formation.

Skin manifestations have been reported in 2.8–28% of patients. Some are directly related to large vessel occlusion such as unilateral Raynaud's phenomenon, digital gangrene or unilateral digital clubbing.

Other skin manifestations frequently thought to be related to this vasculitis included ulcerated or non-ulcerated nodules of the lower limbs, PG, livedo reticularis, papular or papulo-necrotic lesions, superficial phlebitis and Sweet's lesions. Other manifestations which do not have an obvious relationship with Takayasu's arteritis include facial flushing, urticaria, angioedema, erythema multiforme and erythematous eruptions. The prevalence of these different skin lesions varies greatly from Asian to European countries.

In northern America and Europe, acute or subacute inflammatory nodules are the most commonly observed skin lesions. Erythema induratum corresponds to ulcerated subacute nodular lesions.

The histological features of these nodules are variable (granulomatous or necrotising vasculitis, extra-vascular granuloma, septal or lobular panniculitis). Usually, there is no correlation between the localisation of the nodules and large vessel alterations revealed by angiography. Furthermore, these nodules can occur at any stage of the disease. Tuberculoid infiltration has been reported in biopsies from papular or papulo-necrotic lesions, raising the suggestion of an infectious origin of the disease. These lesions mainly occur in the occlusive stage of the disease.

In Japan, PG-like lesions are frequent, especially in the occlusive stage; this type of lesions has also been reported in patients from northern Africa.

The relationship between skin manifestations and Takayasu's arteritis is based on the absence of other aetiology and on the parallel course of skin lesions and vasculitis. Whatever the stage of the disease, recurrence of skin lesions strongly suggests arteritis reactivation.

4.2.9 Giant cell arteritis

Giant cell arteritis (GCA) or Horton's arteritis is a systemic vasculitis with a predilection for cranial arteries in elderly patients. Skin manifestations are often observed in the late stages of the disease and so are actually rare due to early diagnosis.

Classically, the scalp and temples are tender and red, and tender nodules are palpable over the course of temporal, occipital or facial arteries. The pulse in these arteries is diminished or absent. Exceptionally, multiple scalp aneurysms have been reported.

The majority of other skin lesions are the consequence of ischaemia related to cranial artery occlusion and are localised on the tongue and scalp. Glossitis occurs in 10% of patients and may be revealing. The tongue has a red, raw-beef colour and may become blistered, scaling or gangrenous; necrosis usually occurs in the anterior two-thirds. Bullae, ulcers or massive necrosis may affect the scalp.

Patients with scalp necrosis constitute a subgroup of severe GCA with older age of onset and frequent serious complications such as visual loss, gangrene of the tongue or nasal septum necrosis. The mean interval between the onset of symptoms of GCA and scalp necrosis is 3 months. Under treatment, scalp healing is complete or satisfactory in 75% of cases. In other cases, skin grafts are possible. Less severe chronic ischaemia of the scalp leads to thinning or loss of hair. Ischaemic skin lesions of the neck or cheeks are occasionally reported. Rarely, vessels of the lower limbs are involved, leading to ischaemic ulcers or distal gangrene.

Skin biopsy of the border of ulceration or necrotic tissue is rarely helpful.

Senile purpura is frequent on sun-exposed skin in elderly patients, especially when treated with glucocorticoids. However, palpable purpura of the lower limbs due to this vasculitis is exceptional.

In conclusion, dermatological lesions are frequent in many systemic vasculitides. The most frequent cutaneous lesion is palpable purpura. It confirms vasculitis but does not determine its type. Histological examination of all other skin lesions is necessary. There is no correlation between the size of involved vessels and the type of peri-vascular infiltrate in the skin and other organs. Usually, in acute lesions the infiltrate is mostly composed of neutrophils, while lymphocytes are found in subacute lesions, and histiocytes and granulomas are predominant in chronic lesions.

5 Skin manifestations in rheumatoid arthritis

Extra-articular complications including dermatological manifestations occur in more aggressive and long-standing forms of RA.

The cutaneous conditions associated with RA can be divided into four groups: palisading granulomas, vascular and vasculitic lesions, neutrophilic dermatoses and miscellaneous disorders.

5.1 Palisading granulomas

5.1.1 Rheumatoid nodules

These skin changes develop in approximately 25% of patients with RA and represent the most common and most specific extra-articular manifestation of the disease. About 90% of patients with rheumatoid nodules are rheumatoid factor positive. The nodules generally develop as a later disease manifestation but may precede the joint involvement. The most frequently involved regions are areas with mechanically stressed skin such as over the olecranon, the hands (especially the fingers joints), the sacral prominences, Achilles' tendon and, less often, the ears and the head.

Rarely, rheumatoid nodules may be located in the tendons, synovium, bones, sclera, dura, and even the vocal cords and internal organs, particularly the lungs and the heart.

The size of these mostly indolent, hard, flesh-coloured, dome-shaped nodules varies from 5 to 15 mm; they may protrude above the skin or be palpable only subcutaneously or in soft areas (figure 52).

The characteristic histological features of rheumatoid nodules are dense deposits of eosinophilic fibrin surrounded by palisades of histiocytes, lymphocytes, plasma cells, and occasionally neutrophils and neutrophilic dust.

The majority of patients with rheumatoid nodules have severe forms of sero-positive RA, which may indicate a clinically poor prognosis. The nodules as such are mostly benign; only rare complications such as ulceration, infection, sepsis, and fistula formation require surgical intervention. Accelerated growth of rheumatoid nodules (rheumatoid nodulosis) can be observed in RA patients under treatment with methotrexate; besides rheumatoid nodules are more frequent in patients treated with leflunomide and TNF alpha blockers.

The differential diagnoses include pseudorheumatoid nodules (see section 5.1.2), subcutaneous granuloma annulare, Heberden's and Bouchard's nodules, fibrinoid nodules in skin borreliosis (acrodermatitis chronica atrophicans), tendon sheath xanthomas, gout tophi and foreign body reactions.

Figure 52 Rheumatoid nodules in a 72-year-old female patient.



5.1.2 Other cutaneous granulomas in RA (see also interstitial granulomatous dermatitis, chapter 4.1.3.8)

Pseudorheumatoid nodules are mostly seen in children but also in some adults without rheumatic disease. They mainly occur on the scalp and lower legs and are considered a deep, or juxta-articular form of granuloma annulare.

Palisaded neutrophilic granulomatous dermatitis (PNGD) is an uncommon skin manifestation in some patients with RA and has a variable clinical picture: initial lesions can be urticarial and later evolve to skin-coloured nodules. On the elbows, they may clinically resemble rheumatoid nodules. In other patients, cutaneous plaques or linear cords are seen, especially on the lateral aspects of the trunk (see section 4.1.3.8). The histological picture shows interstitial deposition of histiocytes, mucin and a peri-vascular infiltrate of neutrophils and plasma cells. Cutaneous mucinous nodules described mostly in Japanese patients with RA may represent another variant of PNGD clinically and pathologically characterised by extensive subcutaneous mucin deposition and proliferation of fibroblasts and of mononuclear cells.

5.2 Rheumatoid vasculitis

There is no universally accepted definition of rheumatoid vasculitis (RV). This rare condition should be considered in patients with RA when other disorders associated with secondary systemic vasculitis such as diabetes, cryoglobulinaemia, drug hypersensitivity and lymphoproliferative malignancies have been excluded. RV affects about 1–5% of patients with RA, mostly those with severe forms. The spectrum of clinical manifestations in RV is wide and ranges from minute digital petechiae, purpuric papules, or ulcers (Bywater's lesions) to widespread deep peripheral gangrene or PG-like ulceration.

Small to medium arterial or venous vessels are affected, most commonly those of the skin (80–90%) and the vasa nervorum of peripheral nerves (around 40%).

Other clinical manifestations of systemic vasculitis such as involvement of the central nervous system, the eyes and various internal organs are less frequent.

Peripheral nerve involvement typically manifests as distal, symmetric sensory and motor neuropathy and mononeuritis multiplex.

Focal digital purpuric papules, petechiae, leg ulcers and peripheral gangrene are the most common skin manifestations of RV. Cutaneous small-vessel vasculitis may sporadically occur in RA patients as a sign of drug hypersensitivity (see below); more typical are chronic vasculitic lesions resembling livedoid vasculitis or periarteritis nodosa with deep, often painful cutaneous ulcers (figure 53).

Figure 53 Rheumatoid vasculitis.



Whereas Bywater's lesions may occur without other signs of systemic vasculitis, leg ulcers or gangrene mostly represent complications associated with severe organ involvement and a poor prognosis.

Erythema elevatum diutinum (EED), a chronic form of leucocytoclastic small-vessel vasculitis characterised by mostly symmetric erythematous or yellow-brown plaques and nodules over the extensor surfaces of the extremities, represents a rare cutaneous manifestation of RV, but may also be seen in non-rheumatic individuals.

5.3 Neutrophilic dermatoses

5.3.1 *Pyoderma gangrenosum*

PG is the most severe of this heterogeneous group of inflammatory neutrophilic skin diseases; it can occur in about 10% of patients with RA, more often in women, but is also seen in association with other chronic inflammatory and autoimmune disorders such as Crohn's disease or with hematologic malignancies, or presents as an idiopathic disorder without apparent underlying disease.

PG (see section 4.1.3.3) starts with single or multiple small bullous lesions or pustules, mostly on the legs, or in the abdominal or genital-anal area; however, PG can occur elsewhere including on mucous membranes. The initial lesions may coalesce and rapidly progress to mature into ulcerative superficial granulomas and large necrotic and painful ulcers with a purulent base and characteristic reddish-blue undermined borders that extend centrifugally (figure 54). Single lesions can be 20 cm or more in diameter (figure 54), while multiple lesions tend to be smaller. PG ulcers can take years to heal and often require high-dose glucocorticoids and/or immuno-suppressant treatment, and leave behind atrophic, cribriform and often hyperpigmented scars.

Figure 54 *Pyoderma gangrenosum*.



5.3.2 Rheumatoid neutrophilic dermatitis

Rheumatoid neutrophilic dermatitis (RND) is a rare cutaneous finding in patients with severe RA. Clinically, the eruption is characterised by symmetric erythematous papules or plaques. Vesicles are sometimes seen on the extensor surfaces of the arms and hands.

Ulceration or progression to PG has not been described. On histological examination, a dense interstitial dermal neutrophilic infiltrate with leucocytoclasia without signs of leucocytoclastic vasculitis is seen. In most cases, topical treatment with potent glucocorticoids is sufficient.

Acute febrile neutrophilic dermatosis (Sweet's syndrome) may closely resemble RND on histology. Clinically, this neutrophilic dermatosis has a more acute onset with fever and develops with markedly inflamed and oedematous coin- or dome-shaped tender infiltrates and plaques, often on the shoulder and the face.

RA is one of the many known underlying disorders which also include upper respiratory tract infections, gastrointestinal disorders, drug reactions and leukaemia.

In contrast to PG, Sweet's syndrome can resolve spontaneously or with various treatments including colchicine, dapsone and steroids, without scarring. Despite the fever, antibiotics are ineffective in the cases not associated with infection; treatment of the underlying disorder is most important.

5.4 Cutaneous side effects of RA treatment

It is estimated that up to 40% of RA patients develop cutaneous drug adverse events in the course of their treatment. These reactions are mild in most cases, occur within the first few weeks of treatment, and manifest as vasculitis, urticaria or skin rash. The rash may be maculo-papular, vesiculous, bullous or pustular, often affecting the whole integument and the mucosal surfaces; the most severe of these allergic drug reactions to antirheumatic drugs are Stevens-Johnson syndrome (SJS) and TEN (Lyell syndrome), which have a high mortality rate, especially in older patients.

5.4.1 Non-steroidal anti-inflammatory drugs

Skin reactions to aspirin are rare (<1%) in the general population, but much more common among patients with asthma or chronic urticaria. These reactions are mostly of a non-immunological nature and are related to pharmacological intolerance and linked to arachidonic acid metabolism and leukotriene release. On the other hand, some non-steroidal anti-inflammatory drugs are credited with a high risk of allergic skin reactions ranging from transient rash resembling viral exanthema to TEN (such as the many pyrazol and pyrazolon derivatives, including oxicam). However, the absolute risks of SJS and TEN associated with NSAID treatment are low; oxicams have a higher risk of SJS and TEN than the other NSAIDs and patients who have recently begun treatment should be carefully monitored. Selective cyclo-oxygenase-2 inhibitors have been less frequently

reported to be associated with serious drug reactions and in fact seem to be well tolerated by most NSAID-sensitive and aspirin-intolerant patients.

5.4.2 Disease-modifying antirheumatic drugs

Sulfasalazine or its major metabolites 5-aminosalicylic acid and sulfapyridine can cause an itchy rash that usually resolves once the drugs are stopped. Sulfasalazine causes a peculiar orange-tinged discoloration of sweat. Rare adverse muco-cutaneous side effects include oral ulcers, hypersensitivity syndrome (lichenoid skin eruption, leucocytopenia, thrombocytopenia, fever) and SJS or TEN.

Chloroquine and hydroxychloroquine are known to induce a characteristic greyish-blue hyperpigmentation of glabrous skin and mucosal surfaces.

Muco-cutaneous side effects following the administration of gold compounds (oral or intramuscular) are estimated to occur in 10–20% of treated patients. Within weeks or months, a generalised rash, closely resembling lichen planus, pityriasis rosea or eczema may be seen; urticarial, hyperpigmented (Chrysiasis) or vasculitic lesions are less frequent, while SJS and TEN are extremely rare. Gold dermatitis often responds to topical treatment with mid-potent glucocorticoids, and continuation of treatment at a lower dosage may be tried.

Cutaneous toxicity from D-penicillamine can be a major problem requiring definite discontinuation of the drug; in addition to eczematous or lichenoid rashes, as seen with other antirheumatic medications, D-penicillamine can uniquely induce or exacerbate autoimmune diseases such as SLE, DM, myasthenia gravis and, most notably, pemphigus vulgaris or foliaceus. D-penicillamine contains sulfhydryl groups which are believed to have a key role in inducing direct lysis of the epidermis, through alteration of the intercellular bonds through the formation of thiol group–cysteine bonds, instead of cysteine–cysteine bonds.

5.4.3 Biologics

The introduction of biological therapies that target specific proinflammatory cytokines have had a great impact as new treatment options for patients with RA.

Adverse reactions to the IL-1 blocker anakinra and to the TNF- α inhibitors infliximab, etanercept and adalimumab have been estimated to occur in about 25% of RA patients treated with biologics (Scheinfeld, 2004*).

These cutaneous reactions are of special interest to dermatologists, since most biologics are also used for inflammatory skin disorders such as psoriasis.

5.4.3.1 Local reactions

Inflammatory reactions at injection sites are common in RA patients undergoing treatment with anakinra; treatment can be maintained in the great majority of cases. Similar erythematous or oedematous lesions occur mostly within 12–24 h following subcutaneous injection of etanercept and usually disappear within 3–5 days without topical treatment.

Matters of concern are generalised cutaneous reactions seen either immediately or after several days in 10–20% of RA patients following intravenous administration of infliximab; these reactions present with a disseminated erythematous flush or with acute urticaria and pruritus (figure 55). When these skin reactions recur with subsequent injections or are accompanied by systemic symptoms such as fever, dizziness or hypotension, termination of infliximab treatment may become necessary. However, an anaphylactic reaction to infliximab requiring intensive care is very rare.

Figure 55 *Acute urticarial rash induced by infliximab.*



5.4.3.2 Skin infections

About one third of skin changes related to treatment with biologics are infections. The most frequent are pityriasis versicolor caused by excessive proliferation of the saprophyte yeast *Malassezia spp.* and tinea corporis caused by several dermatophytes; less frequent are herpes simplex, zoster or bacterial infections.

5.4.3.3 Inflammatory skin eruptions

Generalised or localised inflammatory skin reactions resembling atopic dermatitis, eczema, psoriasis or lichen planus are the most frequent cutaneous adverse effects related to treatment with biologics. Psoriasiform eruptions seem to be a class effect common to infliximab, etanercept and adalimumab; the eruption may appear immediately after the first injection or several months later, and tends to become pustular, often resembling palmoplantar pustular psoriasis, especially in RA patients treated with infliximab; however, psoriasis vulgaris may also occur. The mechanisms involved remain elusive. In some patients, switching to another TNF- α blocker results in clearing of the skin, although in others discontinuation of biologics altogether and initiation of an antipsoriatic treatment is necessary.

5.4.3.4 Drug-induced lupus erythematosus

Antinuclear antibodies (ANA) are a frequent serological finding in RA patients treated with TNF- α inhibitors (table 4). Lupus erythematosus-like skin manifestations resembling SCLE, DLE or SLE are, however, very rare and are estimated to occur in less than 0.5% of RA patients treated with TNF- α inhibitors. About two-thirds of these patients have systemic manifestations typical of SLE and characterised by arthritis, polyserositis, myositis, vasculitis and other complications including renal disease; serologically, antibodies to double-stranded DNA and hypocomplementaemia are often present. TNF- α -induced SLE differs markedly from drug-induced SLE due to other medications. Other patients develop DLE with erythemato-squamous lesions in UV-exposed skin, alopecia, chilblain-like lesions, and vasculitis or overlap syndromes such as mixed connective tissue disease. In many patients, the lupus reaction resolves with cessation of TNF- α blocker treatment.

Table 4 Frequency of antinuclear antibodies during treatment with biologics

	ANA (%)	Anti-DNA IgM/IgA (%)	Anti- DNA IgG (%)
Infliximab	28–82	49–70	>5
Adalimumab	13–28	>10	–
Etanercept	5–10	>10	–

ANA, antinuclear antibodies.

Besides LE or lupus-like syndromes, other autoimmune diseases may develop during therapy with biologics; these include hypocomplementaemic systemic vasculitis and IgA-nephritis.

5.5 Cutaneous manifestations in subsets of RA

Cutaneous signs of Felty syndrome (a combination of RA, splenomegaly and neutropenia) consist of rheumatoid nodules, hyperpigmentation and leg ulcers. The incidence of rheumatoid nodules in Felty syndrome is about 70% and thus much higher than in RA. The leg ulcers resemble that shown in figure 53; they may be secondary to PG or medium blood vessel vasculitis with ulcerations. They are extremely resistant to treatment and at risk of becoming septic due to the underlying immune defects present in some patients with Felty syndrome.

6 Skin manifestations in Still's disease

In up to 90% of patients, systemic-onset juvenile idiopathic arthritis (Still's disease) is characterised by a typical transient, pink macular rash over the trunk, axillae, face and extremities that is non-pruritic and coincides with acute febrile episodes of the disease, occurring usually in the late afternoon. The patient's skin is hypersensitive, often demonstrating urticarial dermographism. Other cutaneous features include persistent linear and peri-orbital oedema and erythema. Rheumatoid nodules are rare but may appear in the course of treatment with methotrexate.

The transient, rash of adult-onset Still's disease also accompanies fever spikes and shows a characteristic salmon-pink colour. The rash is most often macular or slightly urticarial and appears over pressure points. It usually corresponds to a neutrophilic urticarial dermatosis when biopsied (Kieffer et al, 2009). Persistent red pruritic papules and plaques, sometimes linear, may be also seen in adult patients with more severe forms of Still's disease. A distinctive histopathological aspect associating dyskeratotic/necrotic cells in the upper epidermis and perivascular (and sometimes also interstitial) inflammatory infiltrate of lymphocytes and neutrophils in the upper and mid-dermis is observed.

The differential diagnosis of the rash in Still's disease includes various viral exanthemas, drug eruptions, and erythema marginatum rheumaticum seen in acute rheumatic fever. This rapidly spreading annular erythema occurs mostly on the trunk and is—in contrast to Still's disease—not associated with fever spikes.

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SUMMARY POINTS

- Skin signs are present in more than 80% of lupus erythematosus (LE) cases. They can be divided into four groups: specific lupus lesions, lesions reflecting thrombotic vasculopathy, neutrophilic lupus and miscellaneous lesions. Lupus lesions include acute, subacute and chronic LE. All lupus skin types can be associated to varying degrees with systemic LE.
- Patients with subacute cutaneous LE can develop Gougerot-Sjögren syndrome and reciprocally. This association increases the risk of cutaneous vasculitis, central nervous system involvement and interstitial pulmonary syndrome.
- Sun protection, antimalarials and topical anti-inflammatory creams are the first-line treatment in cutaneous LE, except for neutrophilic LE where anti-neutrophil drugs (colchicine, dapsone) are the treatment of choice.
- Vascular manifestations in LE are rarely related to vasculitis (eg, urticaria) and more frequently to thrombosis (eg, livedo reticularis), implying specific therapeutic interventions (including anti-platelets and/or anticoagulants).
- Heliotrope oedematous erythema of the face and Gottron papules on the finger joints are highly specific of dermatomyositis (DM). Skin calcinosis is a major problem, especially in childhood DM.
- Skin necrosis, skin vasculitis, pruritis and bullous lesions are suggestive of underlying malignancy in adult DM, generally in association with the presence of anti-TIF-1gamma or anti-NXP2 autoantibodies.
- Diagnostic criteria for systemic scleroderma (SS) are skin thickening of the fingers extending proximal to the metacarpophalangeal joints or if that sign is not present, seven additive items are considered, with varying weights for each: skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon and SS-related autoantibodies.
- Skin involvement in SS can be limited to acral areas (hands, feet), the face and the neck or can be diffuse, ascending to the trunk and abdomen. Diffuse skin involvement is associated with multiple internal manifestations and a poorer outcome.
- Fingertip ulcers are a major clinical problem in diffuse cutaneous scleroderma and are frequently associated with Raynaud's syndrome, lung fibrosis and pulmonary arterial hypertension.
- Purpura is the most frequent skin lesion in systemic vasculitis. Cutaneous manifestations are important for confirming the vasculitis, but are rarely suggestive of the type of vasculitis.
- Painful, non-healing skin ulceration is often associated with organ involvement in systemic vasculitis.
- Rheumatoid nodules are the most frequent extra-articular manifestation of rheumatoid arthritis (RA).
- Rheumatoid vasculitis and pyoderma gangrenosum in RA is indicative of advanced disease and poor prognosis.
- Cutaneous side effects of antirheumatic drugs occur in up to 40% of RA patients and range from transient skin rashes to life-threatening toxic epidermal necrolysis.
- In RA patients treated with TNF- α blockers, antinuclear antibodies frequently develop but clinical manifestations of LE are very rare.

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29a

module

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Skin and auto-immune rheumatic diseases

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A previous version was coauthored by Camille Francès, Elisa Cinotti, Franco Rongioletti



IN-DEPTH DISCUSSION I

Differential diagnosis of scleroderma

Scleroderma, meaning "hard skin" in Greek, designs a heterogeneous group of auto-immune fibrosing affections including systemic sclerosis (SSc) and localized scleroderma, which should be better named morphea in our opinion. They share cutaneous induration, consecutive to sclerosis, as a common feature. However, a number of other diseases can also manifest with skin induration and sometimes systemic signs, the distinction with SSc being then crucial to ensure an appropriate and prompt management. Keys to the proper recognition of these scleroderma-like disorders (or sclerodermiform syndromes) are presented in this in-depth discussion. The sclerotic variant of the Graft vs Host disease should be rather considered as an experimental form of morphea than a differential diagnosis, and will not be addressed here.

1. Systemic sclerosis

A detailed description of SSc is available in the main text of module 29a, thus all these features will not be extensively reviewed here. Briefly, the cardinal elements of early SS's diagnosis are:

- Raynaud's phenomenon (RP), which is present in almost all patients, most often as the first sign of disease.
- Symmetrical cutaneous involvement of extremities, typically beginning as finger and/or toe oedema with mild erythema and puffy appearance, slowly progressing to skin sclerosis (sclerodactyly). Of note, skin sclerosis may rarely be absent in some patients with organ involvement (SSc sine scleroderma).
- Anti-nuclear antibodies (ANA), mostly of the anti-centromere, anti-topoisomerase I (Scl-70) or anti-RNA polymerase III type, which collectively are present in up to 95% of patients.

Additional highly suggestive cutaneous features are the abnormal rounded-to-rectangular telangiectasia located on the palmar aspect of the hands and fingers and the face (including the lips and oral mucosa), megacapillaries of the nailfold and pitted scars of the fingertips, lateral aspect of digits and sometimes dorsum of interphalangeal and metacarpophalangeal joints.

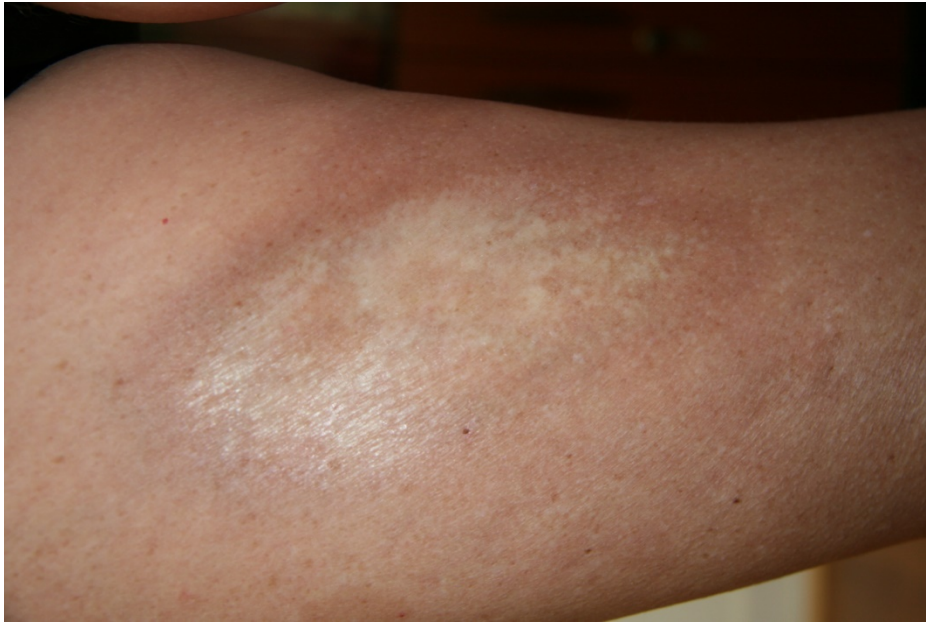
In the absence of both RP and ANA in a patient with sclerotic skin changes, the diagnosis of SSc is highly unlikely, meaning that another SS-like disorder should definitely be considered (Cheeseburger et al, 2012).

2. Morphea (localized scleroderma, including eosinophilic fasciitis)

Morphea is a fibrosing disorder of unknown aetiology affecting less than 3 per 100,000 inhabitants per year, with similar prevalence in children and adults. Multiple environmental factors (infections, skin trauma, radiations...) have been proposed to contribute to disease development (Mertens et al, 2017).

Superficial plaque morphea typically starts as a round or oval lilac patch which progressively evolves to central sclerosis giving a shiny ivory aspect surrounded by a peripheral active lilac ring. In the late phase, sclerosis often regresses to leave atrophy and/or pigmentary changes (figure 1).

Figure 1 Late stage of superficial plaque morphea.



Rare variants are guttate morphea (small white patches < 2 cm), bullous morphea and choroidal morphea. Multiple plaques of morphea may coexist (disseminated plaque morphea). A highly prevalent association exists between plaque morphea and genital lichen sclerosis (figure 2), concerning up to 38% of adult patients (Lutz et al, 2012).

Figure 2 Genital lichen sclerosis associated with plaque morphea. Complete atrophy of minor labia and clitoris hood.



As genital lichen sclerosus bears a risk of evolution into squamous cell carcinoma, full-body examination of patients with morphea by an experienced dermatologist is mandatory. This significant association has not been observed in patients with SSc yet, but such an association might exist, to a lesser degree, in patients with localized systemic sclerosis (D. Lipsker, manuscript in preparation). *Linear morphea* (including the “coup de sabre” variant and Parry-Romberg hemifacial atrophy) predominantly affects young individuals; deep involvement with bone defects may be present.

Deep morphea (or morphea profunda) predominantly involves hypodermis and/or fascia and manifests as poorly defined deep induration with sometimes cobblestone or “peau d’orange” appearance of the overlying skin.

Eosinophilic (Schulman’s) fasciitis (EF) is considered as a variant of deep morphea. Classically, it follows intense and unusual physical activity. Other triggering factors such as infection with *Borrelia burgdorferi*, auto-immune diseases or exposure to certain medications have been described. EF begins as symmetrical burning erythema and pitting oedema evolving to severe induration, affecting the limbs and sometimes the trunk. The skin appears bounded down to the underlying structures, with typical peau d’orange aspect (figure 3) and guttering around the superficial vessel (groove sign).

Figure 3 Eosinophilis fasciitis. Deep induration and peau d’orange appearance.



The fingers / toes and the face are always spared and RP is absent, ruling out SSc. Typical superficial plaque morphea is associated in 20-40% of cases. Hypereosinophilia is a variable transient feature. Considerable

functional impairment may result from joint contracture, thus early diagnosis and treatment are mandatory. MRI is helpful to document deep fascial involvement, guiding the deep surgical biopsy which should sample not only hypodermis but also fascia and superficial muscle to confirm the diagnosis. Sclerosis and tissue eosinophilia are characteristic histological findings. Underlying hematologic disorder of both lymphoid and myeloid type may be present in up to 10% of patients and should thus always be ruled out. Exposure to dietary supplements containing L-tryptophan or 5-hydroxytryptophan should be searched, as it can induce a highly similar picture with prominent myalgia (*eosinophilia myalgia syndrome*).

Generalized morphea is used to designate two distinct entities: *disseminated plaque morphea* (i.e. multiple plaque morphea), and *pansclerotic morphea*. The latter is a debilitating disease consisting in extensive, circumferential morphea starting on the trunk, which progresses to involve the majority of skin surface, but typically spares the fingers, toes and areolae. RP and nail fold capillary changes are absent, but ANA may be present, of the anti-single strand DNA and/or anti-histone type. Major functional disablement due to joint contractures and restrictive respiratory insufficiency is frequent, sometimes leading to death (Kim et al, 2014).

3. Differential diagnosis of acrosclerosis / sclerodactyly

SSc is not the only cause of sclerodactyly, and other conditions may present with sclerotic changes involving the skin of fingers (Ferrelli et al, 2017).

Among them, *mixed connective tissue disease* (Sharp's syndrome, MCTD) and *POEMS* (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) *syndrome* are the only two where RP may also be present. Typical cutaneous presentation of MCTD is erythematous puffy fingers with RP, but evolution to genuine sclerodactyly with nail fold capillary changes has been observed in a few cases, attesting a common spectrum from MCTD to SSc. Skin sclerosis has been reported in acral regions in 10% of POEMS patients, more rarely on the trunk or in a diffuse manner, while RP is present in 20% (Miest et al, 2013). Other skin changes suggestive of this monoclonal plasma cell proliferative disorder-associated syndrome are hyperpigmentation and hypertrichosis (often prominent on the extremities) and angiomatous papules corresponding to glomeruloid haemangiomas histologically.

Genuine sclerodactyly may also be encountered in various conditions such as:

- *porphyria cutanea tarda*, a metabolic disorder caused by dysfunction of hepatic uroporphyrinogen decarboxylase, either in a hereditary context or acquired in association with hemochromatosis, HIV or hepatitis C infection; prominent features of this condition are recurrent blisters on light-exposed areas leaving atrophic scars and milia, pigmentary changes and malar hypertrichosis (figure 4),

Figure 4 *Porphyria cutanea tarda. Sclerodactyly, dried blisters and atrophic scars*



- *carcinoid syndrome*, generally in the context of a digestive or pulmonary neuroendocrine tumours with hepatic metastases, in association with prominent flushing, diarrhoeas and bronchospasm,
- rare genetic diseases, generally obvious because of other suggestive features such as progeroid changes in *Werner's syndrome*, OMIM#277700; or keratoderma of the palm and soles in *sclerotoses* or Huriez syndrome, OMIM#181600).

Other conditions may resemble sclerodactyly but differ according to precise clinical analysis. In *fibroblastic rheumatism*, only palmar aspect of the hands is concerned by sclerosis, and para-articular flesh-coloured nodules are present. In *diabetic cheiroarthropathy*, confluent tiny waxy papules on the dorsum of fingers are responsible for skin induration, leading to flexural joint contractures, generally in the context of patients with long-standing juvenile-onset diabetes mellitus. In *palmar fasciitis and polyarthritits*, a paraneoplastic syndrome associated with ovarian and other cancers, diffuse inflammation of the palmar fascia and tendon sheaths is leading to flexion contracture of the hands without skin sclerosis. In *scleroderma-like amyloidosis* (see below), extremities can be involved, but induration and limitation of movements are not related to sclerosis, but to deposition of amyloid.

4. Differential diagnosis of non-acral skin sclerosis

Beyond diffuse morphea (either EF or pansclerotic morphea), other conditions are classically cited as differential diagnoses of diffuse SSc (Ferrell C et al, 2017; Tyndall et al, 2013). A distinction can generally be easily made on the basis of a careful skin examination, good anamnesis and serum protein electrophoresis plus immunofixation.

Scleromyxedema (or papular mucinosis) presents with an eruption of small waxy dome-shaped or flat-topped papules, often arranged in a linear pattern, with variable erythema and pruritus. Extensor surfaces of limbs, head, neck and trunk are progressively involved in a diffuse manner, with subsequent induration and movement

restriction. A monoclonal gammopathy, usually of the IgG lambda type, is often present (> 80% of cases). Central and peripheral nervous system involvement is frequent, sometimes leading to coma (dermato-neuro syndrome); polyarthralgia or even arthritis may also be present. Thyroid disease should be ruled out. Skin histology demonstrates a triad of dermal mucin deposits, fibrosis and fibroblast proliferation. Scleromyxedema typically exemplifies the concept of monoclonal gammopathy of cutaneous significance (Lipsker, 2017).

Scleredema (Buschke's) predominantly affects men with diabetes mellitus, but forms associated with upper respiratory tract infections or monoclonal gammopathy in the absence of diabetes have been described. It presents with progressive indurated non-pitting oedema of posterior neck and shoulders, with faint erythema and peau d'orange aspect. Extension to the face impairing facial expression is possible, while systemic involvement is rather infrequent. Abundant dermal mucin deposits and septal fibrosis are the main histological anomalies.

Nephrogenic systemic fibrosis is a disease linked to organ deposition of gadolinium-based contrast agents, mainly gadodiamide, subsequent to MRI performed in patients with advanced renal failure (i.e. eGFR <30 mL/min/1.73 m²) and first reported in 2000. The number of new cases has declined dramatically since the cause was identified in 2006. However, the disease can reveal itself years after exposure. It presents with firm and sometimes erythematous and itchy papules coalescing in plaques and / or deep nodules symmetrically distributed on the limbs and the trunk, the face and the fingers / toes being usually spared (figure 5). A suggestive cobblestone or peau d'orange aspect of the skin is often present. Impairment of joint flexibility subsequent to fibrosis and systemic involvement affecting heart and lungs may occur. Histological analysis shows a proliferation of fibroblasts with thickening of collagen bundles that extends into the hypodermis.

Figure 5 Nephrogenic systemic fibrosis. Waxy coalescent papules on a limb.



Scleroderma-like amyloidosis is an extremely rare variant of light chain amyloidosis. Induration of skin can be widespread and can also involve extremities. Skin biopsy will show deposition of amyloid material in the dermis and sometimes hypodermis by Congo-red stain.

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Skin and auto-immune rheumatic diseases

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IN-DEPTH DISCUSSION II

**Cutaneous manifestations of antiphospholipid syndrome
(APS)**

Antiphospholipid Syndrome (APS) is the association of antiphospholipid antibodies (aPL) with hypercoagulability resulting in arterial and/or venous thrombosis, and pregnancy morbidity/obstetric complications (1). Since the first description of antiphospholipid syndrome in 1983 (2), a wide variety of dermatologic manifestations (table I) have been reported (1). Their clinical significance is highly variable. Their management depends on clinical aggressiveness and the presence of other manifestations of APS.

Skin manifestations of APS

A convenient way to classify skin manifestations of APS is to distinguish between lesions reflecting microangiopathy and lesions reflecting large vessels thromboembolic disease. This distinction makes sense as pathophysiology likely differs in some way, which may result in different management strategies (as vascular and heart imaging in the case of large vessel thromboembolism for example).

1. Lesions reflecting microangiopathy

Livedo of the racemose type (LR) is the most frequent dermatologic manifestation. It has been described in sixteen to twenty five percent of two large series of cases (3, 4) and was the inaugural feature of APS in seventeen percent of cases. It is usually extensive or may be localized on the limbs, the trunk and the buttocks. The fishnet reticular pattern is fine and irregular realizing incomplete broken circles (fig. 1). Unlike vasculitic LR, APL livedo is not infiltrated and non-tender. The mechanism of LR in APS remains unclear. Histopathology of skin biopsies (whatever the site sample is) does not show thrombosis except in the catastrophic APS subtype. Vascular proliferation and endarteritis obliterans of arterioles (5) have been reported in some cases. These features do not exclude previous patchy thrombosis. Interaction of antiphospholipid antibodies with the endothelium or other cellular elements of the vessels, in a way that alters their function and induces vasoconstriction, is another possible mechanism (6). In our opinion, LR has to be considered as sequelae and not as an active lesion, in the sense that it won't further evolve to skin necrosis. This doesn't hamper its pathologic significance however, as the underlying thrombotic process may be active in other organs at the same time.

Figure 1: Livedo racemosa in SLE-related APS



Livedoid vasculopathy-like lesions are painful necrotic ulcers located on the legs, ankles and dorsum of feet. It presents as a small painful purpuric macule evolving to a larger geographic-shaped ulceration with purple non- or slightly elevated borders. Healing time is slow, leaving atrophie blanche when achieved. It may be the sole clinical manifestation of APS (fig.2). When a biopsy is performed, small vessel thrombosis may be hard to demonstrate.

Figure 2: Typical atrophic scars of livedoid vasculitis-like ulcers with purpuric necrotic lesions in primary APS



Retiform purpura is likely the most alarming manifestation of APS, as it reflects complete vascular occlusion with vascular damage leading to red blood cells extravasation. It manifests as well-defined angular or branched red to purple macules that fail to blanch under pressure, generally evolving to **superficial gangrene**. It is important to note that small distal lesions of retiform purpura may also be observed in the context of large vessels thromboembolism.

Rapidly extensive retiform purpura (mimicking infectious purpura fulminans) leading to **widespread superficial cutaneous necrosis** may be observed in catastrophic APS, the most severe and fortunately infrequent form of APS, characterised by widespread small-vessel thrombosis with multiorgan failure and high mortality (7). Cutaneous lesions are similar to those observed in other thrombophilic states such as protein C or protein S deficiencies, monoclonal cryoglobulinaemia or cryofibrinogenaemia (fig. 3). Histopathology of early purpuric lesions shows diffuse skin vessels thrombosis, without associated inflammation.

Figure 3: Widespread superficial skin necrosis in SLE-related APS



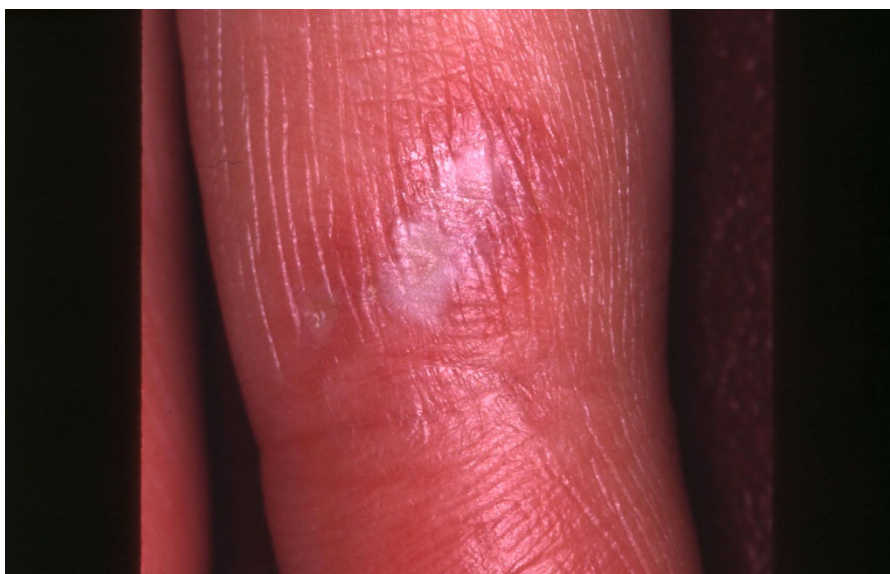
Other lesions reflecting thrombotic microangiopathy in APS are **pseudovasculitis lesions** mimicking cutaneous vasculitis that may be misdiagnosed if skin biopsies are not performed, especially in case of SLE; ill-defined **purpura** (fig. 4); papules or nodules of the limbs, ears, neck or thighs, and **malignant atrophic papulosis-like lesions** (fig. 5). Thrombosis of skin vessels and acellular mucin-rich dermis is usually obvious on biopsies in the latter. The term “vasculitis” is misleading in those cases, which reflect a primary thrombotic vasculopathy and not an inflammatory process affecting the vessel wall.

Pyoderma gangrenosum-like large ulcers have rarely been described on the legs of patients with APS, differing from genuine pyoderma gangrenosum as they lacked undermined elevated borders and demonstrated prominent small vessels thrombosis instead of neutrophilic infiltrate on histology.

Figure 4: Purpuric lesions related to thrombosis can be extremely difficult to distinguish from purpuric lesions related to vasculitis



Figure 5: Malignant atrophic papulosis-like lesions of the digit



2. Lesions reflecting large-vessels thromboembolism

Superficial and deep venous thromboses are common manifestations of APS which may result in common secondary skin changes such as **lipodermatosclerosis** or **venous ulcers**.

Distal gangrene (often preceded by **acrocyanosis** and/or **purple toe or digit**) may reflect distinct pathomechanisms involving large vessels, ranging from acute to slowly evolving processes:

- stenosis or occlusion of medium to large arteries,
- atheroembolism from a ruptured atherosclerotic plaque, heart valve vegetation or intracardiac thrombus,
- venous limb gangrene resulting from phlegmasia cerulea dolens, usually in the setting of catastrophic APS (8).

Multiple splinter haemorrhages under the nails appear as tiny linear longitudinally oriented, reddish-brown to black, distal lesions that fail to blanch under pressure (fig. 6). They may be also observed in various conditions implying or not distal embolism, e.g. subacute bacterial endocarditis, and even in healthy people (9).

Figure 6: Multiple splinter haemorrhages of the nails concomitant to pulmonary embolism in APS



3. Other skin manifestations associated with APS

Primary anetoderma (fig. 7) is a rare elastolytic disorder, characterized clinically by a circumscribed area of slack skin with macular depressions or out-pouchings of skin. Skin lesions are numerous (>10), located on the upper part of chest and arms. Histologically there is a loss of dermal elastic tissue. Anetoderma may be primary or secondary to various dermatoses. When primary, it is frequently observed in patients with autoimmune diseases and especially related to antiphospholipid antibodies (10).

Figure 7: Diffuse anetoderma in SLE-related APS



Relevance of dermatologic manifestations in the diagnosis of APS

In the latest international consensus statement to define APS (table II), clinical criteria include skin vessels thrombosis on strict condition that thrombosis is confirmed by histopathology, with the exception of superficial venous thrombosis (11). As previously stated, thrombosis is rarely detected on skin biopsies of patients with livedo only. Biopsy of splinter haemorrhages of the nails is exceptionally done. On the contrary, thrombosis may be detected in biopsies of all other skin lesions.

Association of skin lesions to other manifestations of APS

LR is significantly correlated with cerebral and ocular ischemic arterial events, seizures, heart valve thickening on ultrasound, and arterial systemic hypertension. Conversely, LR is less frequent in patients with only venous thrombosis (3, 4). Post phlebitic ulcers are correlated with recurrent venous thrombosis,

The onset of multiple splinter haemorrhages of the nails is frequently concomitant to worrying thrombotic events of various sites (brain, digits, skin, adrenal glands...) (9).

The “catastrophic” APS is characterized by widespread vascular occlusions involving multiple organs simultaneously. It is frequently associated with skin lesions (70%). LR, acrocyanosis, extensive cutaneous necrosis, palmar erythema, digital gangrene and ischemic ulcers have been reported in this condition (7).

Treatment

Treatment of patients with skin lesions must be considered according to the different dermatologic manifestations and the clinical situation. Two questions should be answered: (a) how to treat dermatologic manifestations? And, (b) is any prophylactic long term-treatment required in such patients? In the absence of randomized controlled trials, therapy of skin lesions remains empirical.

Widespread cutaneous necrosis and/or digital gangrene are the major thrombotic events that require full anticoagulation with heparin. If extension of these skin lesions persists despite anticoagulation, prostacyclin derivatives and/or plasmapheresis may be prescribed as they have been reported to be successful in isolated cases.

No treatment has been proven to be effective in LR. In our experience, LR may extend or appear despite anticoagulant or anti-platelet therapy. LR is less visible on sun-tanned skin; but sun exposure is not recommended in SLE-related APS.

In isolated other skin lesions such as livedoid vasculitis-like ulcers or pseudo-vasculitis lesions, low dose-aspirin and dipyridamole has been reported to be effective in some patients. If such lesions recur or extend despite anti-platelet agents, anticoagulation with low molecular weight heparin is usually prescribed.

Prevention of recurrence of skin lesions depends not only on the severity of these skin lesions, but also on the other features of the disease. As widespread cutaneous necrosis and/or digital gangrene are considered to be major thrombotic events, the current recommendations for such cases are long term high-intensity warfarin (INR 2.5-3.5).

In the absence of large vessel occlusion, prevention of recurrence of the “minor dermatological manifestations” (i.e. livedoid vasculitis-like ulcers, pseudo-vasculitis skin lesions) is unclear. Antiplatelet therapy such as low-

dose aspirin (75 mg/day) is frequently a logical first choice treatment. Hydroxychloroquine has also well-documented anti-platelet effect and has been shown to reduce the risk of thrombosis in both SLE patients and animal models of APS. However, in our experience, these treatments are frequently insufficient and long term anticoagulation is often required.

The place of other therapeutic options such as rituximab or inhibitors of the mammalian target of rapamycin (mTor) remains to be determined (12).

Whatever the type of skin lesions is, it is important to eradicate or reduce other risk factors of thrombosis. Among others, patients are advised to stop smoking and using oestrogen-containing pills, obtain a perfect control of cardiovascular risk factors (tension, cholesterol) and a regular physical activity is recommended.

Table 1: Dermatologic manifestations of the antiphospholipid syndrome with supposed pathomechanisms

Thrombotic microangiopathy	Livedo racemosa Livedoid vasculopathy-like ulcers Large ulceration resembling pyoderma gangrenosum - Pseudo-vasculitis lesions - purpura - palmar or plantar erythema - nodules - pustules - malignant atrophic papulosis-like lesions Retiform purpura and superficial skin necrosis
Large-vessel thromboembolism	Superficial phlebitis Post phlebitic skin ulcers Acrocyanosis, purple toe / digit Multiple splinter haemorrhages under the nails Digital gangrenes
Other	Anetoderma

Table II: International consensus statement: Classification criteria for definite APS**Clinical criteria****- Vascular thrombosis**

One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

- Pregnancy morbidity

- a) One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th weeks of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus, or
- b) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe pre-eclampsia or eclampsia, or severe placental insufficiency or
- c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

- 1) **Lupus anticoagulant** present in plasma, detected according to the guide-lines of the International Society on Thrombosis and Haemostasis
- 2) **Anticardiolipin antibody** of IgG and/or IgM isotype in blood, present in medium or high titer (> 40 GPL or MPL or > the 99th percentile; detection by a standardized ELISA method)
- 3) **Anti-b2 glycoprotein 1 antibody of IgG and/or IgM isotype** (titer > the 99th percentile, detection by a standardized ELISA method according to the recommended procedure)

Classification of APS should be avoided if less than 12 weeks or more than

5 years separate the + aPL tests and the clinical manifestations. aPL tests have to be positive on two or more occasions, at least 12 weeks apart

Definite APS is considered to be present if at least one of the clinical and one of the laboratory criteria are met.

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Osteoarthritis: pathogenesis, clinical aspects and diagnosis

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LEARNING OBJECTIVES

- Describe the key processes, cell types and the main soluble mediators involved in the pathogenesis of osteoarthritis.
- Outline the main clinical features of osteoarthritis and the specific signs according to the localization.
- Understand risk factors for initiation and for progression of osteoarthritis.
- Explain advantages and limitations of different imaging methods for the diagnosis and assessment of osteoarthritis and their respective utility in daily practice.
- Understand and use standardized tools used to assess pain, function and structural damage in the field of osteoarthritis.
- Get insights into the use of diagnostic recommendations and the value and limitations of classification criteria in the field of osteoarthritis.

1 Summary

Osteoarthritis (OA) is the most common chronic joint disorder. It usually results in joint pain, stiffness, deformity and loss of function, ultimately leading to chronic disability. OA mainly affects the elderly but should not be considered a simple consequence of aging. The American College of Rheumatology defined OA as ‘a heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins’ (Altman et al, 1986). The American Academy of Orthopaedic Surgeons has provided a more extensive definition: ‘OA is the result of both mechanical and biological events that destabilize the normal coupling of degradation and synthesis of articular cartilage and subchondral bone. Although it may be initiated by multiple factors including genetic, developmental, metabolic and traumatic, OA involves all of the tissues of the diarthrodial joint. Ultimately, OA is manifested by morphologic, biochemical, molecular and biomechanical changes of both cells and matrix which lead to softening, fibrillation, ulceration and loss of articular cartilage, sclerosis and eburnation of subchondral bone, osteophytes and subchondral cysts. When clinically evident, OA is characterised by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation’ (Kuettner and Goldberg, 1995).

The burden of OA and associated healthcare expenditures are enormous. In 2002, the World Health Organisation identified OA as the fourth leading global cause of years lived with disability (YLD) (WHO, 2002). An update in 2015 shows that OA is still in the top 30 YLD causes, and that its burden is steadily increasing (GBD 2015, 2016). OA affects an increasing proportion of people, due to the obesity pandemic and overall aging of the population. Therefore, there are serious individual and societal challenges (Hunter et al, 2014).

The above definitions highlight the fact that OA is no longer considered a ‘degenerative’ or ‘tear and wear’ disease but the result of active biochemical, biomechanical and cellular processes. In addition, OA pathophysiology is now viewed not from a chondrocentric position but rather as a disease of the whole joint organ, involving the different structures and influencing their functional interaction. In addition to the focal lesions of the articular cartilage, combined with a hypertrophic reaction (sclerosis) in the subchondral bone and new bone formation (osteophytes) at the joint margin, peri-articular muscle weakness, lax ligaments, low-grade synovitis, meniscal degeneration and neurosensory system alterations all actively contribute to the onset and progression of disease.

Optimal management requires early diagnosis and awareness of the risk factors that can affect prognosis. Diagnosis should be made on clinical grounds with imaging as an additional tool. Different tools and imaging options are available for assessing the severity, impact and progression of disease.

2 Pathology of OA

2.1 A disease of the whole joint

OA is characterised by damage to the articular cartilage, osteophyte formation at the joint margins, subchondral bone sclerosis, and synovial and joint capsule thickening. These changes lead to joint degeneration and associated symptoms: pain, tenderness, stiffness, loss of function and disability. Changes in the individual tissues of the joint affect both tissue homeostasis and the functional cooperation between the joint tissues necessary for maintaining the function of the joint as an organ. Understanding the cellular and molecular processes and mediators involved as well as the communication between cells and tissues should lead to the identification of therapeutic targets and the development of specific strategies to prevent, treat and cure OA.

The main macroscopic changes in an osteoarthritic joint are highlighted in figure 1:

Figure 1 Anatomy of the joint and typical changes associated with osteoarthritis. Typical X-ray changes are highlighted next to the schematic presentation. Osteoarthritis is characterised by loss of cartilage, joint space narrowing, synovial hyperplasia, subchondral bone sclerosis and osteophyte formation. (Reproduced with permission from Luyten et al, Bone 2009;44:522–7.)



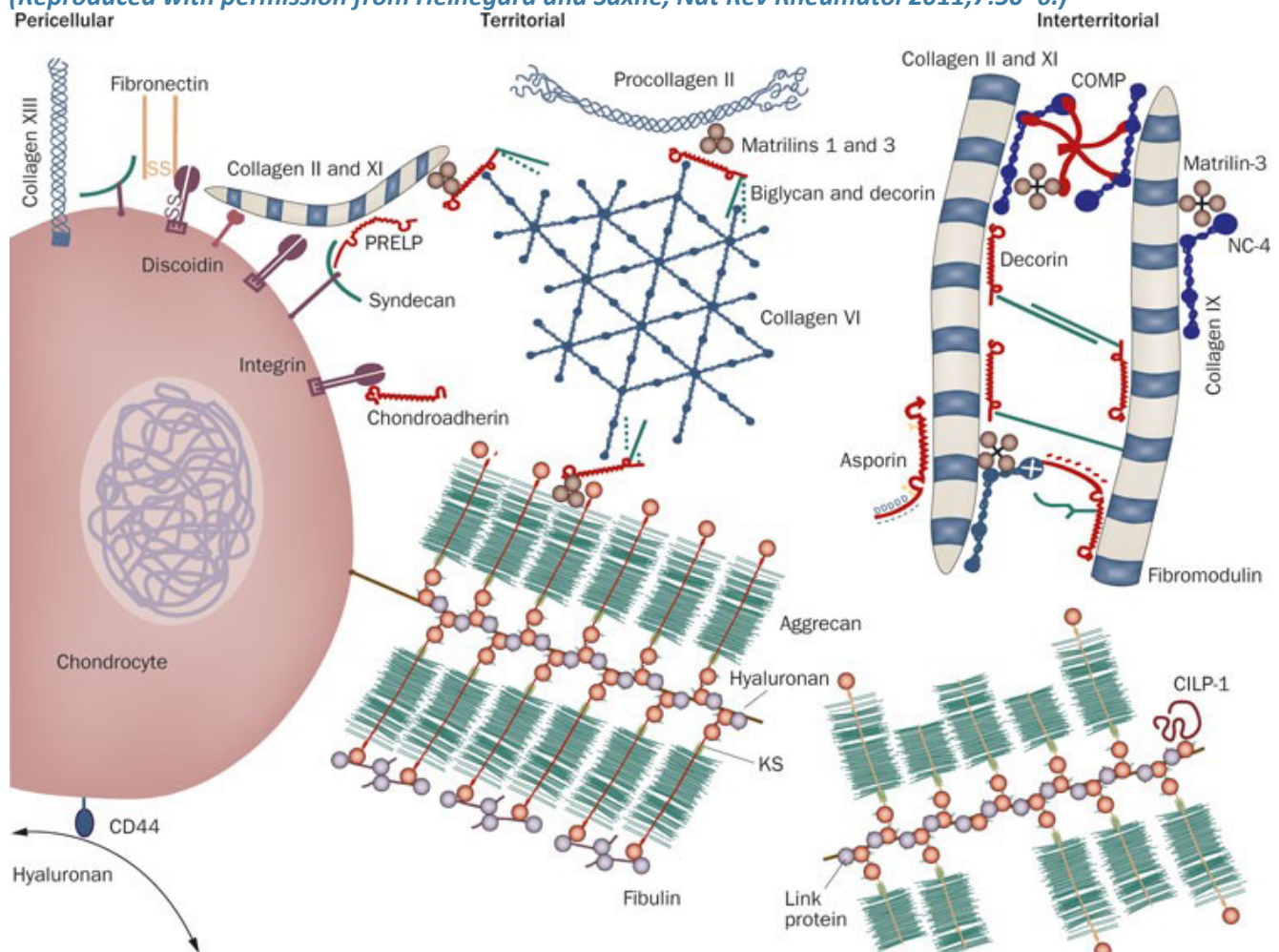
- Reduced joint space related to loss of articular cartilage
- Subchondral bone with hypertrophic reaction (sclerosis) and new bone formation (osteophytes) at the joint margins
- Inflammation and hyperplasia of the synovial membrane and joint capsule.

2.2 Breakdown of articular cartilage

Articular cartilage is a connective tissue composed of the articular chondrocytes as the unique cell type and of extracellular matrix (ECM) or ground substance which contains collagen (mainly type II fibrils associated with

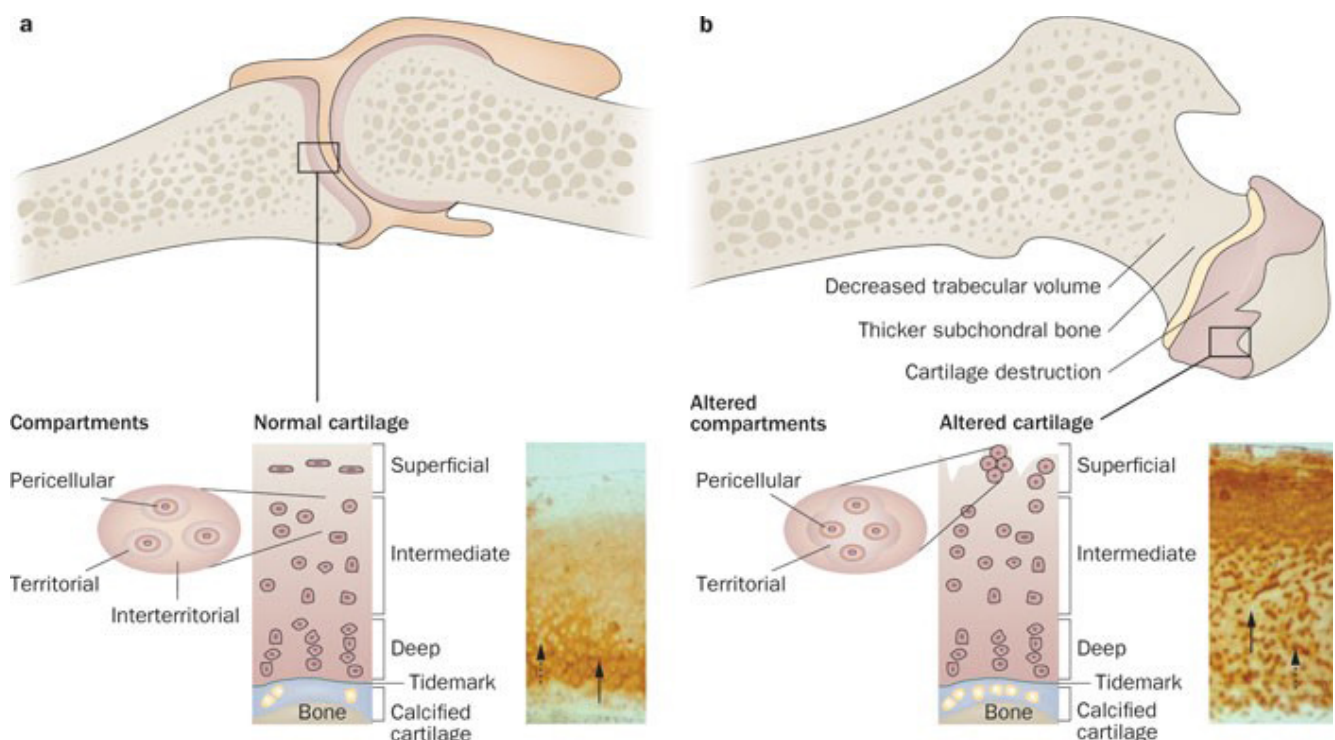
both collagen IX and XI) and proteoglycans. ECM composition defines the biomechanical properties of the articular cartilage. Type II collagen forms highly cross-linked fibrils of triple helix molecules that interact with other collagens and the proteoglycans (figure 2). The collagen fibrils form an organised network that entraps the proteoglycans. Aggrecan is the main proteoglycan in cartilage (figure 2). It consists of a central core protein bearing numerous glycosaminoglycan chains of chondroitin sulfate and keratan sulfate. The side chains are strongly negatively charged and attract polar H₂O molecules. Aggrecan non-covalently associates with hyaluronic acid (HA), a linkage stabilised by link protein. HA binds up to 100 aggrecans and the resulting molecular complexes form the major structural component of articular cartilage giving the cartilage its functional properties such as compressibility and elasticity due to the shift of H₂O molecules (Heinegård and Saxne, 2011). The collagen network provides stability and resistance against shear forces.

Figure 2 The molecular organisation of normal articular cartilage. The cartilage matrix surrounding chondrocytes in healthy articular cartilage is arranged into zones defined by their distance from the cell. The pericellular matrix lies immediately around the cell and it is the zone where molecules that interact with cell surface receptors are located; for example, hyaluronan binds the receptor CD44. The territorial matrix is next to the pericellular matrix, slightly further from the cell. The interterritorial matrix is furthest from the cell. The types of collagens and the collagen-binding proteins that constitute the matrices are different in each zone. CILP-1, cartilage intermediate layer protein 1; COMP, cartilage oligomeric matrix protein; CS, chondroitin sulfate; KS, keratan sulfate; PRELP, proline-arginine-rich end leucine-rich repeat protein. (Reproduced with permission from Heinegård and Saxne, Nat Rev Rheumatol 2011;7:50–6.)



Under ideal physiological circumstances, the water-rich articular cartilage forms a soft cap on top of the bones, allowing smooth movement and transition between the bony bearings of the skeleton. In the first stages of disease, before clinical signs and symptoms start to develop, the smooth surface of the articular cartilage becomes roughened with small irregularities and superficial clefts. As the disease progresses, the cracks become deeper, extending into the middle zone of the cartilage. Lesions may grow and connect, thereby increasing the damaged surface. Clefts become focal erosions and ulcerations, ultimately exposing parts of the underlying bone (figure 3).

Figure 3 Properties of normal and osteoarthritic joints. (A) A healthy joint with normal articular cartilage. The articular cartilage is organised into pericellular, territorial and interterritorial matrices, each of which is present at a specific distance from the chondrocytes. On immunohistochemistry (see inset images), the territorial and pericellular matrices (dashed arrow) show essentially no staining for cartilage oligomeric matrix protein (COMP), whereas the interterritorial matrix stains positive for this cartilage extracellular matrix molecule (solid arrow). **(B) An osteoarthritic joint, which shows partial loss of cartilage and alterations in the underlying bone.** The cartilage compartments are altered even at early stages of disease, and demonstrate cloning and multiplication of cells. However, the immunohistochemistry findings show that cloning is not yet prominent. Loss of COMP staining is evident in the interterritorial matrix (solid arrow) at the same time as the new synthesis of the molecule results in deposition primarily in the pericellular matrix of the cartilage (dashed arrow). (Reproduced with permission from Heinegård and Saxne, *Nat Rev Rheumatol* 2011;7:50–6.)



Chondrocytes are the only cells found in the ECM and are responsible for the production, maintenance, remodelling and eventually destruction of the cartilaginous matrix. Chondrocytes have low metabolic activity and survive under relatively hypoxic conditions. The synovial fluid and subchondral bone provide nutriment,

maintaining chondrocyte cellular activities. Hypoxia modulates the intracellular expression of survival factors, such as hypoxia-inducible factor-1 α (HIF-1 α), which support the survival of chondrocytes and respond to environmental changes (Goldring and Goldring, 2010). The chondrocyte itself possesses limited regenerative capacity, and so significant traumatic cartilage injuries often predispose to OA (Dell'Accio and Vincent, 2010).

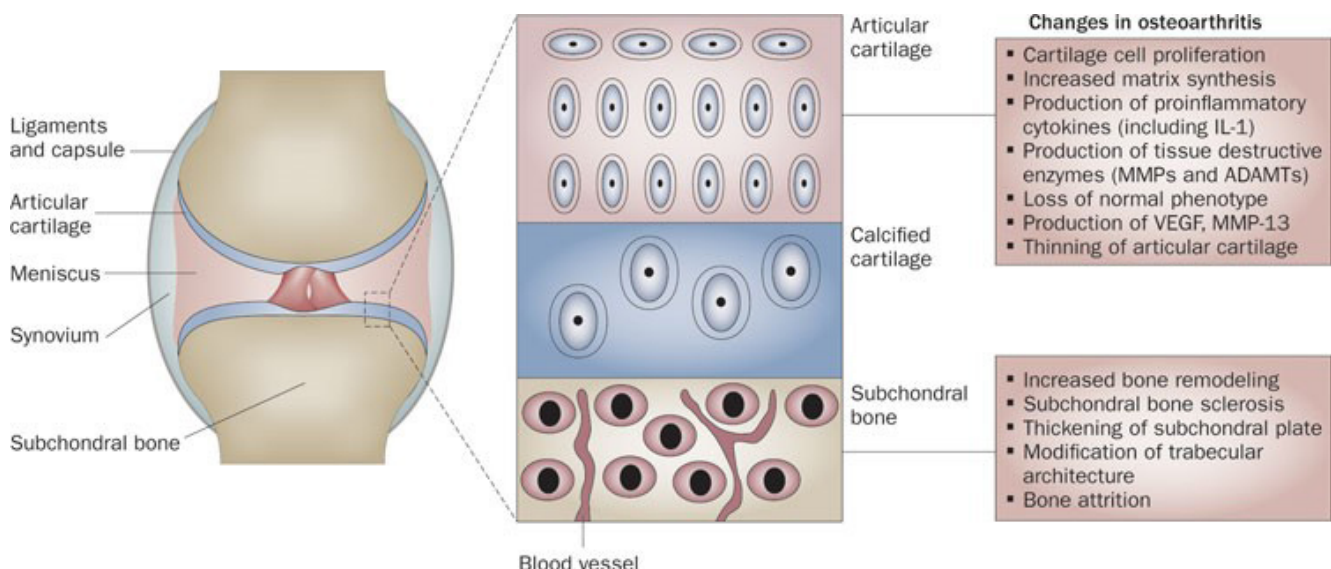
In the early stages of OA, the quiescence of the chondrocytes is disrupted and cells appear to adapt to local stresses such as direct damage or biomechanical strain (figure 4). Proliferating cells can be found, often in clusters. In addition to increased matrix synthesis (type II collagen and aggrecan), some of the chondrocytes also lose their stable molecular characteristics and start expressing markers and molecules associated with hypertrophic chondrocytes. Except for the transition zone of calcified cartilage between the deeper layers of the articular cartilage and the subchondral bone, such cells are not present in the adult joint (see also figure 3 – the tidemark is a histological feature that separates calcified and non-calcified matrix). The hypertrophic chondrocytes represent a terminal differentiation state during development and growth (growth plate) and typically produce collagen type X molecules, vascular endothelial growth factor (VEGF) and matrix metalloproteinase 13. This process affects the properties of the ECM. As outlined in more detail below, the initial response of the chondrocytes also has other negative effects as the cells also release matrix-degrading enzymes and inflammatory cytokines that contribute to progressive destruction. Another important feature of OA is chondrocyte cell death, which apparently can occur through apoptosis and necrosis.

2.3 Subchondral bone remodelling

Parallel changes in the subchondral bone are being elucidated (Funck-Brentano and Cohen-Solal, 2015). When exposed by loss of cartilage, the subchondral bone acquires an ivory-like aspect, a dense substance with a smooth surface. This process is called eburnation. The relationship and primacy of changes in cartilage and bone have been extensively debated (Brandt et al, 2006; Lories and Luyten, 2011; Mahjoub et al, 2012). From a practical point of view, it seems that both processes mutually influence each other and co-contribute to progression of disease (Karsdal et al, 2014). In addition, osteophytes, which are bony outgrowths, are formed at the joint margins. Other features in the bone include the formation of subchondral cysts (secondary to influx of synovial fluid or local necrosis of bone) and areas of bone marrow oedema (which can be recognised on MRI imaging). Such bone marrow lesions are considered predictors of OA progression, with biomechanical factors such as limb alignment playing a likely role (Felson et al, 2003). Subchondral bone is a global term that includes the subchondral bone plate (cortical bone) and the underlying trabecular bone and bone marrow space. An important feature of OA pathophysiology is subchondral bone remodelling. Bone remodelling is characterised by increased subchondral bone thickness (sclerosis), formation of new bone at the joint margins (osteophytes), subchondral bone cyst development and bone marrow lesions (BML) (Henrotin et al, 2009). Interestingly, these abnormalities develop during the final stage of OA and also earlier at the very onset of the disease, maybe even before cartilage degradation (Hilal et al, 1998*; Lajeunesse et al, 1999). Subchondral

bone remodelling is characterised by the accumulation of osteoid substance (sclerosis) and decreased mineralisation related to the production of an abnormal trimeric type I collagen which has a low affinity for calcium (Dequeker et al, 1993; Henrotin et al, 2009). Thus, subchondral bone stiffness is due to an increase in material density, not mineral density (Henrotin et al, 2009). As highlighted above, from a functional and pathophysiological perspective, bone and cartilage are best considered as a biomechanical and biological unit in joint health and disease (Lories and Luyten, 2011).

Figure 4 The bone–cartilage unit is the centre of joint function and disease. The joint enables movement by concerted interaction between its different tissues. Progressive development of osteoarthritis results in activation of different processes and pathways in the distinct tissues and cells of the joint. The current paradigm suggests that these changes evolve simultaneously and that osteoarthritis is not simply a disease of the cartilage or bone. New evidence supports the existence of several types of communication between cartilage and bone. ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor. (Reproduced with permission from Lories and Luyten, *Nat Rev Rheumatol* 2011;7:43–9.)



3 Molecular pathogenesis of OA

The pathogenesis of OA should be viewed as a progressive loss of homeostasis within the joint organ involving cartilage, bone, the synovium, ligaments and muscles. Molecular mediators of this process have been extensively studied in cartilage and to a lesser extent in bone and synovium. In chondrocytes, changes occur in extra-cellular matrix synthesis. In addition, the cells start producing proinflammatory cytokines and tissue destructive enzymes. In bone, remodelling and angiogenesis are driven by different types of growth factors. Synovitis is driven by immune cells and proinflammatory cytokines. Systemic factors such as adipokines and sex hormones may also play an active role.

3.1 Changes in cartilage matrix composition and properties

In the early stages of disease, water content is increasing, leading to tissue oedema and weakening of the collagen network. Type II collagen synthesis decreases and is replaced to some extent by type I collagen. Similarly, proteoglycan content strongly decreases and shorter glycosaminoglycans (GAGs) appear. Of note, the concentration of type 6 keratan sulfate increases during the osteoarthritic process to the detriment of type 4 keratan sulfate. These changes modify the capacity of the ECM to retain water, changing the distribution of force in the weight-bearing zone and the transmission of load to the subchondral bone. Of note, some of these effects are also seen in ageing cartilage without strong evidence for the presence of OA. Therefore, a sharp distinction between normal ageing and OA cannot always be made. A prominent feature of ageing cartilage is the accumulation of advanced glycation end products (AGE) leading to protein modification by non-enzymatic glycation. The presence of AGE leads to alteration of biomechanical properties. Moreover, AGE can bind to specific receptors present on the surface of chondrocytes, called receptors of advanced glycation end products (RAGE). The AGE/RAGE system is involved in the catabolic activity of the chondrocytes (Loeser et al, 2005). The loss of proteoglycans may be partially reversible. However, it changes the properties of the ECM, making the collagen structure more susceptible to degradation by collagenases. Importantly, unlike GAGs, the turnover of type II collagen in articular cartilage is very low in adults (Heinemeier et al, 2016). Consequently, damage to the collagen network is generally considered irreversible and may represent the point of no return in joint breakdown.

3.2 Activation of catabolic factors

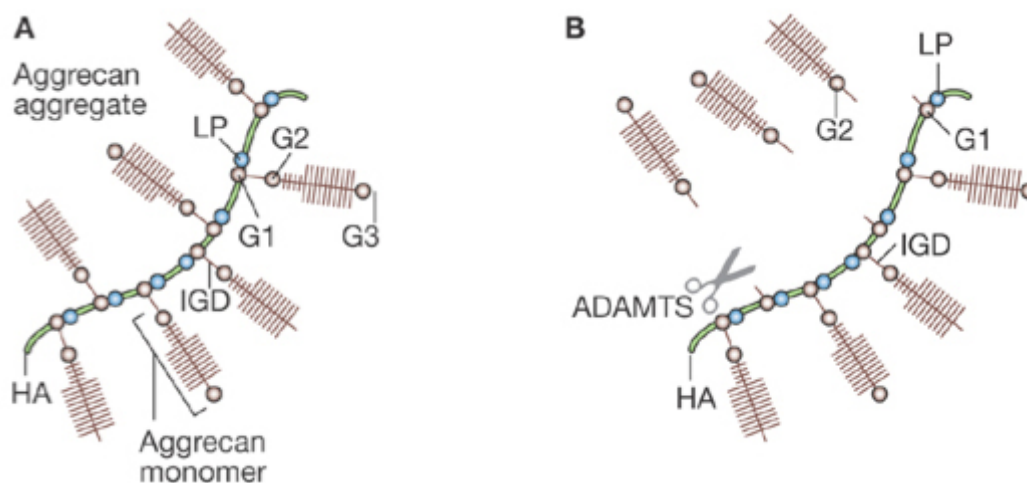
In OA, the association between matrix-degrading enzymes (including matrix metalloproteinases (MMPs) and aggrecanases) and cartilage damage has been well established (Goldring and Goldring, 2007*). ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) are matrix degrading enzymes, and a family of peptidases. In particular, aggrecanase 1 (or ADAMTS-4) and aggrecanase 2 (or ADAMTS-5, which is the same as ADAMTS-11) play a major role in the cleavage of aggrecan (figure 5) (Fosang and Little, 2008; Fosang and Rogerson, 2010).

MMPs are zinc-dependant endopeptidases and belong to the family of proteases known as the metzincin super-family. They are capable of degrading all kinds of ECM proteins. Because they are active at neutral pH, the MMPs can act on the cartilaginous matrix at some distance from the chondrocytes. MMPs can be synthesised by chondrocytes, synoviocytes and osteoblasts, mostly after stimulation by cytokines or mechanical stress.

OA chondrocytes produce a variety of matrix-degrading enzymes including MMP-1, MMP-3, MMP-9, MMP-13, MMP-14 and aggrecanases ADAMTS-4 and ADAMTS-5, thus demonstrating that cartilage cells contribute to the degradation of their own tissue (Cawston and Young, 2010). The activity of MMPs is regulated by serine

proteases (plasminogen activator, plasminogen, plasmin), free radicals, cathepsins and some membrane-type MMPs. Their effect is further controlled by natural inhibitors including the tissue inhibitors of metalloproteinases (TIMPs) by stoichiometric inhibition and the inhibitor of plasminogen activator. Therefore, the balance between the amounts of MMPs and TIMPs in the cartilage determines the level of degradation (Cawston and Young, 2010). Oxygen tension may also regulate MMP13 activity, since hypoxia has been shown to prevent MMP13 expression in chondrocytes and OA-like cartilage catabolism (Bouaziz et al, 2016).

Figure 5 Aggrecanase activity. (A) The aggrecan aggregate comprises numerous aggrecan monomers bound to HA (green) and LP (blue) to form stable trimeric complexes. The aggrecan core protein contains globular G1, G2 and G3 domains, with chondroitin sulfate and keratan sulfate glycosaminoglycans substituted between the G2 and G3 domains. (B) The aggrecanases, ADAMTS-4 and ADAMTS-5, cleave the aggrecan core protein at specific sites. The most detrimental cleavage site is in the IGD between the G1 and G2 domains. Cleavage in the IGD releases the bulk of the monomer from its HA anchor. Other known ADAMTS cleavage sites in the chondroitin sulfate-rich region are not shown. ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; HA, hyaluronan; IGD, interglobular domain; LP, link protein. (Reproduced with permission from Fosang and Little, *Nat Clin Pract Rheumatol* 2008;4:420–7.)



Breakdown of type II collagen is mainly due to collagenase-1 (MMP-1) and collagenase-3 (MMP-13). Their expressions differ in term of proteolytic potency, target sensitivity, expression and localisation. Likewise, their respective actions are dependent on the stage of OA. Within the OA cartilage, collagenase-1 is localised in the superficial zone, whereas collagenase-3 is in the deep zone. MMP-13-specific type II collagen cleavage products have been immunolocalised in OA cartilage with cytokines and their receptors (Goldring and Otero, 2011). Stromelysin-1 (MMP-3), Stromelysin-2 (MMP-10) and Stromelysin-3 (MMP-11) are also involved in the degradation of cartilage. Their substrates are proteoglycans, fibronectin, elastin, laminin and type IX collagen (Okada et al, 1992). Matrisylin (MMP-7) is over-expressed in OA cartilage and may play an important role in the degradation of various ECM components such as proteoglycans (Ohta et al, 1998). In rapid destructive hip OA, MMP-3 and MMP-9 are preferentially elevated in synovial fluid and plasma (Masuhara et al, 2002).

3.3 Activation of developmental pathways

Different molecular cascades well-known for their roles in skeletal development are also active in the healthy and osteoarthritic joint. Pathways of particular interest include the transforming growth factor- β (TGF β) family, bone morphogenetic proteins (BMPs) and the Wnt signalling cascade. Although initially considered potential strategies to induce cartilage repair, it has become clear that their effects on joint homeostasis and disease are more complex than anticipated. TGF β is considered an anabolic factor for cartilage. Despite its physiological role in healthy cartilage, the pathway and its downstream effects appear dysregulated in OA (van der Kraan, 2017). In aging cartilage, there appears to be a critical shift in TGF β –receptor interaction, with preferential activation of the activin-like kinase (ALK)-1 receptor over the ALK5 receptor. This process stimulates chondrocyte hypertrophy. In addition, excess production of TGF β also contributes to osteophyte formation and synovial fibrosis (figure 6). A similar view has been developed regarding BMP signalling. BMPs have chondroprotective and stimulating properties but within a specific context may also lead to further differentiation of chondrocytes (hypertrophy) and stimulate osteophyte formation (van der Kraan et al, 2010; Lories, 2011).

The potential role of Wnt signalling, a complex cascade with critical roles in development, growth, homeostasis and disease, appears even more complex (Lories et al, 2013). Cartilage and bone homeostasis require finely tuned Wnt signalling; both activation and suppression of the Wnt– β -catenin cascade can lead to OA in rodent models. Genetic associations and functional studies of the Wnt antagonist encoded by FRZB and the transcriptional regulator encoded by DOT1L (see below) with OA further corroborate the essential part played by Wnts in the joint (Thysen et al, 2015; Monteagudo et al, 2017). Wnts also have a role in the terminal differentiation of chondrocytes, a deleterious outcome in the context of OA.

Therefore, different OA models with genetic-based de-repression of Wnt signalling in vivo demonstrate more severe disease compared with wild-type controls. On the other hand, a complete absence of canonical Wnt signalling also has adverse effects, as survival of cells within cartilage seems to be impaired (figure 7). This suggests that balanced control of Wnt signalling in articular cartilage is required for joint homeostasis.

Figure 6 Transforming growth factor- β (TGF β) plays a role in key characteristics of osteoarthritis (OA): cartilage damage, osteophyte formation and synovial fibrosis. TGF β is required for the maintenance of healthy cartilage during which it signals primarily via Smad2/3. With age and OA, a shift in the activin receptor-like kinase 5 (ALK5):ALK1 ratio is established, favouring Smad1/5/8 signalling and leading to a loss of the cartilage-protective role of Smad2/3. A role is suggested for this balance shift towards ALK1 in cartilage damage during OA development. In addition, TGF β is a crucial factor in the onset of osteophyte development. In later stages of osteophyte development, bone morphogenetic proteins (BMP) might be equally important. TGF β is a major player in fibrotic diseases and, during OA, it induces synovial fibrosis. (Reproduced with permission from van der Kraan et al, Cell Tissue Res 2012;347:257–65.)

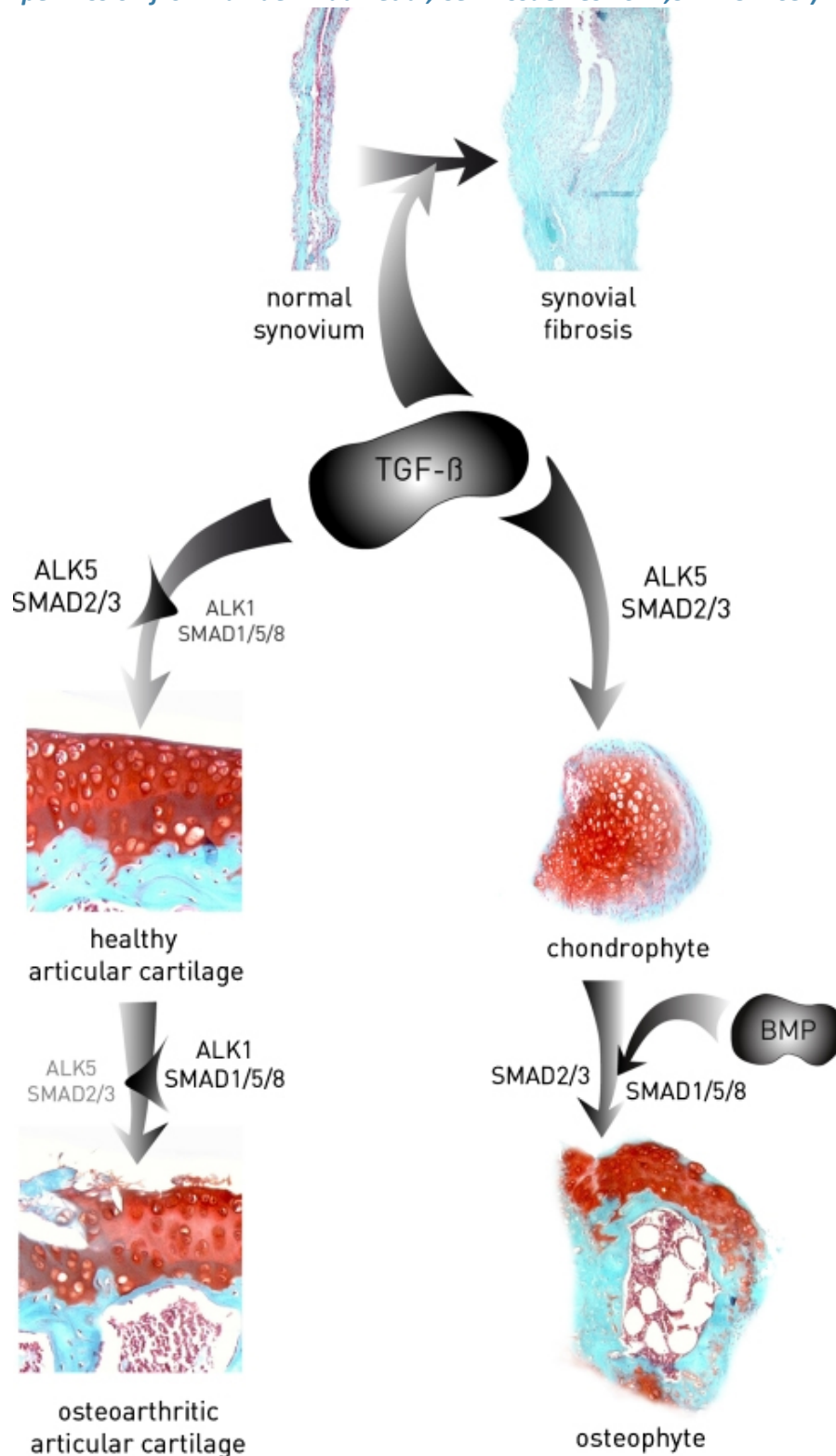
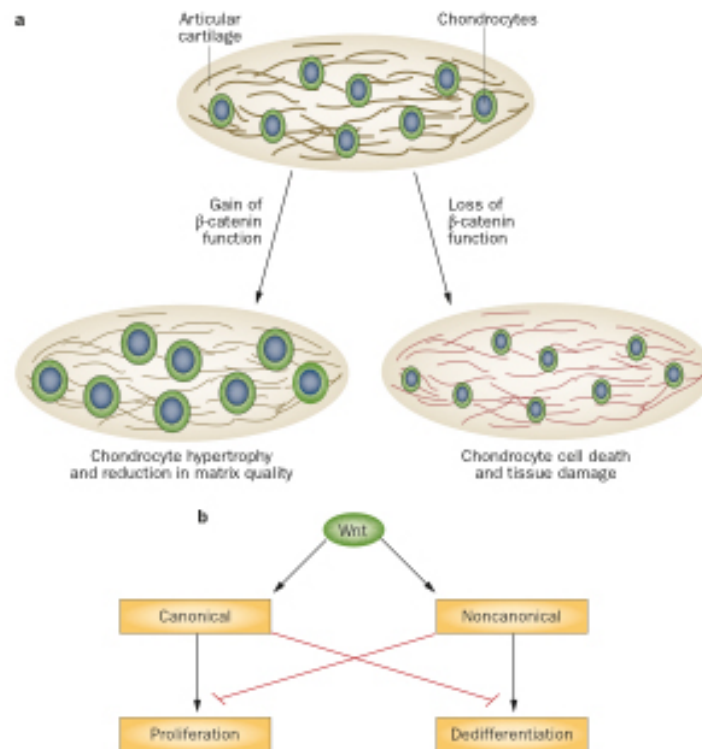


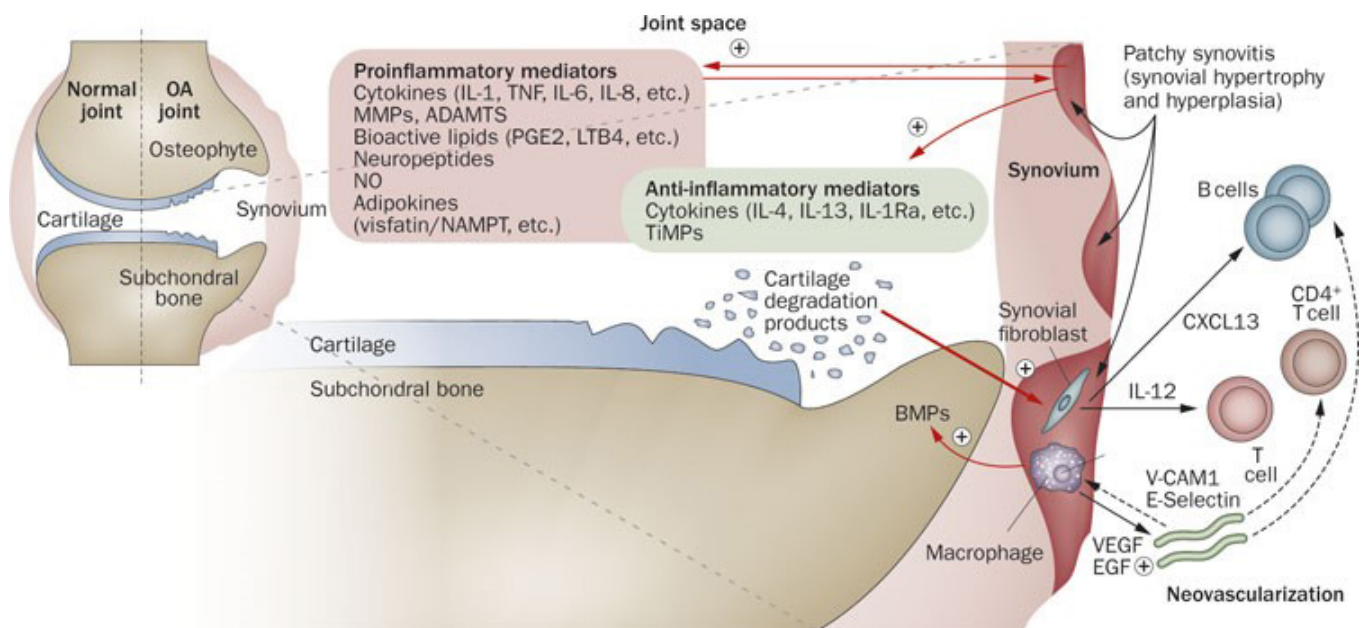
Figure 7 The complex roles of Wnts in cartilage homeostasis and disease. (A) Both overexpression and loss of β -catenin in the articular cartilage lead to joint damage. Overexpression of β -catenin results in chondrocyte hypertrophy and loss of matrix quality, whereas loss of β -catenin function results in tissue damage through chondrocyte death. (B) Canonical and non-canonical Wnt signalling pathways keep each other in check through reciprocal inhibition. The canonical pathway appears to stimulate proliferation. The non-canonical pathway stimulates dedifferentiation. (Reproduced with permission from Lories et al, *Nat Rev Rheumatol* 2013;9:328–39.)



3.4 Synovitis and low-grade inflammation

Low-grade inflammation is an important feature of OA pathogenesis. In particular, synovial inflammation plays an important and increasingly recognised role in OA. Cartilage breakdown products released into the joint space increase synovial inflammation. In turn, the inflamed synovium produces catabolic and proinflammatory mediators that lead to excess production of proteolytic enzymes responsible for cartilage breakdown, creating a positive feedback loop (figure 8). The macroscopic distribution of inflammation in OA synovium is patchy and may be confined to areas adjacent to the site of chondropathy (Ayril et al, 2005). The most common histological feature of inflammation of synovial tissue is hyperplasia, with an increased number of lining cells and a mixed cellular infiltrate (Myers et al, 1990; Smith et al, 1997; Mathiessen and Conaghan, 2017). Macrophages and T cells are the most common cells in OA synovial tissue (Sellam and Berenbaum, 2010*), although there is little evidence of a fully developed adaptive immune response. Inflammatory cells and their cytokines are present in both early and late OA (Benito et al, 2005).

Figure 8 Products of cartilage breakdown that are released into the synovial fluid are phagocytosed by synovial cells, increasing synovial inflammation. In turn, activated synovial cells in the inflamed synovium produce catabolic and proinflammatory mediators that lead to excess production of the proteolytic enzymes responsible for cartilage breakdown, creating a positive feedback loop. The inflammatory response is amplified by activated synovial T cells, B cells and infiltrating macrophages. To counteract this inflammatory response, the synovium and cartilage may produce anti-inflammatory cytokines. In addition to these effects on cartilage inflammation and breakdown, the inflamed synovium contributes to the formation of osteophytes via BMPs. ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; BMP, bone morphogenetic protein; CXCL13, CXC-chemokine ligand 13; EGF, endothelial growth factor; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; LTB4, leukotriene B4; MMP, matrix metalloproteinase; NAMPT, nicotinamide phosphoribosyl transferase (also called visfatin); NO, nitric oxide; OA, osteoarthritis; PGE2, prostaglandin E2; TIMP, tissue inhibitor of metalloproteinase; TNF, tumour necrosis factor; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor. (Reproduced with permission from Sellam and Berenbaum, *Nat Rev Rheumatol* 2010;6:625–35*.)



Why the synovium becomes inflamed in OA remains unclear. A common hypothesis states that, once degraded, cartilage fragments fall into the joint and contact the synovium. As the cartilage fragments are considered foreign bodies, synovial cells react by producing inflammatory mediators. Another theory considers synovial tissue to be a primary trigger of the OA process. Indeed, many cell types usually present in immunological processes have been described in OA as bystanders and as actors (Berenbaum, 2013). In addition, different triggers of the innate immune system may be active early in the disease process in OA. These triggers include matrix molecules, but also complement and crystals. Additional data point towards a role for systemic inflammation. In other words, inflammatory events occurring within joint tissues could be reflected outside the joint in the plasma and peripheral blood leucocytes of patients with OA. A provocative hypothesis therefore states that OA could be initiated and/or aggravated by the presence of a systemic low-grade inflammation and also that OA could be at the initiation of distant age-related diseases via joint release of inflammatory mediators into the blood stream.

Of note, the infra-patellar fat pad (IFP) may be a specific tissue associated with inflammation and knee OA (Ioan-Facsinay and Kloppenburg, 2013; Eymard et al, 2014). The IFP is a source of several soluble factors. It is composed of adipocytes and stromal vascular cells, such as macrophages, T cells and mesenchymal stem cells. Cellular interactions have been described within the IFP, such as between adipocytes and macrophages or T cells but also between IFP and other joint tissues. Moreover, some differences between the adipose tissue from IFP and the one from synovium have been reported, supporting a specific role for IFP in OA (Harasymowicz et al, 2017).

Both synovium and IFP represent important sources of pro-inflammatory mediators in OA. In addition, chondrocytes and subchondral bone cells are also able to produce cytokines or chemokines upon different types of stimuli, such as mechanical stress. Pro-inflammatory cytokines such as IL-1 β , TNF α or IL-6 are key mediators for the cartilage catabolic process. Chondrocytes have the capacity to produce these cytokines themselves and respond to them by acting via autocrine/paracrine pathways (Robinson et al, 2016). Abnormal mechanical forces and inflammatory mediators can also activate chondrocyte catabolism in a synergistic manner (Kurz et al, 2005). In OA joints, pro-inflammatory cytokines are synthesized in concentrations that are capable of inducing the expression and activation of MMPs, aggrecanases and other catabolic genes. IL-1 is co-localised with TNF α , MMP-1, MMP-3, MMP-8, MMP-13 and type II collagen cleavage epitopes in OA cartilage. Furthermore, IL-1 appears to induce ADAMTS-4, whereas TNF α and IL-6 induce both ADAMTS-4 and ADAMTS-5. Both IL-1 and TNF α increase the synthesis of prostaglandin E2 (PGE2) by stimulating the gene expression and/or the activity of COX-2, microsomal PGE synthetase-1 (mPGES-1) and soluble phospholipase A2 (sPLA2). They also increase the amount of nitric oxide via inducible nitric oxide synthetase (iNOS or NOS2) and induce production of other cytokines, such as the proinflammatory cytokines IL-6, LIF (leucocyte inhibiting factor), IL-17 and IL-18, and also of chemokines such as IL-8. Finally, IL-1 and TNF α suppress a number of genes associated with the differentiated chondrocyte phenotype, including aggrecan (AGAN) and type II collagen (COL2A1) (Goldring and Otero, 2011).

Chemokines (such as IL-8, CCL2, CCL5, CCL19) and their receptors (such as CCR1, CCR2, CCR3 and CCR5) are also important inflammatory mediators during OA. In particular, data from animal models indicate that CCL2/CCR2 signaling might be involved in OA-related pain and in the accumulation of macrophages in OA synovium. However, the role of CCR2 in cartilage degradation is still a matter of debate (Miller and Malfait, 2017).

3.5 Systemic mediators

Chondrocytes bear oestrogen receptors and their stimulation can trigger the production of growth factors. The concentration of oestrogens decreases during menopause, leading to a decrease in the synthesis of these growth factors. Obesity is a risk factor for OA for both weight-bearing joints and also for non-weight-bearing joints such as the hands, suggesting a role for the adipose tissue which secretes many soluble mediators. Among them, adipocytokines (or adipokines) have been described as mediators of inflammation. Moreover, these adipokines are not restricted to the adipose tissue and could also be secreted by other tissue. It has been shown that adipokines (resistin, leptin and adiponectin) are found in synovial fluid (Schaffler et al, 2003) and have multiple functions (table 1).

Table 1 The role of adipocytokines in the pathogenesis of osteoarthritis (Adapted from Lago et al, *Nat Clin Pract Rheumatol* 2007;3:716–24 and Gosset et al, *Arthritis Rheum* 2008;58:1399–409)

	Observations
Leptin	Leptin expression in cartilage is positively associated with the severity of OA ↑ NO (synergy with IFN-γ and IL-1) ↑ MMPs 9–13 ↑ IGF-1, ↑ TGFβ ↑ Synovial concentration versus serum concentration?
Adiponectin	↑ IL-6 and ↑ MMP-1 by synovial fibroblasts ↓ Synovial concentration versus serum concentration
Visfatin	Produced by human chondrocytes Increased expression by IL-1 stimulation ↑ PGE2, ADAMTS-4, ADAMTS-5, MMP-63, MMP-13
Resistin	Induces osteoarthritis when injected into mouse knee joints

ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; IL, interleukin; MMP, matrix metalloproteinase; NO, nitric oxide; OA, osteoarthritis; PGE2, prostaglandin E2.

Thus, OA may be related to the metabolic syndrome. In this context, at least some patients may develop OA as a consequence of metabolic abnormalities. For instance, studies have demonstrated associations linking OA to several components of the metabolic syndrome, such as hypertension and type 2 diabetes (Eymard et al, 2015; Courties et al, 2017). However, it should be underlined that body mass index (BMI) represent a potential confounder in these epidemiological associations with knee OA (Niu et al, 2017). Preclinical findings indicate a deleterious effect of lipid and glucose abnormalities on cartilage homeostasis. Chronic low-grade inflammation, as highlighted above, is a feature shared by OA and metabolic disorders and may contribute to the genesis of both. Thus, OA is emerging as a disease that has a variety of phenotypes including a metabolic phenotype, in addition to the age-related and injury-related phenotypes.

4 Epidemiology and risk factors

4.1 Prevalence of OA

The prevalence of OA depends on the precise definition used. For example, the classification criteria of the American College of Rheumatology have been rarely used in epidemiological studies. One limitation of

epidemiological studies concerning OA is that individuals differ in their threshold for reporting pain. Furthermore, other conditions such as bursitis, tendonitis or fibromyalgia may mimic OA pain. Definitions of OA differ and cross-sectional studies have the limitation that individuals without OA at a given time-point, may have become patients a few years later.

Autopsies can be a way to investigate OA prevalence. These studies have shown that degenerative joint changes begin in the second decade (Lowman, 1955). This result corroborates the fact that radiological OA is more prevalent than symptomatic OA (Kelsey and Hochberg, 1988).

The occurrence of OA differs according to geographical area and country, since these are associated with variation in risks, genetics and environmental factors. For example, congenital acetabular hip dysplasia increases the risk of hip OA, while squatting predisposes to knee OA but protects against hip OA. Thus, interpretation of epidemiological studies on OA should take into account their geographical origin (Cimmino and Parodi, 2005).

The knee is the most clinically significant site affected by OA. The age- and sex-standardised incidence of knee OA is 240/100 000 person-years. The incidence of hand OA is 100/100 000 person-years, while for hip OA it is 88/100 000 person-years (Oliveria et al, 1995). Hand, hip and knee OA become more frequent with age, and more women are affected than men after age 50.

Gender plays a role in both radiographic and symptomatic OA. The prevalence of knee OA is higher in women than in men, while hip OA seems more frequent in men (Kellgren and Lawrence, 1958). Hand OA is more frequent in women (van Saase et al, 1989). In patients above 70 years of age, the prevalence of radiographic hand OA is 90% in women and 80% in men. Interestingly, female hand OA risk is greatest around the menopause, suggesting a role for systemic hormonal factors in the onset of the disease (Prieto-Alhambra et al, 2014).

In the USA, the number of people with clinical OA has increased to nearly 27 million, up from an estimate for 1995 of 21 million, as would be expected for such a strongly age-related disease (Lawrence et al, 2008*).

4.2 Natural history of OA

Primary OA is a chronic disorder but its natural history can vary greatly. OA generally develops progressively over several years, although symptoms may remain relatively stable for prolonged periods. Previous trauma, causing articular, meniscal or ligament damage or joint incongruity, can reveal or accelerate OA progression and symptom appearance and deterioration, especially in knee OA. Prodromal symptoms may occur and worsen in the years preceding the first diagnosis of radiographic OA, and in most cases, remain stable afterwards (Whittle et al, 2016). The correlation between clinical outcome and the radiographic course of disease is relatively poor at the individual level. Thus, whereas symptoms can improve, the radiographic

picture rarely does (Duncan et al, 2011). Prospective studies indicate that only a small subset of knees with OA will show radiographic progression in the following year, whereas most patients will remain stable (Felson et al, 2013).

Although OA is considered to be a chronic degenerative process, flares can occur during the course of the disease. Inflammatory arthritis, infection and crystal arthropathies should be excluded in such cases. Flares do not have a consensual definition but are characterised by sudden episodes of increased pain (possibly nocturnal), with morning stiffness and the development of synovial effusions or synovitis. Joint deterioration is especially seen with increasing age. Furthermore, knee deterioration is associated with obesity, varus malalignment, the presence of OA in other joints and radiographic features (Chapple et al, 2011). Hip deterioration is associated with radiographic features such as femoral head migration, femoral osteophytes and joint space narrowing, and pain and disability (Wright et al, 2009). Occasionally there may be rapid destruction of joints, which is associated with a poor prognosis. Regional localisation of destruction is classified into discrete clinical syndromes including those affecting the hip ('rapid destructive hip arthropathy'), the shoulder ('Milwaukee shoulder'), the spine ('pseudotuberculosis spondylodiscitis') and the knee.

4.3 Predisposing factors

A causal risk factor must fulfil several criteria, including a time relationship, a strong statistical association after exclusion of confounding factors, consistent published findings and biological plausibility. The predisposing risk factors for idiopathic OA act by increasing the susceptibility of joints to injury, by direct damage to joints, or by impairing the process of repair of damaged joint tissue. OA can develop in a normal joint through excessive injury or in a primarily altered joint (i.e., dysplasia, genu varum) by normal physical stress. Table 2 shows some of the main risk factors identified to date (Cimmino and Parodi, 2005). We must differentiate between factors for occurrence and factors for progression. Clinicians should also distinguish 'not modifiable' risk factors, which are valuable from a pathophysiological point of view and in groups, and 'modifiable' factors, which are potentially more valuable for individuals in routine practice.

Table 2 Risk factors for the occurrence or progression of osteoarthritis (OA) in the knees, hips and hands

	Location		
	Knee	Hip	Hand
Occurrence of OA	Age	Age	Age
	Female	Ethnicity	Female
	Ethnicity	Physical activity	Ethnicity
	Physical activity	Body Mass Index	Grip strength
	Body Mass Index	Previous injury	Body Mass Index
	Bone density	Intense sport activities	Occupation
	Previous injury	Occupation	Intense sport activities
	Smoking (protective)		
	Alignment		
	Quadriceps strength		
	Intense sport activities		
Progression of OA	Age	Age	Unknown
	Bone density	Symptomatic activity	
	Alignment	Gender	
	Hyarthrodial OA	Intense sport activities	
	Synovitis		
	Intense sport activities		
	Subchondral bone oedema on MRI		

4.4 Obesity and metabolic disorder

Obesity, the main modifiable risk factor for OA, seems to be independently implicated in the pathogenesis of OA. It is among the strongest risk factor for knee OA, especially in the case of bilateral knee involvement and in OA in women (Felson, 1996; Cimmino and Parodi, 2005). Obese patients also have a higher risk of bilateral hip OA but to a lesser extent than for the knee (Tepper and Hochberg, 1993). Obesity is associated with OA in weight-bearing joints, possibly due to cartilage breakdown upon abnormal loading, but also with OA in non-weight-bearing joints, such as the hand. This shows that obesity is a real systemic risk factor for OA (Pottie et al, 2006). The link between obesity and OA is stronger in women than in men.

Two mechanisms can explain the role of obesity in OA development. First, obesity increases mechanical stress on weight-bearing joints. Moreover, obese patients have a higher bone mass, which may increase stiffness in the subchondral bone and facilitate cartilage breakdown. Second, several proteins that are over-expressed in obesity are also involved in OA development, such as cytokines or adipokines like visfatin, explaining the putative effect of obesity on non-weight-bearing joints (Gosset et al, 2008; Courties et al, 2017).

Other metabolic disorders, such as hyperglycaemia, have also been associated with OA occurrence and severity, probably through changes in matrix macromolecules (Cimmino and Parodi, 2005). Diabetes was

associated with risk for bilateral knee OA and hypercholesterolemia was independently associated with generalised OA (Felson, 1996; Sturmer et al, 2001). This has been incorporated in the hypothesis that at least a subset of OA patients actually have metabolic OA (Courties et al, 2017).

4.5 Dietary intake and nutriment

Some studies have shown that the antioxidants, some carotenoids and vitamin C are associated with lower progression or lower incidence of OA (McAlindon et al, 1996a; Seki et al, 2010). However, their effect is not very strong and there is no convincing evidence that supplementation will be beneficial for individual patients. Dietary fibre, which may help to reduce body weight and have a protective effect on several metabolic disorders and systemic inflammation, might also decrease the risk of symptomatic knee OA, but not radiographic knee OA (Dai et al, 2017). The impact of vitamin D deficiency on OA have been extensively studied, and results are controversial. Overall, there is only a weak association between low levels of vitamin D and knee OA, but not with hip or hand OA (Bergink et al, 2016), and most randomized controlled trials investigating vitamin D supplementation in knee OA are negative (McAlindon et al, 2013).

4.6 Age, sex and ethnicity

Patient age is the best recognised risk factor, since the incidence of radiographic and symptomatic OA increases sharply with age. This is probably mediated by increases in systemic and local factors, including obesity, ligament laxity, and impaired neuromuscular joint-protective mechanisms. A systemic pro-inflammatory state promoted by aging called “inflamm-aging” may also contribute to age-related OA pathogenesis (Greene and Loeser, 2015).

Women are at greater risk than men of developing hand, knee and generalised OA (Dougados et al, 1996*; Jonsson et al, 2003; Arden and Nevitt, 2006*). In contrast, the frequency of hip OA increases at about the same rate in women and men, but the disease seems to progress more rapidly in women (Kellgren and Lawrence, 1958; Botha-Scheepers et al, 2008). On the same line, radiographic lesions are more severe in women than men after 55 years (Srikanth et al, 2005).

The prevalence of OA in different ethnic groups and races has been extensively studied. In the USA, knee OA is more common and more severe in the African-American population than in the Caucasian population (Dillon et al, 2006; Braga et al, 2009). The prevalence of knee OA seems to be similar between Chinese and Caucasian men of the same age, while Chinese women had a significantly higher prevalence of knee OA (Zhang et al, 2001). Both hip and hand OA are less common among the Chinese population than among the US Caucasian population (Nevitt et al, 2002; Zhang et al, 2003).

4.7 Bone density

A link between bone mineral density (BMD) and the occurrence of OA has been reported, but the mechanism requires further elucidation. According to epidemiological studies, radiographic hip OA seems to be associated with higher BMD (Nevitt et al, 1995; Stewart et al, 1999; Lane and Nevitt, 2002). The prevalence of radiographic knee OA also increases with increasing BMD (Lane and Nevitt, 2002). Prospective studies have shown that high BMD or an increase in BMD increases the incidence of new radiographic knee OA (Zhang et al, 2000; Hart et al, 2002). At the same time, high BMD and an increase in BMD may also decrease the risk of progression of knee OA (Zhang et al, 2000). The relationship between BMD and OA has been controversial for decades. An inverse relationship between osteoporosis and OA has been extensively supported but also challenged (Dequeker et al, 2003). A recent review of the literature provides detailed insights: OA is inversely related to osteoporosis in general when studied cross-sectionally and systematically. However, when analysed in individual bones, the BMD of the appendicular skeleton in OA-affected joints may decrease, particularly in the upper extremities. Low BMD at the lumbar spine is associated with a lower incidence of knee OA does not impact the progression of knee OA (Im and Kim, 2014).

4.8 Sex hormones

Sex hormones seem to be involved in OA pathogenesis since the prevalence and incidence of OA is higher in women than in men, especially around the menopause (Richette et al, 2003; Prieto-Alhambra et al, 2014). This can be explained by the presence of oestrogen receptors in chondrocytes and modulation of their function depending on sex hormones (Richette et al, 2007). Numerous animal studies found that ovariectomy resulted in cartilage damage (Sniekers et al, 2008). However, the association between OA and hormone replacement therapy is unclear (de Klerk et al, 2009).

4.9 Occupational factors

The occurrence of OA is associated with particular physical activity during work, for instance laying floors and carpentry is associated with knee OA (Rytter et al, 2009). Frequent climbing of stairs can favour hip and knee OA (Lau et al, 2000). Hip OA seems also favoured by occupational activities such as farming, prolonged standing, weight lifting and walking over rough ground (Croft et al, 1992a). On the other hand, more active individuals may have a reduction in risk of knee OA from avoiding weight gain than those less active (Martin et al, 2013).

Hand use may have a protective effect on finger joint OA, whereas continuous joint overload may lead to joint impairment (Solovieva et al, 2005). The pattern of work task history is associated with its localisation (Solovieva et al, 2006). Carpo-metacarpal OA of the thumb mainly occurs in occupations involving repetitive

thumb use such as tailoring and dressmaking, while severe OA of the right thumb, index and middle fingers occurs in dentists (Solovieva et al, 2005; Fontana et al, 2007).

4.10 Joint deformity and laxity

Joint deformity is associated with the development of OA. Congenital abnormal joint shapes, such as acetabular dysplasia, slipped capital femoral epiphysis, abnormal femoral head shape or abnormal femoral neck shaft angle of the hip, can be considered as aetiologies of secondary OA. They act by disturbing the load distribution within the joint (Harris, 1986; Lane et al, 2000; Doherty et al, 2008). Angular misalignment increases the degree of focal loading, creating a vicious cycle of joint damage, contributing to the development and progression of single compartment OA of the knee. About 65% of the weight-bearing load is transmitted through the medial compartment in a normally aligned knee, which explains the greater frequency of tibiofemoral medial knee OA (Andriacchi, 1994). Globally, varus misalignment increases the risk of joint space narrowing three- to fourfold (Sharma et al, 2001). Valgus malalignment also increases the risk of knee OA incidence and radiographic progression, possibly by increasing the risk of meniscal damage (Felson et al, 2013).

Obesity and misalignment act in combination to increase the risk of structural radiographic progression. Longstanding obesity seems to increase the risk of structural radiographic progression in cases of moderate misalignment, presumably due to the combined effect of the focus of load from misalignment and the excess load from increased weight (Felson et al, 2004; Runhaar et al, 2014).

Joint laxity, responsible for malalignment, may be a further accelerating factor for OA.

4.11 Acute injury and repetitive joint loading

It has been estimated that approximately 12% of symptomatic OA is attributable to post-traumatic OA of the hip, knee, or ankle (Brown et al, 2006). Fractures of the limbs are potential causes of secondary OA (Volpin et al, 1990; Honkonen et al, 1995). For instance, intra-articular fractures may increase the risk of subsequent OA more than 20-fold (Anderson et al, 2011). The pathomechanisms linking these fractures to cartilage destruction are poorly understood, although secondary load changes on the joint play a role. Furthermore, a link has been made between injury and chondrocyte death (McKinley et al, 2010).

Previous hip and knee injuries are independent risk factors for OA according to several epidemiological studies (Cooper et al, 1998; Gelber et al, 2000).

Acute joint injuries, especially anterior cruciate ligament (ACL) damage or tears of the meniscus, are clearly associated with knee OA and its progression (Roos et al, 1998b; Sowers et al, 1999; Cooper et al, 2000; Gelber et al, 2000; Englund et al, 2004). There is a combined effect of the injury itself and its biomechanical consequences which alter load distribution on the joint. Capsular or ligamentous injury can increase the risk of

subsequent OA by 10-fold (Anderson et al, 2011). Unfortunately, the development and progression of OA may still occur even if the damaged anterior cruciate ligament is surgically repaired, especially in patients with anterior laxity or combined injuries (Oiestad et al, 2010; Struwer et al, 2011). OA often presents as a slight reduction of joint space about 10–20 years after anterior cruciate ligament injury, but usually without any major clinical symptoms (Gillquist and Messner, 1999).

Meniscus damage may play an important role in OA pathophysiology (Hunter, 2009). However, whether meniscus damage or cartilage degradation occurs first is still unknown. It seems clear that a torn meniscus and extrusion are strong risk factors for the development and progression of knee OA. Meniscectomy increases the risk of knee OA twofold and even more if it is combined with ligament injury. There is a significant risk of radiographic tibiofemoral and patella-femoral OA 20 years after the surgical removal of a meniscus following knee injury, with the relative risk estimated to be 14 (Roos et al, 1998a; Englund and Lohmander, 2005). Moreover, obesity enhances the effect of meniscal damage. Partial meniscus resection seems to have less impact than total meniscectomy (Englund and Lohmander, 2004).

The mechanisms leading to OA following joint injury are poorly known, but inflammation is likely to play an important role in this process. Several inflammatory mediators such as IL-6 or CCL2 are released into synovial fluid early after knee joint injury (Watt et al, 2016). Interestingly, IL-6 levels in synovial fluid are also associated with progression of radiographic knee OA in patients with history of meniscectomy (Larsson et al, 2015). On the same line, the pivotal role of IL-6 in post-traumatic OA has been pointed out in preclinical studies (Nasi et al, 2016; Latourte et al, 2017). However, the exact contribution of inflammatory mediators in the pathogenesis of posttraumatic OA remains to be further elucidated (Lieberthal et al, 2015).

Repetitive activities with joint overuse increase the risk of developing OA, particularly in the knee, hip and distal interphalangeal joints. Obesity amplifies this effect on the knee (Felson et al, 1991; Coggon et al, 2000). Professional and elite sporting activities are also associated with the development of OA, even without major injury: for example, marathon athletes may suffer from hip OA (Buckwalter and Lane, 1997) and professional soccer players from knee OA. However, reasonable sports during leisure time, such as recreational running, are not likely to be harmful for most individuals in terms of the occurrence or progression of hip and knee OA in the absence of sudden impacts, previous injury, meniscectomy or joint dysplasia (Cimmino and Parodi, 2005; Lo et al, 2017).

Furthermore, walking in high-heeled shoes may predispose to degenerative changes in the patellofemoral and medial compartments of the knee (Kerrigan, 2005), but the direct association with OA remains inconclusive (Barnish and Barnish, 2016).

4.12 Muscle weakness

Quadriceps weakness has been described as a risk factor for knee pain, disability and progression of knee OA (Slemenda et al, 1997). However, data about the effect of quadriceps strength on OA development and progression are conflicting. While quadriceps weakness has been associated with the development of radiographic knee OA, quadriceps muscle strength is also associated with faster progression in deformed knees (Arden and Nevitt, 2006*). Lower-limb muscles, particularly the quadriceps, influence knee joint load, a major contributor to knee OA. Impairments in muscle function including weakness, altered activation patterns and proprioceptive deficits are commonly found in association with knee OA. Furthermore, there is some evidence that muscle weakness may predispose to the onset and potentially the progression of knee OA. For instance, a lower thigh muscle strength might predict the risk of total knee replacement in women (Culvenor et al, 2016). Several studies indicate that muscle strength might be associated to knee pain or function but not to radiographic outcomes (van der Esch et al, 2014; Muraki et al, 2015). Exercise is a key component of conservative management of knee OA and has been found to be effective in symptom reduction (Bennell et al, 2014). Whether exercise influences disease development and progression requires further research, especially given the contradictory data. As in many other examples regarding OA, specific subtypes and patient characteristics are likely to influence individual treatment decisions. Moreover, muscle power might be more important than muscle strength to investigate this association in patients with OA (Reid et al, 2015).

4.13 Genetic and epigenetic factors

OA has a complex aetiology to which genetic factors also contribute (Reynard and Loughlin, 2013). Evidence of a genetic influence on OA comes from a number of sources, including epidemiological studies, linkage studies, candidate gene approaches and genome-wide association studies (GWAS). Discovery of genetic susceptibility factors associated with OA has been hindered by the different phenotypical manifestations, and the difficulty of selecting an appropriate definition of disease, thereby clearly discriminating patients and controls in view of the progressive nature of the disease (Kerkhof et al, 2011). Candidate gene approaches, once very popular, had power issues and suggested associations rarely replicated in other populations. Novel technologies, in particular GWAS, and meta-analyses on large datasets and multiple cohorts have been welcomed but mainly identified regions with multiple candidate genes (Kerkhof et al, 2010; Zeggini et al, 2012; Evangelou et al, 2013; Rodriguez-Fontenla et al, 2014; Styrkarsdottir et al, 2014). Often these regions have a number of potential candidate genes but for many, insights into their role in joint biology is lacking. A list of loci of strong interest is found in table 3. Ultimately, genetic studies can lead to unravelling of molecular mechanisms involved in OA development and progression. These mechanisms can be potential targets for treatment. Ideally, identification of genetic risk factors for OA can be used to recognise subjects at risk for OA onset or progression.

Table 3 (Possible) genes of interest in osteoarthritis

SNP (chromosomal location)	Genes implicated	Protein	Protein function
rs6976 (3p21.1)	<i>STAB1</i>	Stabilin-1	Transmembrane receptor
	<i>NT5DC2</i>	5'-Nucleotidase domain-containing protein 2	Unknown
	<i>PBRM1</i>	Polybromo-1	Transcriptional activation
	<i>GNL3</i>	Guanine nucleotide-binding protein-like 3	Stem cell proliferation
	<i>GLT8D1</i>	Glycosyltransferase 8 domain-containing protein 1	Glycosyltransferase
	<i>SPCS1</i>	Signal peptidase complex subunit 1	Unknown
	<i>NEK4</i>	Serine/threonine-protein kinase Nek4	Kinase
	<i>ITIH1</i>	Inter-alpha-trypsin inhibitor heavy chain H1	Serine protease inhibitor
	<i>ITIH3</i>	Inter-alpha-trypsin inhibitor heavy chain H3	Serine protease inhibitor
	<i>ITIH4</i>	Inter-alpha-trypsin inhibitor heavy chain H4	Serine protease inhibitor
	<i>MUSTN1</i>	Musculoskeletal embryonic nuclear protein 1	Nuclear protein
	<i>TMEM110</i>	Transmembrane protein 110	Unknown
rs12107036† (3q28)	<i>TP63</i>	Tumour protein 63	Transcription factor
rs10948172† (6p21.1)	<i>SUPT3H</i>	Transcription initiation protein SPT3 homologue	Unknown
	<i>RUNX2</i>	Runt-related transcription factor 2	Transcription factor
rs9350591 (6q13–q14.1)	<i>COL12A1</i>	Collagen α1(XII) chain	FACIT collagen
	<i>COX7A2</i>	Mitochondrial cytochrome c oxidase subunit 7A2	Cytochrome C oxidase
	<i>TMEM30A</i>	Cell cycle control protein 50A	Transporter
	<i>FILIP1</i>	Filamin-A-interacting protein 1	Interacts with filamin
	<i>SEN6</i>	Sentrin-specific protease 6	Ubiquitin-like molecule
	<i>MYO6</i>	Unconventional myosin-VI	Vesicle and organelle transport
	<i>IMPG1</i>	Interphotoreceptor matrix proteoglycan 1	Proteoglycan
rs3815148 (7q22)	<i>PRKAR2B</i>	cAMP-dependent protein kinase type IIβ regulatory	cAMP signalling
	<i>HPB1</i>	HMG-box transcription factor 1	Transcription factor
	<i>COG5</i>	Conserved oligomeric Golgi complex subunit 5	Golgi morphology and function
	<i>GPR22</i>	G-protein-coupled receptor 22	Probable G-protein-coupled receptor
	<i>DUS4L</i>	tRNA-dihydrouridine(20a/20b) synthase [NAD(P) ⁺]-like	Unknown

rs4836732 (9q33.1)	BCAP29	B-cell receptor-associated protein 29	Unknown
	PAPPA	Pappalysin-1	Secreted metalloproteinase
	ASTN2	Astrotactin-2	Neural migration
	TRIM32	E3 ubiquitin-protein ligase TRIM32	Protein ubiquitylation
rs10492367 (12p11.22)	KLHDC5	Kelch domain-containing protein 5	Protein ubiquitylation
rs835487 (12q23.3)	PTH1H	Parathyroid hormone-related protein	Hormone
rs11842874 (13q34)11	CHST11	Carbohydrate sulphotransferase 11	Chondroitin sulphation
	MCF2L	Guanine nucleotide exchange factor DBS	Cell movement
rs8044769‡ (16q12.2)3	FTO	α-Ketoglutarate-dependent dioxygenase FTO	Unknown
rs12982744 (19p13.3)77, 78	DOT1L	Histone-lysine N-methyltransferase, H3 lysine-79 specific	Histone and chromatin modifier
rs143383 (20q11.22)12	GDF5	Growth/differentiation factor 5	Extracellular growth factor

Genome-wide association studies and meta-analyses on large datasets and multiple cohorts have identified regions with multiple candidate genes. Often these regions have a number of potential candidate genes but for many, insights into their role in joint biology is (still) lacking.

According to genetic studies in non-consanguineous families, including patients with precocious development of diffuse OA and mild spondylo-epiphyseal dysplasia characterised by genetic Mendelian transmission, polymorphisms of the type II collagen gene (COL2A1) located in chromosome 12 have been implicated in diffuse OA development (Ala-Kokko et al, 1990). However, in large populations this gene does not seem to have a major effect (Baldwin et al, 2002).

From recent genetic studies in primary OA, two pathways may be deduced that are putatively involved in OA aetiology. The first group of genes is involved in the inflammatory pathway: variants in the IL1 gene cluster, the HLA cluster and the cyclooxygenase 2 (COX2) gene (Attur et al, 2010; Moxley et al, 2010; Nakajima et al, 2010; Schneider et al, 2011). Associations with the IL1 gene cluster are shown for knee, hip and hand OA (Loughlin et al, 2002; Meulenbelt et al, 2004; Smith et al, 2004; Moxley et al, 2007; Kanoh et al, 2008; Attur et al, 2010). However, genetic variation at the IL1 gene cluster was associated with lower IL-1 β bio-availability on the one hand and with OA at a large number of joint locations in an individual on the other hand, illustrating the complexity of predisposition through genetic variation (Meulenbelt et al, 2010).

The second group of genes appears to be either involved in early skeletal developmental processes or maintenance of cartilage and bone: growth/differentiation factor 5 (GDF5) (Miyamoto et al, 2007), frizzled-related protein β (FRZB) (Loughlin et al, 2004; Lories et al, 2007; Lories et al, 2009), osteoprotegerin (OPG) (Ramos et al, 2015), transforming growth factor (TGF) β / SMAD3 (Valdes and Spector, 2010*) and type 2 iodothyronine deiodinase (DIO2) (Meulenbelt et al, 2008). These genes are involved in the orchestration of

growth-plate chondrocytes and implicated in the formation of cartilage and endochondral ossification in early skeletal development (Goldring et al, 2006).

The strongest and best reproduced genetic signal is the GDF5 gene. GDF5, also known as cartilage derived morphogenic protein 1 (CDMP1), is a member of the bone morphogenetic protein (BMP)/transforming growth factor (TGF)- β superfamily and was originally identified from a chondrogenic extract of articular cartilage. During joint development it is specifically expressed in the joint interzone, the region in which the prospective joint is formed (Storm and Kingsley, 1996). GDF5 stimulates proliferation and differentiation of chondrocytes. A 5' UTR C/T single nucleotide polymorphism (SNP) (rs143383) has been associated with OA, with the susceptibility variant resulting in lower expression levels (Miyamoto et al, 2007). This association is one of a few genetic variants confirmed in different ethnic groups and by meta-analysis (Evangelou et al, 2009; Valdes and Spector, 2011; Yau et al, 2017). Taking GDF5's chondrogenic properties into account, its potential as a cartilage growth factor is obvious. However, the biology of GDF5 appears much more complex, with effects on different tissues in the joint. Cells expressing GDF5 during embryogenesis may become a subpopulation of synovial cells with stem cells properties, contributing to cartilage repair in case of injury (Roelofs et al, 2017). Intra-articular injections of recombinant GDF5 has protective effects in a rat model of OA (Parrish et al, 2017). Conversely, lack of or a reduction in GDF5 may result in abnormal ligament laxity and thereby contribute to OA development through joint instability (Daans et al, 2011). In addition, GDF5 likely also contributes to subchondral bone modelling and remodelling with reduced GDF5 levels associated with abnormal structure of the collagen network (Daans et al, 2011).

One of the difficulties in genetic studies focusing on OA is the lack of a standardised definition of the OA phenotype, which leads to heterogeneity (Kerkhof et al, 2011). Radiographic or symptomatic findings or the presence of total joint replacement are used to define OA in these studies. However, attempts are being made to introduce more standardisation in future studies. Therefore, alternative 'endpoints' for disease have also been proposed. An example of such an alternative approach is a GWAS that has been performed to identify genes involved in hip joint space width as a proxy for cartilage thickness and OA (Castaño Betancourt et al, 2012). This study identified a genetic variant in the DOT1-like, histone H3 methyltransferase (DOT1L) gene robustly associated with joint space width and hip OA. The DOT1L association is interesting for different reasons. First, DOT1L is an enzyme and can be targeted pharmaceutically (Barry et al, 2010). DOT1L inhibitors are currently in clinical trial in cancer research (Daigle et al, 2011; Deshpande et al, 2012). Second, DOT1L biology links with the Wnt signalling cascade (Mahmoudi et al, 2010; Castaño Betancourt et al, 2012). Third, the DOT1L gene has also been associated with human height (Sovio et al, 2009). This quantitative phenotypical trait has also been linked with other OA susceptibility genes (Sanna et al, 2008), emphasising the likely involvement of growth factors in the disease. Preclinical data have pointed out a critical role for DOT1L in

cartilage health and osteoarthritis by regulating Wnt signalling, thereby opening up interesting therapeutic perspectives (Monteagudo et al, 2017).

DOT1L links to epigenetic regulation of genes. This is defined as heritable changes in DNA without changes in the sequence and could also be involved in the OA process. An example of epigenetic regulation is DNA methylation, as de-methylation can lead to an increase in the gene transcription. Several enzymes involved in cartilage breakdown in OA undergo epigenetic regulation (MMP-3, MMP-9, MMP-13, ADAMTS-4) and also the IL1B promoter region in chondrocytes and leptin which regulates expression of MMP-13 (Roach et al, 2005; Iliopoulos et al, 2007; Hashimoto et al, 2009). The role of epigenetics is currently being studied. The main hypothesis is that growth factors and proinflammatory cytokines regulate the methylation state of pro-degradative agent genes. Ageing and cellular senescence can also participate in changing methylation status (Roach and Aigner, 2007).

A bunch of genome-wide methylation studies have been performed in osteoarthritic cartilage, identifying different methylation profiles in enhancers or promoters of genes involved in embryogenesis and skeletal development, matrix regulation, Wnt pathway, angiogenesis and inflammation (Ramos and Meulenbelt, 2017). The interpretation of these studies is limited by their important variability in terms of study set up, statistical analysis protocols or types of platforms used to measure methylation. Moreover, their cross-sectional design precludes any conclusion on the causal relationship of the epigenetic modifications observed. However, the study of different cartilage regions of tibial plateau representing early, intermediate and late stages of OA suggests that changes in DNA methylation in cartilage occur at the late stages of OA (Zhang et al, 2016). The specific study of subchondral bone might also reveal a particular epigenetic phenotype for this joint tissue during OA (Jeffries et al, 2016). Other epigenetic control mechanisms, such as micro RNAs (miRNAs) or histone modifications, are also under investigation in OA (Ramos and Meulenbelt, 2017).

4.14 Consequence of the identification of a risk factor

Some of the most important risk factors for OA identified to date are ‘non-modifiable’, such as female gender, joint malformation and previous trauma. Knowledge of these factors may help to prevent OA in certain subpopulations.

Prevention and/or treatment of a modifiable risk factor for OA also do not guarantee OA evolution will be influenced. Physical exercise and weight reduction, for example, have both been shown to affect pain and function in knee OA. On the other hand, it is still not clear if modifying footwear is effective, or if muscle strengthening leads to structural progression in patients with misaligned or lax knees (Roddy and Doherty, 2006).

5 Clinical features

5.1 Symptoms of OA

Pain or stiffness in and around one or more joints is the most common reason for patients with OA to seek the advice of a physician. This feature, sometimes together with the clear presence of risk factors in the patient such as age and obesity, should prompt a detailed history and clinical examination. Symptoms are often initially insidious and can be highly variable, depending on the joint affected, the severity and the number of joints affected (Peat et al, 2001*). Involvement of many joints may suggest a systemic form of arthritis (metabolic or inflammatory). Familial history is important, in particular for patients presenting with pain and stiffness in the hands or hip. Imaging, discussed below, can aid in the diagnostic process but frequently there is no correlation between the joint symptoms and the structural alterations on radiographs. However, definitive structural radiographic signs of OA such as joint space narrowing or eburnation on a peripheral joint are associated with the risk of developing related symptoms.

A few general principles should be applied. The rheumatologist should keep in mind that the main challenges in the differential diagnosis of OA are to distinguish OA patients from those with chronic inflammatory disorders and to specifically identify the relatively rare patients with a clear secondary form of OA who have an underlying and often treatable endocrine or metabolic disorder.

Pain is the first and predominant symptom of OA. It typically occurs after joint use and is relieved by rest. With disease progression, pain occurs with minimal motion or even at rest and finally even during sleep. Although OA pain is not usually present at night or at rest, there are exceptions: patients with mild OA using joints for several hours, especially during sport; patients with advanced OA and destructive arthropathy; and patients with an acute inflammatory flare of OA mimicking inflammatory arthropathy, especially regarding erosive hand OA. Because cartilage has no nerve supply and is insensitive to pain, the pain in OA must arise from non-cartilaginous structures such as the periosteum, intra-articular ligaments, pressure on subchondral bone with venous engorgement, intramedullary engorgement, capsular distension, and alterations in synovium or tendons and fascia. Pain may also arise in the presence of an associated bursitis. Peri-articular tissue such as tendons and fascia are also sources of pain during the OA process. Furthermore, central pain processing is altered in patients with OA (Lee et al, 2011). Indeed, central sensitisation, its correlation with structural changes in the joint, and the efficacy of novel analgesics have led to new insights into the pathophysiology of OA pain. This will likely offer new opportunities for targeting and improving the safety of analgesia. In addition, using clinical and genetic approaches, subsets of patients with pain of different pathophysiology could be identified, thus enabling a tailored approach to pain management (Malfait and Schnitzer, 2013). Finally, there is no agreement as to whether a decrease in atmospheric pressure or a change in the weather increases OA

pain, although such an observation is frequently reported by individual patients (Wilder et al, 2003; Verges et al, 2004).

Stiffness may also occur in the morning or after periods of inactivity during the day. Morning stiffness generally resolves after less than 15 min. A so-called ‘gel phenomenon’, defined as stiffness appearing after rest or inactivity, is usually limited to a few minutes.

Limitations of motion and function develop as OA progresses and are related to joint surface incongruity with reduced joint space, muscle spasm or diminished strength leading to instability and mechanical block from osteophytes and loose bodies. Moreover, joint proprioceptor sensitivity may be altered. Patients report limitations in their ability to perform day-to-day activities, like kneeling for knee OA, or cutting one’s toenails for hip OA. OA can also hamper stair climbing, walking and performing household chores. In weight-bearing joints, an abrupt ‘giving way’ may occur. In hand OA, impaired hand function is associated with the severity of OA, pain, joint involvement and the presence of nodes (Bagis et al, 2003). Furthermore, symptomatic OA may be associated with depression and disturbed sleep, which are additional contributors to disability (Allen et al, 2008; Parmelee et al, 2015).

Thus, OA, wherever it occurs, typically causes pain, alters function and leads to a significant deterioration in the quality of life (CDC, 2001).

The art of history taking in diagnosing and assessing the severity of OA is focused on differentiating OA joint pain and loss of function from other joint diseases, in particular the chronic inflammatory arthritides as well as acute joint diseases such as gout, septic arthritis and flares of crystal-induced arthritis.

5.2 Physical examination

A physical examination should be performed to confirm and characterise joint involvement and to exclude pain and functional syndromes arising from other causes, especially peri-articular structures, neurological disorder and inflammatory arthritis. Note however, that a normal examination does not rule out the diagnosis of OA, especially early or mild OA.

- **Joint swelling:** joint enlargement results from joint effusion and/or osteophytes and/or synovitis. Bony swelling is easily recognised in superficial joints such as the finger joints or knees. A synovial effusion may be seen during OA flares, but can also occur during chronic phases as a persistent feature. It is most easily detected in knees by the evidence of patellar shock (tap) or by elicitation of a fluid thrill (wave test). In the digital joint, only synovitis can be detected since it is a small joint with a limited cavity.
- **Joint tenderness:** joints are usually tender during active motion testing and under pressure. Limited passive movement can be the first and only physical sign of symptomatic OA. Bursitis, tendinitis, muscle spasm and,

especially for the knee, a torn meniscus, can cause the same pain syndrome and must be carefully sought during examination. Crepitus, an audible or palpable sensation of crunching or crackling, is commonly felt on passive or active mobilisation of an OA joint and may result from cartilage loss, joint surface irregularity or intra-articular debris. Although crepitus can be present with passive motion, it is most commonly demonstrated by active motion of the joint.

- Joint deformities and subluxation reflect advanced disease resulting from cartilage loss, collapse of subchondral bone, formation of bone cysts and bony overgrowth. This destruction contributes to misalignment, joint instability and limb (usually manifest as leg) shortening.
- Gait: examination of the legs with the patient standing and walking (i.e., to facilitate detection of varus or valgus malalignment) is necessary to investigate the presence of malalignment and abnormal gait (see sections 8.2 and 8.4). The appropriate use of a cane may be assessed during walk examination. Altered gait patterns can also be caused by a conscious or subconscious attempt to protect the joint or minimise pain.
- Soft tissues and bursa areas should be examined in parallel, as they can be amenable to local treatment, such as glucocorticoid injections.

Caution should be exercised in attributing pain to the correct region, for example patients with hip OA may report pain in the knee region due to referred pain or biomechanical dysfunction. In these cases, moving the knee causes no pain, whereas hip movement is painful, and the range of hip motion is limited. Patients with hip OA also have symptoms mimicking a crural pain. Careful neurological and spine examination usually rules out this diagnosis.

6 Imaging OA

The diagnosis of OA is often obvious after an interview and physical examination, in particular when other diagnoses can be excluded. In straightforward presentations, radiological investigation is often not necessary to confirm the diagnosis of hand, knee or forefoot OA. However, some regions and clinical scenarios require a radiological examination to support the history and clinical assessment and to facilitate the exclusion of other diseases including avascular osteonecrosis, Paget's disease, algodystrophy, inflammatory arthropathies and stress fractures. Less commonly involved locations such as the ankle, shoulder or elbow, also require radiological examination. Radiographic assessment is helpful to diagnose OA, and also useful to establish the severity of joint damage, to monitor disease activity progression and any response to therapy, and to look for complications of the disorder or the treatment (Cibere, 2006).

EULAR has developed guidelines for the use of imaging in the management of peripheral joint OA (Sakellariou et al, 2017*) (Table 4). Seven pragmatic recommendations based on scientific evidence and expert opinion were provided, focusing on clinical practice rather than research.

Table 4 Use of imaging in peripheral joint OA: recommendations, levels of evidence and level of agreement (LoA) – order according to topic (making a diagnosis, monitoring disease, role in prognosis, treatment) (Reproduced from Sakellariou et al, Ann Rheum Dis 2017. doi: 10.1136/annrheumdis-2016-210815.)

No.	Proposition	LoE	LoA, mean (95% CI)
1	Imaging is not required to make the diagnosis in patients with typical presentation of OA (usage-related pain, short duration morning stiffness, age > 40, symptoms affecting one or a few joints)	III-IV	8.7 (7.9 to 9.4)
2	In atypical presentations, imaging is recommended to help confirm the diagnosis of OA and/or make alternative or additional diagnoses.	IV	9.6 (9.1 to 10)
3	Routine imaging in OA follow-up is not recommended. However, imaging is recommended if there is unexpected rapid progression of symptoms or change in clinical characteristics to determine if this relates to OA severity or an additional diagnosis.	III-IV	8.8 (7.9 to 9.7)
4	If imaging is needed, conventional (plain) radiography should be used before other modalities. To make additional diagnoses, soft tissues are best imaged by US or MRI and bone by CT or MRI.	III-IV	8.7 (7.9 to 9.6)
5	Consideration of radiographic views is important for optimising detection of OA features; in particular for the knee, weightbearing and patellofemoral views are recommended.	III	9.4 (8.7 to 9.9)
6	According to current evidence, imaging features do not predict non-surgical treatment response and imaging cannot be recommended for this purpose.	II-III	8.7 (7.5 to 9.7)
7	The accuracy of intra-articular injection depends on the joint and on the skills of the practitioner and imaging may improve accuracy. Imaging is particularly recommended for joints that are difficult to access due to factors including site (eg, hip), degree of deformity and obesity.	III-IV	9.4 (8.9 to 9.9)

LoE, level of evidence (Ia, meta-analysis of randomised controlled trials; Ib, at least one randomised controlled trial; IIa, at least one controlled study without randomisation; IIb, at least one other type of quasi-experimental study; III, non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies; IV, expert committee reports or opinions or clinical experience of respected authorities, or both); LoA: 0-10 numerical rating scale. OA, osteoarthritis; US, ultrasonography.

6.1 X-ray imaging

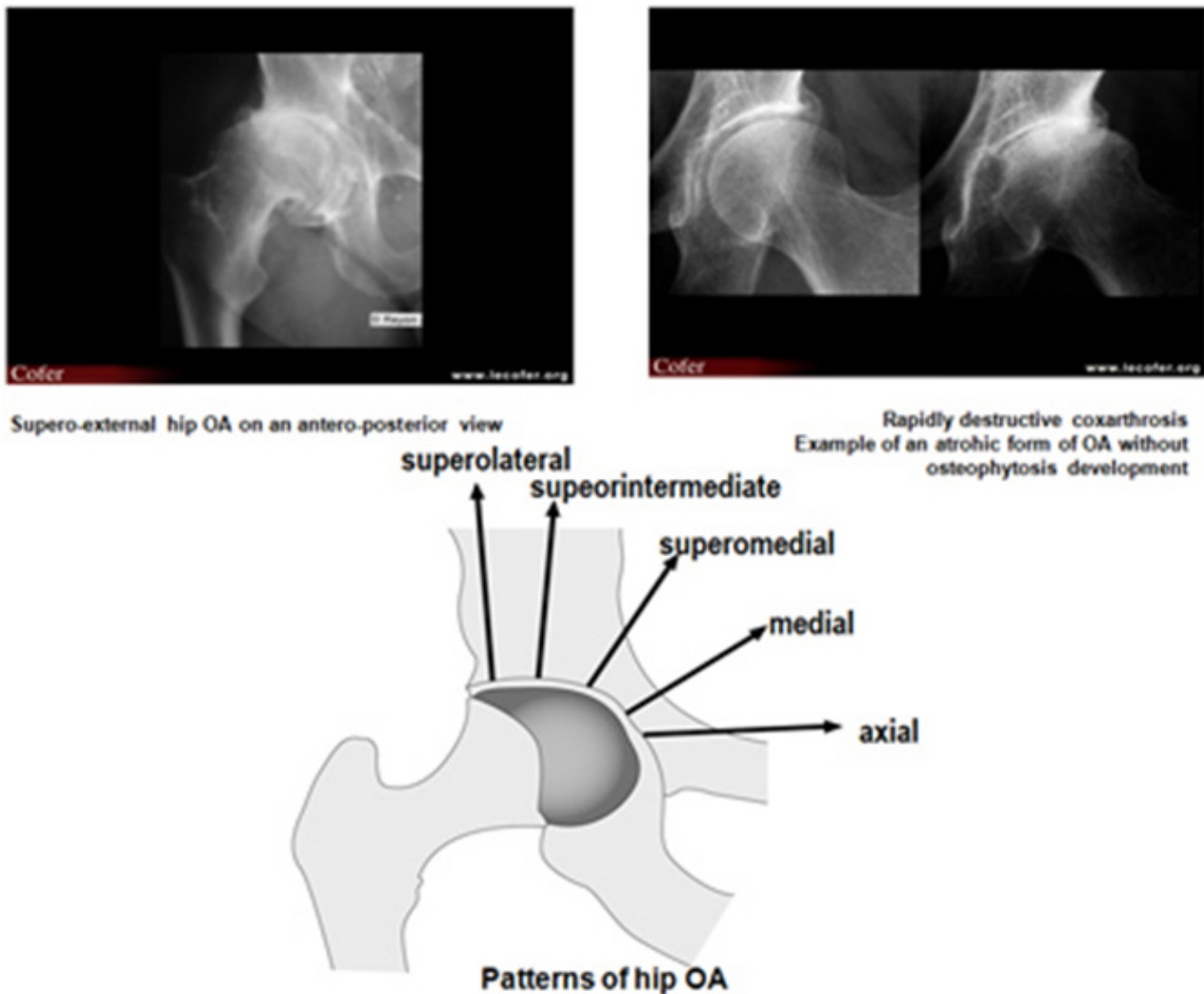
Weight-bearing X-rays are mandatory for knee and hip OA. However, standard radiographs cannot always diagnose early OA. The radiographic hallmarks of the most common form of OA, also called 'hypertrophic OA', include localised joint space narrowing, subchondral bone sclerosis, osteophyte formation and bone cysts. Subchondral bone sclerosis and joint space narrowing are classically seen in more advanced OA. However, clinical symptoms and radiographic findings are poorly correlated, many joints with radiographic evidence of OA remain asymptomatic and, conversely, the joints of many patients with severe symptoms can appear only marginally affected on X-ray (Dieppe et al, 1997; Hannan et al, 2000; Bedson and Croft, 2008). Adequate

radiographic views should be considered for detection of OA features. For the knee, flexed views demonstrated superiority compared to fully extended views in detecting joint space narrowing, and greater sensitivity to change and reproducibility. In addition, patellofemoral compartment is better assessed with skyline views than with lateral projections (Sakellariou et al, 2017*).

Demineralisation is not a classical feature of OA and its presence strongly suggests an inflammatory arthropathy or algodystrophy. Joint space narrowing is related to a decreased volume of articular cartilage, and also to meniscal cartilage lesions and cartilage extrusion (Raynauld, 2003). Although standard X-rays are useful for monitoring the evolution of OA, the optimal frequency of radiographs that can best inform practice is not well defined. Gross deformity, subluxation and loose bodies may occur in advanced cases. 'Atrophic' OA is a rare form of OA, characterised by an absence of osteophytes and sclerosis; it usually involves the hip and especially rapidly destructive hip (figure 9) (Ledingham et al, 1992; Rosenberg et al, 1992) and may chiefly occur in women (Conrozier et al, 2004). Ankylosis in OA is not a feature, with the exception of erosive hand OA (Punzi et al, 2004).

Other investigations are rarely necessary to confirm the diagnosis of OA, but they are sometimes useful to exclude alternate possibilities in a difficult differential diagnosis. In addition, recent developments in imaging are providing novel insights into the pathophysiology and course of the disease (Roemer et al, 2014). MRI and ultrasound are more suitable for the assessment of soft tissues, while bone is better explored with CT. Although such imaging techniques, in particular MRI, are receiving a lot of attention in the literature, there is a gap between their use in study settings and their usefulness in daily clinical practice.

Figure 9 Hip osteoarthritis. (A) Antero-posterior view of supero-external hip osteoarthritis (OA). (B) Rapidly destructive coxarthrosis; example of an atrophic form of OA without osteophytosis development. (C) Patterns of hip OA. (Source: Cofer, <http://www.lecofer.org/>)



6.2 MRI imaging

All the tissues involved in OA, including cartilage lesions, fluid effusion, subchondral bone marrow oedema, low-grade synovitis, and meniscus or ligament lesions, can be seen by MRI (Peterfy, 2000). MRI can be useful for excluding tumour or avascular osteonecrosis. Changes in cartilage thickness can be detected early by MRI (Calvo et al, 2001). The pain and progression of knee OA seem to be associated with synovitis and bone marrow oedema seen on MRI, but this remains controversial (Felson et al, 2003; Conaghan, 2006; Conaghan et al, 2006; Yusuf et al, 2011). Bone marrow oedema is an MRI observation, but comparisons with histological specimens from knee replacement have shown that necrosis, fibrosis and abnormal remodelled trabecula are the most common features (Conaghan et al, 2006), therefore bone marrow lesion is a more appropriate name. The presence of bone resorption is also clearly recognised as part of OA progression (Felson et al, 2001; Felson et al, 2003). The meniscus tears seen by MRI are common in middle-aged and older adults, with or without knee pain. Thus, although MRI accurately detects meniscus or ligament damage, which are known to be

associated with increased OA progression, this finding is not unusual at the age of osteoarthritic patients and thus does not influence therapeutic management and should not by default lead to aggressive procedures (Pessis et al, 2003; Englund et al, 2012). MRI is now being used to assess the quantity and function of cartilage, synovium and bone. For instance, quantitative MRI provides non-invasive measures of cartilage degeneration at the earliest stages of joint degeneration and will likely be an important tool in early OA studies (Sharma et al, 2014). In hand OA, MRI gives more information than X-ray alone, and might be reliable to assess both structural and inflammatory changes (Kortekaas MC et al, 2015). MRI lesions (bone marrow lesions, synovitis and joint space narrowing) may also predict radiographic progression of hand OA (Haugen et al, 2016; Damman et al, 2017). However, as stated above, the routine use of MRI has no clinical application in daily practice (Sakellariou et al, 2017*). In addition, meta-analyses suggest that MRI can detect OA with an overall high specificity and moderate sensitivity when compared with various reference standards, thus lending more utility to ruling out OA than ruling it in. The sensitivity of MRI appeared to be below the current clinical diagnostic standards (Menashe et al, 2012).

6.3 Ultrasound

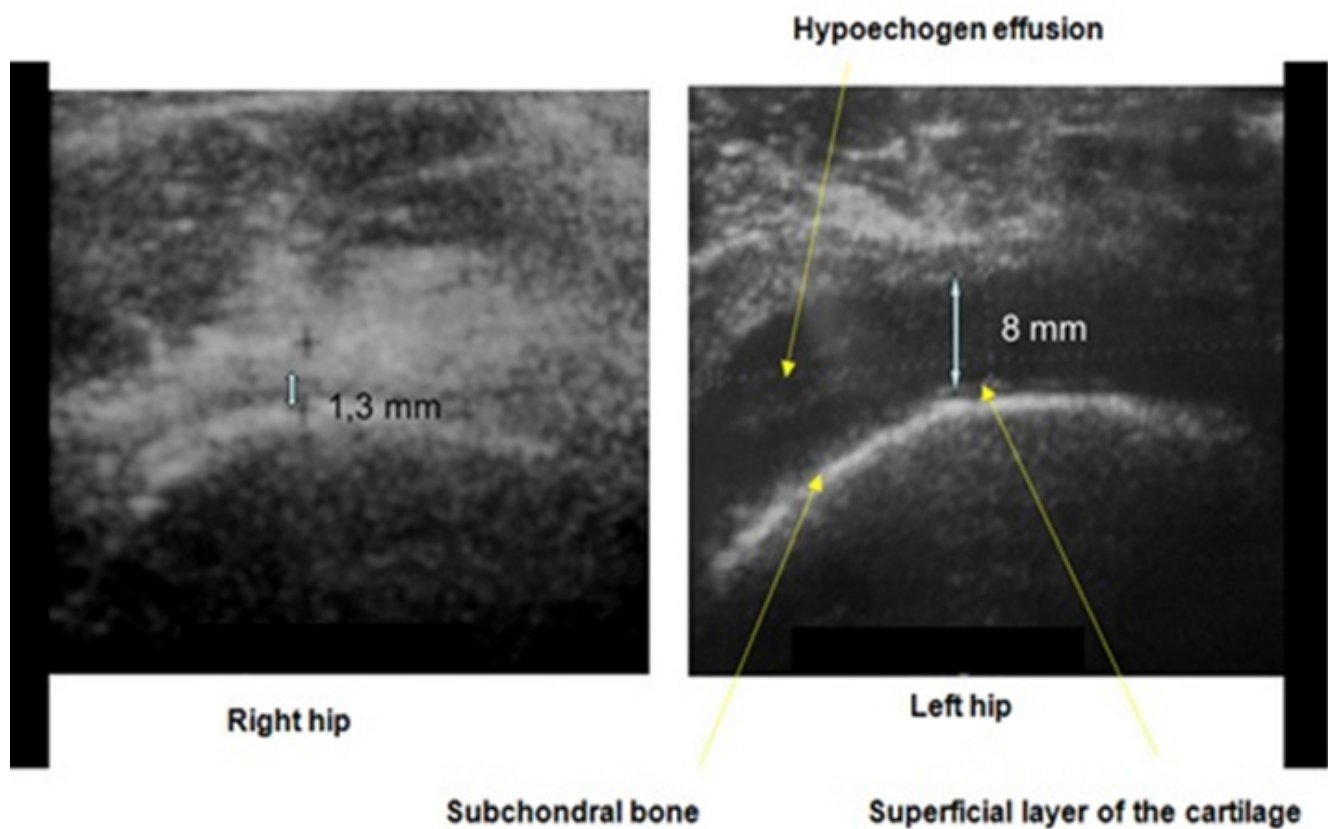
Ultrasound is currently only useful for detecting joint effusions, including a minimal effusion undetectable upon clinical examination, changes in cartilage such as fibrillation of cartilage or cleft formation, synovitis and osteophytes (Iagnocco, 2014) (figure 10). Popliteal cysts can also be visualised by ultrasound, and potential complications including compression of adjacent vascular structures can be diagnosed. Many studies are currently evaluating the advantages of this procedure in terms of early diagnosis, evaluation of pain symptoms, severity and prognosis. Ultrasonography has been extensively studied in knee OA to detect inflammatory flares and popliteal cysts and could serve to assess treatment efficacy (Acebes et al, 2006). Ultrasonography may also be useful in hand OA, to differentiate between erosive and non-erosive OA. Ultrasound-detected inflammatory features may also predict the development of erosions in hand OA (Kortekaas et al, 2016). Ultrasonography can be used to perform aspirations and injections within the joint and peri-articular tissue. However, ultrasound imaging is limited by its inability to visualise the entire cartilage surface, by artefacts caused by the position of the probe, and finally by inter- and intra-observer variations. Thus, this imaging procedure needs standardisation before it can be used in daily clinical practice, except for specific situations (i.e., popliteal cysts, guided aspiration or injection) (Sakellariou et al, 2017*).

6.4 Arthroscopy

Arthroscopy visualises cartilage, synovial membranes, osteophytes and meniscal lesions. Note that this approach, like MRI, may detect findings of dubious significance such as meniscal lesions, which are frequent in patients over 60 but rarely the cause of pain. On the other hand, dissection of the meniscus could be highly deleterious by accelerating the progression of OA. This procedure is employed less since the use of MRI

became more common. Definite conclusions about the global clinical utility of MRI when compared with arthroscopy have not yet been made (Quatman et al, 2011).

Figure 10 Hip osteoarthritis: ultrasonography.



7 Laboratory tests

Blood tests are not routinely indicated to confirm the diagnosis of uncomplicated chronic pain arising from clearly defined OA. The erythrocyte sedimentation rate and C-reactive protein concentration are usually within the normal range for age. Highly sensitive C-reactive protein seems elevated in some patients with erosive hand OA, but its use is not recommended for daily clinical practice (Punzi et al, 2004). Low titres of rheumatoid factors can be found, reflecting the median age of patients with OA and not differing in that respect from control populations. Laboratory tests may be performed to rule out a metabolic arthropathy (such as gout or haemochromatosis) or inflammatory arthritis, or to investigate the adverse effects of drugs.

Synovial fluid in primary OA is non-inflammatory and should only be examined if another arthropathy or septic arthritis is suspected. Assessment of crystals is thus necessary. Analysis of synovial fluid typically reveals a white blood cell count of less than 2000 per mm³, sterile, without any crystals (Dougados et al, 1996*). However, apatite crystals may appear in synovial fluid with progression of the disease in patients with OA, and their presence is common in the most severe forms of OA (Nalbant et al, 2003).

Histological examination, performed during surgical joint replacement, reveals non-specific changes of chronic mild inflammation or some degree of fibrosis (see section 2, Pathology). For OA, synovial biopsies currently do not contribute to the diagnostic process.

Biochemical markers of cartilage or bone turnover or remodelling are not currently assayed in the day-to-day management of OA because no single marker is yet adequate for predicting or monitoring OA in an individual patient. Biomarkers in cohort studies and in clinical trials are useful to elucidate the physiopathology of disease and to support a clinical impression of the disease state of OA. Candidate biochemical markers of joint tissues in OA can reflect different actors of OA (bone, cartilage, synovitis, systemic inflammation) and the different states of these tissues (i.e., degradation or synthesis).

The objective in the future will be to use biomarkers in OA diagnosis, before damage can be observed on radiographs. The main limitation in using tissue-derived biomarkers including collagen breakdown products is the need to adjust for different clinical features such as sex, age, body mass index and hormonal status (including hormone replacement therapy). Biomarkers may have some other sources of variations such as diurnal variation or influence of exercise, and reflect not just one target joint but all joints in an individual. Biomarkers are also used in the prediction of progression. In some studies, joint space narrowing progression seems positively correlated with markers of degradation of type I and II collagen (i.e., C- and N-telopeptide) and cartilage oligomeric matrix protein (COMP) corresponding to degradation of non-aggreacan and non-collagen proteins (Charni-Ben and Garner, 2007). Because of the complex involvement of bone cartilage synovium and systemic inflammation, only a combination of several biochemical markers will adequately predict disease progression (Davis et al, 2007). These new biomarkers will serve probably also to predict and/or monitor the efficacy of new disease-modifying OA treatment (Martel-Pelletier et al, 2017). Whether it will be possible to utilise biomarkers meaningfully to characterise the disease state in an individual patient remains to be seen (Kraus, 2006*; van Spil et al, 2010). As stated above, there is no evidence that one of the biomarkers currently under study should be used to diagnose, monitor or predict disease course.

8 Clinical subsets of OA

8.1 Several forms of OA

OA tends to affect distal interphalangeal joints, the trapezio-metacarpal joint, the knee, hip and intervertebral facet joints. Commonly, more than one joint is involved and there is a significant association between contralateral joints that is stronger than the association between different joint groups. Knee and hip OA are both associated with hand OA, the association between knee and hand OA being stronger (Crushnagan and Dieppe, 1991; Croft et al, 1992b; Hochberg et al, 1995; Cooper et al, 1996; Hirsch et al, 1996). Wrists, elbows, metacarpophalangeal joints and shoulders are usually less likely to be affected by OA. If they are, this may suggest the presence of secondary OA or another diagnosis.

Some authors individualise several forms of OA:

- Primary OA, corresponding to the classical definition and description of the disorder, differs from the secondary form which has an identifiable aetiology such as a congenital, inflammatory or metabolic disease able to explain the degenerative process occurring in the joint. Thus, if there is concomitant disease, the target joint is generally considered to be affected by secondary OA. Secondary OA shares some features with primary OA but, in addition, is characterised by the presence of signs and symptoms suggesting an underlying cause. The identification of the primary disease is valuable since specific therapies can be used.
- Sometimes, physical symptoms can suggest such a diagnosis: for example, metacarpophalangeal involvement during hand OA suggests the presence of an inflammatory or metabolic disorder. Secondary causes of OA are reported in box 1. Some of them are more of a risk factor (i.e., meniscectomy or occupational arthropathy) and the distinction between aetiological and predisposing factors is not always easy. Of note, several predisposing factors may be present in case of primary OA.
- As mentioned above, the most common form of OA, also called ‘hypertrophic OA’, including classical features of OA (i.e., localised joint space narrowing, subchondral bone sclerosis, osteophyte formation and bone cysts) has to be differentiated from the rare ‘atrophic’ form in which an absence of osteophytes and sclerosis is observed. This last form is often associated with rapid progression and is thus called ‘rapidly destructive arthropathy’ (figure 9).
- Primary generalised nodal OA corresponds to a more severe disease differentiated only by polyarticular involvement and the presence of multiple Heberden’s and Bouchard’s nodes. This subtype of OA should lead to investigation for a metabolic arthropathy such as chondrocalcinosis.
- Erosive inflammatory OA involving the hand, which has a greater clinical burden than non-erosive hand OA in the general population (Kwok et al, 2013). However, whether erosive hand OA is a specific entity or simply a severe form of the disease remains debated (Marshall et al, 2015).

8.2 Knee

OA can involve the medial tibiofemoral, the lateral tibiofemoral and the patellofemoral compartments. First, a misalignment of the lower limb might be noted if present. It is a cause of compartmental knee OA (e.g., varus angulation of the knee responsible for medial tibiofemoral damage and valgus angulation for lateral tibiofemoral damage). The lateral tibiofemoral compartment is involved mainly in women with a genu-valgum misalignment. Varus and valgus angulations can affect the range of motion and accelerate joint space narrowing. They may thus enhance the development of OA. The precise location of pain can indicate which compartment of the joint is involved. Patients also sometimes report knee instability—the knee ‘gives way’.

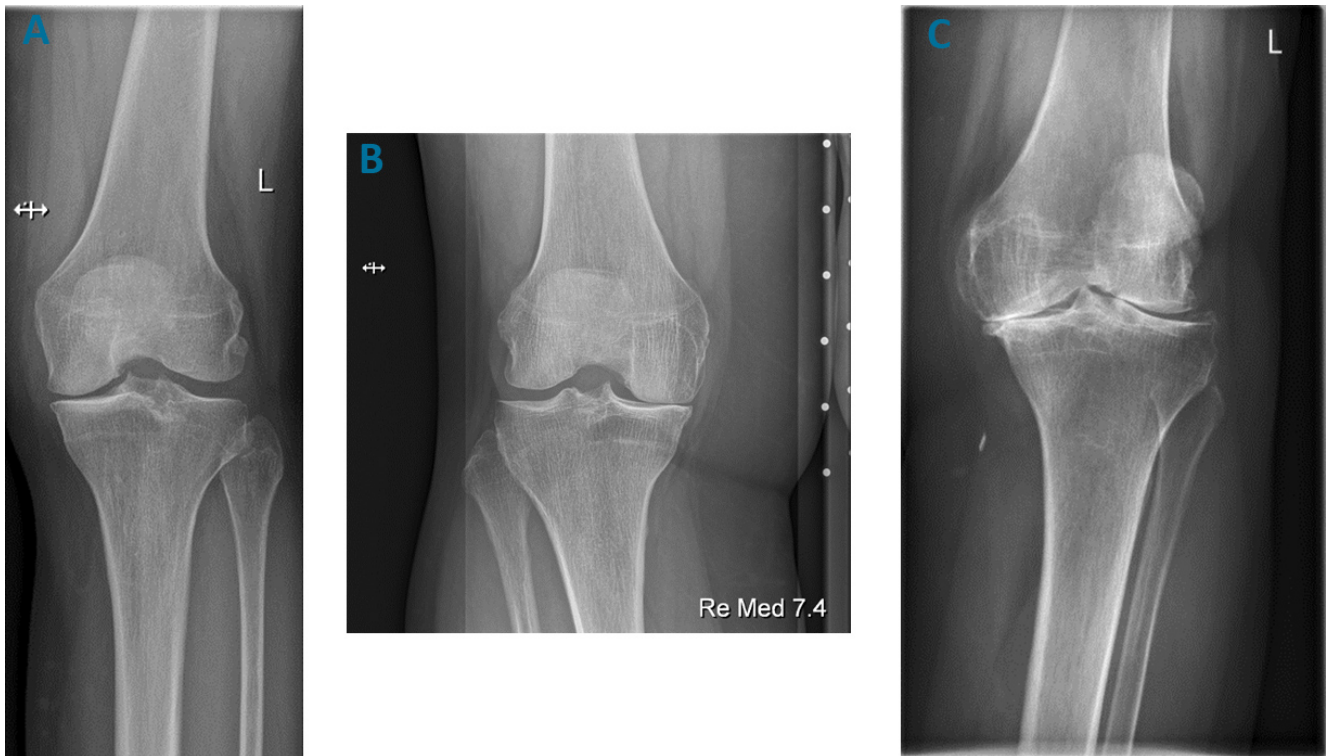
This is likely linked to decreased muscle strength rather than true meniscus damage. Posterior pain can be due to an abundant effusion.

The knee can lock if loose bodies or fragments of cartilage get into the joint space. This is relatively rare, but care should be taken to distinguish between the stiffness experienced after prolonged immobilisation of a limb and true mechanical locking, which suggests a meniscus lesion. Physical examination for knee OA should begin by investigating the gait, using a slow walk to check for an extension defect. The presence of bone swelling should be noted. Physical examination may find synovitis or fluid effusion. Crepitus is detected upon passive motion of the patella or knee flexion/extension testing. The range of motion may be normal or limited by structural alterations or abundant effusion. A popliteal (Baker's) cyst communicating with the joint space is common. The cyst may rupture into the posterior calf muscles, mimicking venous thrombosis, and should be considered in 'Doppler negative' leg swelling in the acute setting. Local tenderness along the joint line is characteristic of tibiofemoral OA. Peri-articular structure examination may reveal anserine bursitis, infrapatellar or prepatellar bursitis, and instability of the collateral ligament. Trochanteric bursitis can also cause pain radiating through the tensor of fascia lata and ilial-tibial band to the lateral part of the knee. An acute tear of the anterior cruciate ligament may cause pain, but is unusual in middle-aged subjects. The presence of anterior laxity should also be evaluated, since a decrease in anterior-posterior laxity is associated with decreased joint space. A lax joint is defined by the excess displacement or rotation of the tibia with respect to the femur in the varus-valgus direction. Joint laxity increases functional disability due to weak muscles. A positive Lachman's test may be elicited. Of note, cartilage erosion is frequently associated with meniscal degeneration which is not considered the source of pain and does not require specific therapeutic management (Ike and Arnold, 1992). The circumference of the quadriceps muscle should be noted to detect any atrophy. A weak quadriceps femoris is a known disability factor in knee OA. This weakness can more convincingly explain the knee 'giving way' than the often-suggested ligament instability. Finally, the hip should be examined routinely since it may refer pain to the knee.

The syndrome of patellofemoral OA is very specific: pain occurs mainly during climbing or descending stairs, while pain during walking on level ground is usually a symptom originating in the tibiofemoral compartment. Involvement of the patellofemoral compartment can cause anterior and/or posterior pain. Patellofemoral pain is produced by the patella pressing on the femoral condyles, or after patella subluxation or blocking elevation of the patella during quadriceps contraction when the knee is extended. Patellofemoral OA is usually better tolerated than tibiofemoral OA, but severe disability is also possible.

X-rays for knee OA should include bilateral comparative images of both knees: a weight-bearing, semi flexed posterior-anterior (PA) view and a lateral and skyline view (Sakellariou et al, 2017*). Classical features are focal joint space narrowing, osteophytes, subchondral bone sclerosis and subchondral 'cysts' (Zhang et al, 2010*) (figure 11).

Figure 11 Osteoarthritis of the knee. (A) Slightly narrowed medial femoro tibial joint space of the left knee with osteophytes (Kellgren–Lawrence grade II). (B) Moderately narrowed medial femoro tibial joint space of the right knee with multiple osteophytes (Kellgren–Lawrence grade III). (C) Marked joint space narrowing (tricompartimental) of the left knee with large osteophytes (Kellgren–Lawrence grade IV).



The patellofemoral compartment is investigated using an axial (skyline) view with variable degrees of knee flexion or a lateral view. Skyline view have a greater reliability and sensitivity to change than lateral view (Sakellariou et al, 2017*). However, when both the skyline and lateral views are used with the PA, 98.7% cases of radiographic OA can be identified (Duncan et al, 2006). The tibiofemoral compartment is evaluated by a semi-flexed posterior-anterior view (Zhang et al, 2010*).

Squaring of the femoral condyle, intercondylar spurring and varus or valgus misalignment of the affected limb can occur. Radiographs of the hip, the knee and the ankle made on one long film with the patient standing upright may identify angular deformity. The patient must be able to place his/her full weight on the affected limb for a true measurement of limb deformity. A mechanical axis of 0° to 3° of varus is considered to be within normal limits (Iorio and Healey, 2003).

8.3 Hand

The hand is one of the most common sites of OA. Post-menopausal women are more frequently affected than men (sex ratio 10:1) and genetic factors explain familial aggregation (Spector et al, 1996). Hand OA begins mostly after 40 years of age (Zhang et al, 2009*) and usually affects multiple hand joints at the same time, especially the distal interphalangeal, proximal interphalangeal and first carpometacarpal joints of the hand

(Kloppenburg and Kwok, 2011). A preferential pattern of distribution is found, consisting of involvement by row, by ray and symmetrical. The metacarpophalangeal joints are less commonly involved, but if implicated, an inflammatory or metabolic arthropathy, such as rheumatoid arthritis or haemochromatosis, should be investigated.

The four main complaints of hand OA are: pain on usage, mild morning stiffness, disfigurement and disability, with impaired manual dexterity and reduced hand mobility leading to restriction of occupational activity. Bony enlargements of the proximal interphalangeal joints are called Bouchard's nodes, whereas those of the distal interphalangeal joints are called Heberden's nodes (figure 12). These nodes are responsible for malalignment of the fingers. They can develop gradually with acute inflammatory phases characterised by severe pain and synovitis mimicking an inflammatory arthropathy, such as psoriatic arthritis. A differential diagnosis can be very difficult in such cases, in particular since psoriasis is a common disease. A diagnosis of psoriatic arthritis should be suspected more strongly when the patient shows signs of psoriatic nail disease or in the presence of other affected joints. In hand OA, the swollen joints may feel either soft and fluctuant (corresponding to small synovitis) or hard (because of the presence of osteophytes). Nodes can be associated with mucinous cysts which can disappear spontaneously or persist indefinitely or sometimes communicate with distal interphalangeal joint space. As the disease progresses, there is characteristic loss of mobility and flexion and deviation of the distal phalanx. The disease course is usually insidious, but sometimes acute.

OA frequently involves the first carpometacarpal joints, causing painful motion, tenderness, and squared deformation of the radial base of the thumb, and fixed adduction that in turn leads to severe disability (Bijsterbosch et al, 2010) (figure 12). This location is clearly associated with hypermobility as a risk factor (Jonsson et al, 1996). De Quervain's tenosynovitis can be associated throughout the disease process and exacerbates this functional limitation.

Polyarticular hand OA often co-occurs with knee and hip OA, and with OA at other joint sites (generalised OA). Therefore, patients with hand OA should also be examined for OA at other joint sites.

Posterior-anterior X-rays of both hands, including the wrists, can reveal characteristic features of OA (figure 13), but radiography is not necessary for diagnosing hand OA. Erosions of the interphalangeal distal joints on X-rays (seagull erosions) are prominent features in a subset of OA patients called "erosive OA". This is more common in post-menopausal women and characterised by inflammatory pain and synovitis and leads to joint deformity and occasionally ankylosis. The fingers are often significantly deformed within a short number of years, with firm bony swelling and consequent reduced joint motion. At advanced stages, flares and pain tend to subside. A slight increase in erythrocyte sedimentation rate or C-reactive protein may be present. The differential diagnoses are psoriatic arthritis, less likely rheumatoid arthritis and, very rarely, multicentric reticulo-histiocytosis.

Figure 12 Hand osteoarthritis: clinical aspects. (A) Typical features of hand osteoarthritis (OA) with Heberden's and Bouchard's nodes. Note the misalignment related to the distal (Heberden's) nodes. (B) Typical feature of trapezo-metacarpal OA with deformation of the base of the thumb. (Source: Cofer, <http://www.lecofer.org/>)

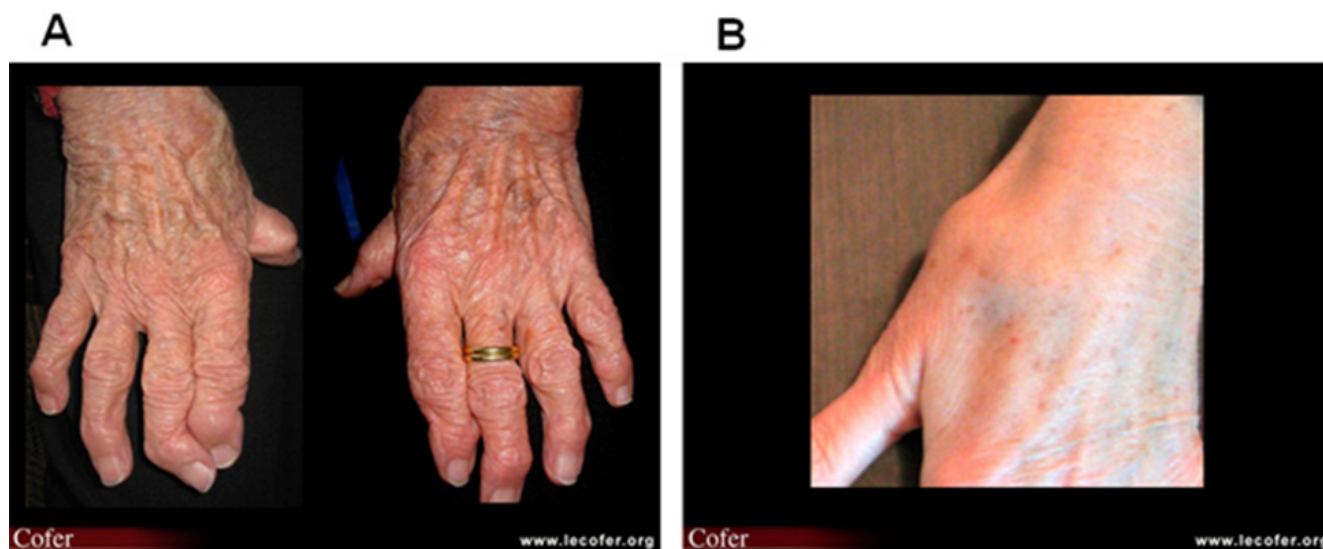


Figure 13 Osteoarthritis of the hand. Diffuse osteoarthritic impairment of bilateral PIP and DIP joints with signs of destruction, bilateral osteoarthritis of MCP V and bilateral thumb osteoarthritis (CMC I and STT joint). CMC, carpometacarpal; DIP, distal interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; STT, scaphotrapezotrapezoidal.



8.4 Hip

Hip OA develops equally in men and in women (Srikanth et al, 2005) and may be unilateral or bilateral.

Unilateral hip OA increases the likelihood of involvement of the contralateral joint (Cooper et al, 1996). Beside

age and genetics, common risk factors include incongruency (such as dysplasias), joint laxity, increasing BMI, high levels of certain exercise and heavy manual labour (Aresti et al, 2016).

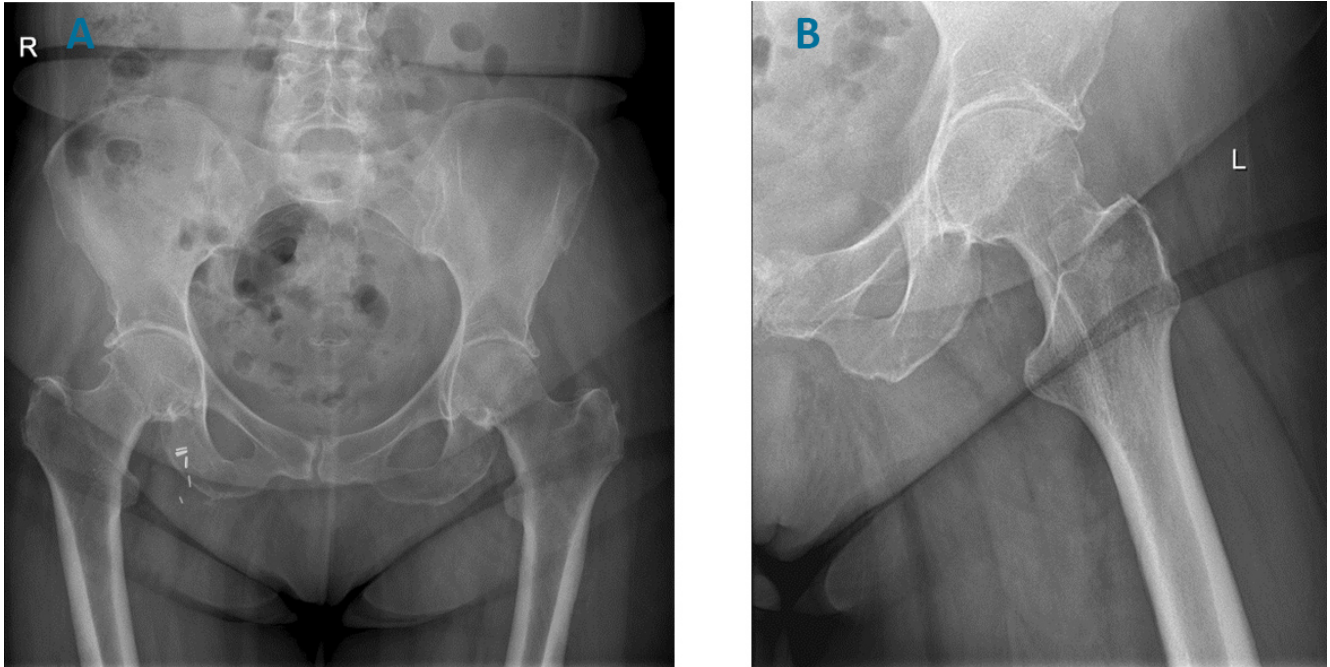
Hip pain is classically present during weight-bearing and associated with antalgic gait. Pain can be located in the buttocks and the groin region, and may radiate down to the anterior thigh. Occasionally, patients present with predominantly knee pain (referred pain) and its true origin (hip OA) is overlooked.

Patients often report significant disability during activities of daily life, for example they find it difficult to reach their feet to cut their toenails or to tie their shoelaces. Flares are frequent, with pain at night and morning stiffness, sometimes associated with the presence of an effusion. In this case, further investigations, such as ultrasonography or MRI, should be considered in order to identify an inflammatory flare with synovitis or effusion. Advanced OA is often preceded by a progressive phase with increasing aggravation of symptoms (between 3 months and 3 years). The symptoms seldom improve, except in concentric hip OA with marked osteophytosis. Examination reveals a limited range of movement, although this is not always present. The leg is often held in external rotation with the hip flexed and adducted. In early disease, limited movement may only be seen when extension is tested. Groin pain can be reproduced by palpation during physical examination. This pain can also be reproduced by passive movement of the hip, especially upon internal rotation and flexion. Quadriceps muscle weakness is also a common finding. The main differential diagnoses are cruralgia (in which neurological signs are usually present), psoas and iliopsoas lesions, and trochanteric bursitis (characterised by pain at the external surface of the hip and thigh but normal hip motion). Consideration should also be given to intra-pelvic lesions if clinical examination is entirely normal in the face of a convincing history. In case of difficult diagnosis, injection with local glucocorticoids and lidocaine in the joint or in the trochanteric bursitis can be helpful.

Radiological examination should be bilateral and comparative, and include an anteroposterior pelvis view in the weight-bearing position with internal rotation of the feet (15° to 20°), an anteroposterior view centred on one hip, and a false profile incidence corresponding to an oblique view which seems especially of interest in case of superolateral space narrowing OA (Lequesne, 2002). All these radiological images are useful to assess with precision joint space narrowing of the hip (figure 14). The superior-external pole is most often involved (superior-lateral, superior-intermediate and superior-medial) (figure 9). Medial OA is much rarer, occurs mainly in women and progresses slowly. Hip OA may be rapidly destructive, defined by Lequesne as joint space narrowing at more than 2 mm/year, that is, a loss of more than 50% of the joint space within 1 year (Lequesne and Ray, 1989). Bone sclerosis and osteophytes are rare in such patients. Importantly, hip pain and radiographic hip OA are two substantially discordant outcomes: a minority of patients with hip pain has radiographic hip OA, and only a minority of patients with radiographic hip OA has hip pain (Kim et al, 2015). A hip joint replacement is usually considered within a few months of the first symptoms being recognised. The

common aetiologies of secondary hip OA include congenital dysplasia, avascular osteonecrosis and previous trauma.

Figure 14 Osteoarthritis of the hip. (A) Bilateral joint space narrowing and presence of osteophytes. (B) More detailed view of the left hip; clear signs of joint space narrowing, osteophytes and sclerosis.



8.5 Spine

Spine and peripheral OA share anatomical similarities and common pathophysiological processes. The posterior facet articulations are true diarthrodial joints and as such are susceptible to OA. The other structures involved in spine OA are intervertebral fibrocartilaginous discs and vertebral bodies which are damaged. Some authors make the distinction between degenerative changes involving the discs and vertebral bodies and those involving apophyseal joints, the latter being generally considered similar to peripheral joint OA.

Common regions of involvement include the cervical and lumbar spine, whereas the dorsal spine is only exceptionally involved because of the stability provided by the thoracic cage. Osteophytes of the vertebrae can narrow the foramina and compress nerve roots producing, in addition to back pain, a radicular pain with specific topography, especially when it is associated with disc herniation, ligamentous hypertrophy, spondylolisthesis or foraminal narrowing from apophyseal joint subluxation. Weakness and numbness of the arms or legs have also to be assessed. Spinal cord lesions as a result of OA of cervical and dorsal spine are possible but classically not in the case of lumbosacral spine involvement because the spinal cord ends at the level of L1; however, cauda equina syndrome with sphincter dysfunction may develop.

The pain has some typical features such as intermittent radicular claudication, exacerbation during extension of the spine and relief during flexion. The patient may stand with the lumbar spine flexed to reduce pain.

In some individuals, osteophytes may extend along the entire length of the spine, with prominent involvement of the thoracic region and osteophyte fusions. This hyperostosis is also called Forestier's disease and can include extraspinal sites. The usual term used for this condition is diffuse idiopathic skeletal hyperostosis (figure 15).

Figure 15 Diffuse idiopathic skeletal hyperostosis (also called Forestier's disease). Dorso-lumbar radiographs showing extensive osteophytosis. (Source: Cofer, <http://www.lecofer.org/>)

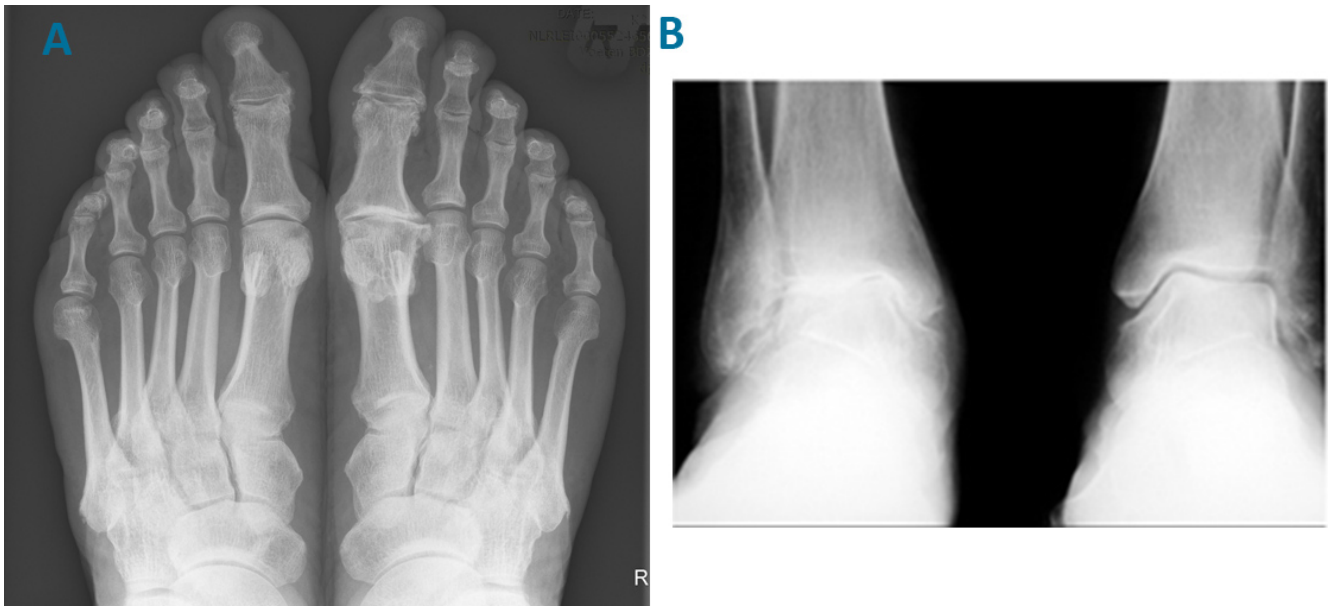


Radiological evidence of degenerative disease in the spine may be extensive but sometimes without major pain. However, minor spur formation located in a critical area can be symptomatic.

8.6 Foot and ankle

OA commonly attacks the first metatarsophalangeal joint. OA at the other metatarsophalangeal joints occurs to a lesser degree. Patients have difficulty walking and the overlying skin can appear inflamed, especially if tight shoes are worn. A bursitis can also appear. A valgus deformity is very frequent (hallux valgus) and there may be ankylosis of the joint (hallux rigidus). There are usually radiological features of foot and ankle OA, even in subjects aged less than 40 years. The tarsal joints may be involved in cases of pes planus. Tibial-talar and subtalar OA are generally due to trauma, misalignment or neuropathic arthropathy (figure 16). Importantly, in the absence of trauma history, ankle arthropathy should prompt diagnostic tests for hereditary haemochromatosis (Husar-Memmer et al, 2014; Richardson et al, 2017).

Figure 16 Foot/ankle osteoarthritis. (A) Osteoarthritis (OA) of the first metatarsophalangeal joint. (B) Post-traumatic ankle OA (right) with tibiotarsal joint space narrowing and subchondral bone sclerosis.



8.7 Shoulder

OA is less common in the shoulder than in weight-bearing joints (figure 17). Pain is poorly localised and occurs on movement, but pain at night during motion is also common. Examination reveals limitation of passive movement. Shoulder OA sometimes follows lesions of the rotator cuff, which promotes ascension of the humeral head. Milwaukee shoulder is a particular form of shoulder OA characterised by hydroxyapatite deposits and severe destruction of the joint (Halverson et al, 1984) (figure 18). The differential diagnosis includes acromio-clavicular disease, which gives elective tenderness on direct palpation of the joint with medial irradiation. The acromio-clavicular joints are often affected in subjects like construction workers subject to direct weight bearing to the shoulder area. Shoulder OA can also develop after vascular osteonecrosis, causing the humeral head to become aspherical.

Figure 17 Shoulder osteoarthritis. Strongly pronounced glenohumeral osteoarthritis of the left shoulder with an extremely voluminous caudal osteophyte at the humeral head.

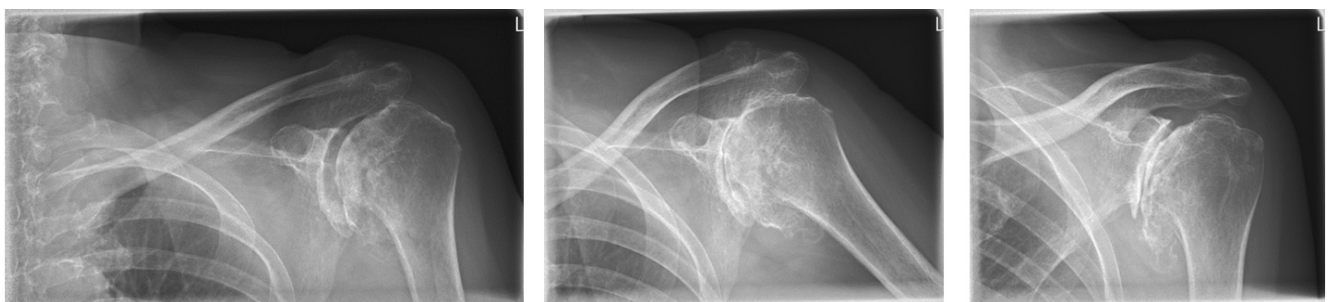


figure 18 Milwaukee shoulder. (Source: Cofer, <http://www.lecofer.org/>)



9 Tools for diagnosis, classification and assessment of OA

9.1 Criteria for OA

Criteria for any disease may serve different purposes. Criteria can be used for the classification of patient groups, typically used for inclusion in clinical trials or population surveys, for the diagnosis of individual patients with a direct impact on clinical practice, and for the evaluation of disease severity and outcome. Caution is important when considering the use of criteria in daily clinical practice. Most disease criteria have been developed to aid the correctness of diagnosis in patients taking part in clinical studies rather than the effectiveness of individual patient diagnosis. However, many such criteria sets have been used or mis-used as guidelines or tools in patient diagnosis. The physician should always keep in mind that classification criteria have been developed by specific methods and in a specific setting (eg, primary care or tertiary referral clinics) with the goal of achieving optimal group discrimination and not the diagnosis of disease in an individual patient. Therefore, most classification criteria used in rheumatology should not be used to formally make or exclude a diagnosis in the individual patient.

As mentioned above, OA can be defined in different ways, based on clinical signs and symptoms, radiographs or other imaging tools, and by pathology. Radiographic definitions of OA usually include joint space narrowing or the presence of osteophytes; clinical definitions include the detection of abnormalities upon clinical examination such as limited movement or crepitus in a joint. As radiographs and clinics do not always agree,

symptomatic OA (and therefore probably clinically relevant OA) is usually defined as pain, aching or stiffness in a joint that also shows radiographic signs of OA.

The American College of Rheumatology (ACR) has defined 'Criteria for the classification and reporting of OA' of the hand, hip and knees (table 5) (Altman et al, 1986; Altman et al, 1990; Altman et al, 1991). These criteria are excellent examples of classification criteria. From this perspective and taking into account their goals (correct definition of groups in clinical research), sensitivity and specificity are considered very good to excellent. The sensitivity and specificity of the ACR hip criteria are estimated to be 91% and 89%, respectively, while the sensitivity and specificity of ACR knee criteria are estimated to be 91% and 86%. For hand OA, the sensitivity is 92% and specificity 98%. Taking into account their overall high specificity, such criteria can be useful as a tool in clinical practice in order to differentiate patients with OA from those with inflammatory disease. Their sensitivity is less impressive, illustrated by their limitation in differentiating patients with early OA from healthy controls. When these criteria are used, the prevalence of OA is underestimated compared with a definition based on radiographic criteria (McAlindon and Dieppe, 1989), and also these criteria cannot be used to rule out a diagnosis of OA in routine clinical practice, in particular in early stages of disease.

EULAR has developed recommendation sets for the clinical diagnosis of hand and knee OA, and showed that thorough clinical assessment alone can provide a confident diagnosis (Zhang et al 2009*; Zhang et al, 2010*). The recommendations for diagnosis can also be found on the EULAR website (www.eular.org). For knee OA, 10 recommendations were developed (table 6). According to the recommendations and the supporting evidence, the diagnosis of knee OA can be made based on the background risk (the population prevalence of knee OA), the patient's risk factors for OA (eg, age, gender, BMI, occupation), their symptoms and an adequate physical examination. Plain radiographs are the main test to consider, but are an adjunct rather than a central feature, for the purposes of diagnosis. The more positive results a patient presents, the more likely the diagnosis of OA. Knowledge of the background risk (eg, the local source population prevalence of knee OA) is crucial for estimating the likelihood of knee OA. The higher the risk in the source population, the more possible it is to diagnose knee OA based on clinical features. A confident diagnosis may therefore be made according to three symptoms (knee pain, short-lived morning stiffness and functional limitation) and determination of three signs on examination (crepitus, restricted movement and bony enlargement) without a requirement for imaging. This may be especially useful for primary care. Nevertheless, plain radiography and occasionally other investigations should be considered for the diagnosis of atypical cases when additional pathology is suspected.

Table 5 American College of Rheumatology radiological and clinical criteria for hand, hip and knee osteoarthritis

		Diagnosis of OA can be made if following criteria are met:
Hand	Clinical 1. Hand pain, aching or stiffness 2. Hard tissue enlargement of 2 or more of 10 selected joints* 3. Fewer than 3 swollen metacarpophalangeal joints 4a. Hard tissue enlargement of 2 or more distal interphalangeal joints 4b. Deformity of 2 or more of 10 selected hand joints*	1, 2, 3 and 4a or 1, 2, 3 and 4b (tree format)
Hip	Combined clinical and radiographical 1. Hip pain 2. Femoral and/or acetabular osteophytes on radiographs 3a. ESR \leq 20 mm/h 3b. Axial joint space narrowing on radiographs	1 and 2 or 1, 3a and 3b (tree format)
Knee	Clinical 1. Knee pain 2. Age >50 years 3. Morning stiffness for <30 min 4. Crepitus on active joint motion 5. Bony tenderness 6. Bony enlargement of the knee on examination 7. No palpable warmth Combined clinical and radiographical 1. Knee pain 2. Age >50 years 3. Morning stiffness for <30 min 4. Crepitus on active joint motion 5. Osteophytes at joint margins on radiographs	1 + at least 3 of the other clinical criteria 1 and 5 + at least 1 of the other criteria (2, 3 or 4)

*The 10 selected joints include bilateral second and third interphalangeal proximal joints, second and third proximal interphalangeal joints, and first carpometacarpal joint. ESR, erythrocyte sedimentation rate; OA, osteoarthritis.

Table 6 Diagnosis of knee OA: propositions and strength of recommendation – order according to topic (definition, subsets, symptoms, physical findings, images, laboratory tests, risk factor and differential diagnosis) (Reproduced from Zhang et al, Ann Rheum Dis 2010;69:483–9)

No.	Proposition	LoE	SOR (95% CI)
1	Knee OA is characterised clinically by usage-related pain and/or functional limitation. It is a common complex joint disorder showing focal loss, new bone formation and involvement of all joint tissue. Structural tissue changes are mirrored in classic radiographic features.	IIb	88 (83 to 92)

2	Risk factors that are strongly associated with the incidence of knee OA can help identify patients in whom knee OA is the most likely diagnosis. These include increasing age over 50 years, female gender, higher body mass index, previous knee injury of malalignment, joint laxity, occupational or recreational usage, family history and the presence of Heberden's nodes.	Ia–IIb	89 (83 to 95)
3	Subsets with different risk factors and outcomes can be defined according to: varying compartmental involvement (patellofemoral, medial tibiofemoral, lateral tibiofemoral); bone response (atrophic, hypertrophic); the global pattern of OA (generalised, localised); by crystal presence (pyrophosphate, basic calcium phosphates); and by the degree of inflammation. However, the ability to discriminate subsets and the relevance for routine practice are unclear.	Ib–IIb	72 (63 to 87)
4	Typical symptoms of knee OA are usage-related pain, often worse towards the end of the day, relieved by rest; the feeling of 'giving away'; only mild morning or inactivity stiffness; and impaired function. More persistent rest and night pain may occur in advanced OA. OA symptoms are often episodic or variable in severity and slow to change.	Ib–IIb	76 (64 to 87)
5	In adults aged >40 years with usage-related knee pain, only short-lived morning stiffness, functional limitation and one or more typical examination findings (crepitus, restricted movement, bony enlargement), a confident diagnosis of knee OA can be made without a radiographic examination. This applies even if radiographs appear normal.	Ib	80 (67 to 92)
6	All patients with knee pain should be examined. Findings indicative for knee OA include: crepitus; painful and/or restricted movement; bony enlargement; and absent or modest effusion. Additional features that may be present include: deformity (fixed flexion and/or varus – less commonly valgus); instability; periarticular or joint-line tenderness; and pain on patellofemoral compression.	Ia–III	90 (85 to 95)
7	Red flags (eg, severe local inflammation, erythema, progressive pain unrelated to usage) suggest sepsis, crystals or serious bone pathology. Involvement of other joints may suggest a wide range of alternative diagnoses. Other important considerations are referred pain, ligamentous and meniscal lesions and localised bursitis.	IV	87 (80 to 94)
8	Plain radiography (both knees, weight bearing, semi-flexed PA (MTP) view, plus a lateral and skyline view) is the current 'gold' standard for morphological assessment of knee OA. Classic features are focal joint space narrowing, osteophyte, subchondral bone sclerosis and subchondral 'cysts'. Further imaging modalities (MRI, sonography, scintigraphy) are seldom indicated for diagnosis of OA.	Ib–IIb	83 (71 to 95)
9	Laboratory test on blood, urine or synovial fluid are not required for the diagnosis of knee OA, but may be used to confirm or exclude coexistent inflammatory disease (eg, pyrophosphate crystal deposition, gout, rheumatoid arthritis) in patients with suggestive symptoms or signs.	IIb	86 (78 to 94)
10	If a palpable effusion is present, synovial fluid should be aspirated and analysed to exclude inflammatory disease and to identify urate and calcium pyrophosphate crystals. OA synovial fluid is typically non-inflammatory with <2000 leukocytes/mm ³ ; if specially sought, basic calcium phosphate crystals are often present.	IIb	73 (56 to 89)

LoE, level of evidence (Ia, meta-analysis of cohort studies; Ib, meta-analysis of case-control or cross-sectional studies; IIa, cohort study; IIb, case-control or cross-sectional studies; III, non-comparative descriptive studies; IV, expert opinion); MTP, metatarsophalangeal joint; OA, osteoarthritis; PA, posterior-anterior; SOR, strength of recommendation on visual analogue scale (0–100 mm; 0, not recommended at all; 100, fully recommended).

For hand OA, 10 recommendations were also made (table 7). The 10 recommendations cover a wide range of topics, including risk factors for hand OA, clinical manifestations, subsets, differential diagnosis, imaging and laboratory tests. The diagnosis of hand OA cannot be determined with confidence using a single feature and so several features are required. The probability of a subject having hand OA was 20% when Heberden's nodes alone were present, but this increased to 88% when in addition the subject was over 40 years old, had a family history of nodes and had joint space narrowing in any finger joint.

The radiological definition of OA is widely used in epidemiological studies and in many clinical studies. The most commonly used grading system is that of Kellgren and Lawrence, which is a composite score based on the presence of osteophytes, joint space narrowing, subchondral sclerosis and bony cysts (Kellgren et al, 1963). This system divides OA into five grades (0–4), giving a global score at various joint sites in comparison to a radiographic atlas. A score of 2 or more has traditionally been considered to be a definitive radiographic diagnosis of OA and has been widely used in research. However, Kellgren–Lawrence grade I (doubtful) is more likely to evolve to OA than is grade 0, suggesting that it corresponds to an early disease subgroup (Lachance et al, 2002). Because the Kellgren–Lawrence grading system relies predominantly on osteophyte size to determine OA severity, the atrophic form of OA, which consists mainly of joint space narrowing, is underestimated. Unfortunately, Kellgren–Lawrence grading is characterised by discrepancy with hip or knee pain. MRI, ultrasonography and biochemical markers are not included in any set of criteria yet, but new definitions and criteria for OA based on such approaches are being developed.

Table 7 Diagnosis of hand OA: propositions and strength of recommendation – order according to topic (risk factors, clinical, subsets, differential diagnosis, images and laboratory tests) (Reproduced from Zhang et al, *Ann Rheum Dis* 2009;68:8–17.)

No.	Proposition	LoE	SOR (95% CI)
1	Risk factors for HOA include female sex, increasing age over 40, menopausal status, family history, obesity, higher bone density, greater forearm muscle strength, joint laxity, prior hand injury and occupation or recreation-related usage.	Ib–IIb	69 (54 to 84)
2	Typical symptoms of HOA are pain on usage and only mild morning or inactivity stiffness affecting just one or a few joints at any one time; symptoms are often intermittent and target characteristic sites (DIPJs, PIPJs, thumb base, index and middle MCPJs). With such typical features, a confident clinical diagnosis can be made in adults aged over 40.	IIb	85 (77 to 92)
3	Clinical hallmarks of HOA are Heberden's and Bouchard's nodes and/or bony enlargement with or without deformity (eg, lateral deviation of IPJs, subluxation and adduction of thumb base) affecting characteristic target joints (DIPJs, PIPJs, thumb base, and index and middle MCPJs).	Ib–IV	80 (69 to 90)
4	Functional impairment in hand OA may be as severe as in rheumatoid arthritis. Function should be carefully assessed and monitored using validated outcome measures.	IIb	57 (42 to 73)
5	Patients with polyarticular HOA are at increased risk of knee OA, hip OA and OA at other common target sites (generalised OA) and should be assessed and examined accordingly.	IIa–IIb	77 (62 to 92)
6	Recognised subsets with different risk factors, associations and outcomes (requiring different assessment and management) include IPJ OA (with or without nodes), thumb base OA and erosive OA. Each may be symptomatic or asymptomatic.	IIa–IIb	68 (56 to 79)
7	Erosive HOA targets IPJs and shows radiographic subchondral erosion, which may progress to marked bone and cartilage attrition, instability and bony ankylosis. Typically, it has an abrupt onset, marked pain and functional impairment, inflammatory symptoms and signs (stiffness, soft tissue swelling, erythema, paraesthesia), mildly elevated CRP levels, and a worse outcome than non-erosive IPJ OA.	IIa–IIb	87 (81 to 93)
8	The differential diagnosis for HOA is wide. The commonest conditions to consider are psoriatic arthritis (which may target DIPJs or affect just one ray), rheumatoid arthritis (mainly targeting MCPJs, PIPJs, wrists), gout (which may superimpose on pre-existing HOA), and haemochromatosis (mainly targeting MCPJs, wrists).	Ib–IIb	81 (73 to 89)
9	Plain radiographs provide the gold standard for morphological assessment of HOA. A postero-anterior radiograph of both hands on a single film/field of view is adequate for diagnosis. Classic features are joint space narrowing, osteophyte, subchondral bone sclerosis and subchondral cysts, and subchondral erosion occurs in erosive HOA. Further imaging modalities are seldom indicated for diagnosis.	Ib–IIb	87 (81 to 93)
10	Blood tests are not required for diagnosis of HOA but may be required to exclude coexistent disease. In a patient with HOA who has marked inflammatory symptoms and/or signs, especially involving atypical sites, blood tests should be undertaken to screen for additional inflammatory arthritides.	Ib–IIb	78 (63 to 92)

CRP, C-reactive protein; DIPJ, distal IPJ; HOA, hand osteoarthritis; IPJ, interphalangeal joint; LoE, level of evidence, presented in range upon components assessed; MCPJ, metacarpophalangeal joints; OA, osteoarthritis; PIPJ, proximal IPJ; SOR, strength on recommendation on visual analogue scale (0–100 mm; 0, not recommended at all; 100, fully recommended).

9.2 Primary or secondary OA?

The traditional concept holds that primary OA is defined in the absence of a history of injury or predisposing disease and that the presence of such feature defines secondary OA. The complexity of OA pathogenesis and the ever-growing list of risk factors identified (eg, genetic, biomechanical and environmental) make this division far less obvious. From the clinical perspective, it may be most useful to consider OA as a common outcome of complex processes with different mechanisms that variably contribute to disease. Nevertheless, as some of the aetiologies or risk factors (table 2 and box 1) are amenable to intervention, they should be carefully identified and managed if possible.

Box 1 Aetiologies of secondary osteoarthritis

1. Metabolic

- Crystal-associated arthritis (gout, calcium pyrophosphate dihydrate arthropathy, pseudogout)
- Acromegaly
- Ochronosis
- Haemochromatosis
- Wilson's disease

2. Anatomic

- Slipped femoral epiphysis
- Epiphyseal dysplasias
- Blount's disease
- Legg-Perthe disease
- Congenital dislocation of the hip
- Unequal leg lengths
- Hypermobility syndromes

3. Traumatic

- Major joint trauma
- Fracture through a joint or osteonecrosis
- Joint surgery (eg, meniscectomy)
- Chronic injury (occupational arthropathy)

4. Inflammatory

- Any inflammatory arthropathy
- Septic arthritis

5. Septic arthritis

9.3 OA clinical assessment

The assessment of a patient with OA should include discrete evaluation of pain and function with an emphasis on patient-reported outcomes. This is important since therapeutic decisions, such as prosthetic surgery, depend mainly on this. Evaluation of walking distance without pain or before the need to sit down and the need for external support (i.e., canes) is valuable. The activities of daily living such as climbing stairs and loss of

time from work, and the capacity to perform household chores or recreational activities are also important. Of note, all these data must be interpreted with the age, weight and lifestyle of the patient.

Overall assessment, global pain or disability can also be quantitatively evaluated using simple tools such as a five-point Likert scale (none, mild, moderate, severe, very severe), or on a 100 mm visual analogue scale (VAS). Pain can also be assessed indirectly by estimating the symptomatic treatment required, such as the number of days per week that drugs are required or their consistent dose usage (Constant et al, 1997).

Box 2 Western Ontario and McMaster Universities (WOMAC) composite index

1. Pain subscale (5 questions)

How much pain do you have...

- Walking on a flat surface?
- Going up or down stairs?
- At night while in bed?
- Sitting or lying?
- Standing upright?

2. Stiffness subscale (2 questions)

- How severe is your stiffness after first walking in the morning?
- How severe is your stiffness after sitting, lying down, or resting later in the day?

3. Function subscale (17 questions)

What degree of difficulty do you have with...

- Descending stairs?
- Ascending stairs?
- Rising from sitting?
- Standing?
- Bending to floor?
- Walking on the flat?
- Getting in or out of a car?
- Going shopping?
- Putting on socks or stockings?
- Rising from bed?
- Taking off socks/stockings?
- Lying in bed?
- Getting in and out of the bath?
- Sitting?
- Getting on or off the toilet?
- Heavy domestic duties?
- Light domestic duties?

One of the instruments widely used to assess pain and disability is the Western Ontario and McMaster Universities (WOMAC) composite index (Bellamy et al, 1988) (box 2). It is used mainly for the knee or the hip. Within the WOMAC composite index, pain is evaluated with a VAS or Likert scale in five different situations:

walking on a flat surface, going up and down stairs, at night while in bed, sitting or lying, and standing upright. Functional disability due to knee or hip OA is usually evaluated using the WOMAC function subscale, which is a questionnaire of 17 items related to daily activities, and by the Lequesne functional index (table 8), which is an index including questions related to pain, performance and function impairment (Lequesne et al, 1987).

Table 8 Lequesne algo-functional index

Pain or discomfort	Points
<i>During nocturnal bed rest</i>	0
None or insignificant	1
Only on movement or in certain positions	2
With no movement	
<i>Morning stiffness or regressive pain after rising</i>	0
1 min or less	1
More than 1 but less than 15 min	
<i>After standing for 30 min</i>	0 or 1
<i>While walking</i>	0
None	1
Only after walking some distance	2
After initial walking and increasingly with continued walking	
<i>With prolonged sitting (2 h)</i>	0 or 1
<i>Maximum distance walked (even with pain)</i>	0
Unlimited	1
More than 1 km but limited	2
About 1 km (0.6 mile) in about 15 min	3
500–600 m (1640–2952 ft or 0.31–0.56 miles) in about 8–15 min	4
300–500 m (987–1640 ft)	5
100–300 m (328–985 ft)	6
Less than 100 m (328 ft)	1
With one walking stick or crutch	2
With two walking sticks or crutches	
<i>Day-to-day activities*</i>	0 or 2
Put on socks by bending forward	0 or 2
Pick up an object from the floor	0 or 2
Climb up and down a standard flight of stairs	0 or 2
Get into and out of a car	

0, without difficulty; 1 (or 0.5 or 1.5), with difficulty; 2, unable.

The Knee injury OA Outcome Score (KOOS) was developed as an extension of the WOMAC OA index (Roos et al, 1998a) (<http://www.koos.nu>) and is a 42-item self-administered knee-specific questionnaire. It consists of five subscales (pain, other symptoms, function in daily living, function in sport and recreation, and knee-related quality of life). Standardised answer options are given, and the response to each question is scored from 0 to 4 in Likert boxes. A score of 0 to 100 is calculated for each subscale; 100 is the best result (Roos and Lohmander, 2003). A difference of 10 points is considered to be clinically significant. The Foot and Ankle

Outcome Score (FAOS) and Hip disability and OA Outcome Score (HOOS) are also available (Roos et al, 2001; Nilsson et al, 2003). Short measures of physical function for knee and hip OA are available, derived from KOOS and HOOS (Davis et al, 2008; Perruccio et al, 2008). Recently, the Intermittent and Constant OA Pain (ICOAP) questionnaire for hip and knee OA was developed. The patient's perspective was taken into account in the development of these questionnaires (Hawker et al, 2008; Maillefert et al, 2009). The Short-Form 36 (SF-36) is a generic instrument that can be used to assess health-related quality of life.

Impaired function in hand OA can be assessed in clinical trials using the Functional Index for Hand OA (FIHOA) or the Australian/Canadian OA Hand Index (AUSCAN) (box 3) (Dreiser et al, 2000; Bellamy et al, 2002; Allen et al, 2006). In addition, the AUSCAN, a self-administered questionnaire, also investigates pain and stiffness.

Box 3 Functional Index for Hand OA (FIHOA)

1. Are you able to turn a key in a lock?
2. Are you able to cut meat with a knife?
3. Are you able to cut cloth paper with a pair of scissors?
4. Are you able to lift a full bottle with the hand?
5. Are you able to clench your fist?
6. Are you able to tie a knot?
7. For women: are you able to sew? For men: are you able to use a screwdriver?
8. Are you able to fasten buttons?
9. Are you able to write for a long period of time?
10. Would you accept a handshake without reluctance?

In daily practice, all these tools can be used for clinical assessment, because they contribute to better communication between physicians and between patients and physicians. Their limitation is the time consumption accepted by the clinician. In organised settings, for instance when seeing patients with a confirmed diagnosis in a dedicated clinic, questionnaires can be filled out by the patients before they see the physician, and such tools can then be very useful for patient follow-up. For clinical trials, responder criteria are recommended so that results of changes after treatment can be presented in three symptomatic domains (pain, function and patient's global assessment) preferably as a single variable (Pham et al, 2004). The above-mentioned questionnaires and indexes are commonly used in addition to radiographic outcome measures in clinical trial settings.

9.4 Structural severity assessment

Standard plain radiographs have been extensively used to detect and stage the articular changes of OA. They remain the gold standard in clinical trials, even though this method has many weaknesses such as poor sensitivity and specificity in patients with early OA. Furthermore, there are differences in the interpretation of radiographic signs. Structural progression has not yet been accurately defined, despite the fact that this

feature is essential for evaluating the structural efficacy of treatment. MRI and ultrasonography can be useful tools for investigating alterations of joint structure in the future. The advantage of MRI is that it can be used to study cartilage, subchondral bone and synovial tissue simultaneously. The obvious disadvantage is the greater complexity of the assessment and the standardisation of protocols between centres. A variety of grading systems has been proposed with some specificity according to the site. They include several items such as joint space narrowing, sclerosis and osteophytes (Altman et al, 1987). Joint space narrowing seems to be the most important feature for defining progression of hip or knee OA (Ornetti et al, 2009). To attain sufficient sensitivity in change over time, standardised acquisition of radiographs is warranted.

The Kellgren–Lawrence grading system remains the most commonly used method (see above) for assessing the severity of structural abnormalities. The OARSI grading system separates osteophyte formation and joint space narrowing with semi-quantitative scales supported by the OARSI atlas (Altman and Gold, 2007) (i.e., minimal, moderate, severe joint space narrowing).

9.5 Biological markers

Many laboratories are working to find surrogate biomarkers that can reveal a correlation between joint space narrowing and the concentration of specific biological parameters in blood or urine (Garnero, 2002). These include components of matrix proteins including several collagens and cross-linked derivative peptides and matrix metalloproteinases. There is still no consensus about the optimal biomarkers and, to date, there is no indication to apply them in daily practice.

9.6 Time to total joint replacement

Total joint replacement can be considered as the best endpoint for clinical trials evaluating disease-modifying OA drugs. However, many parameters other than the severity of the disease itself influence the decision for surgery, including socio-economic factors, access to health services, and the age and BMI of the patient (Escalante et al, 2000; March et al, 2002; Fielden et al, 2005; Steel et al, 2006). An attempt to develop a composite index including pain and functional disability corresponding to an indication for total joint replacement (TJR) in hip and knee OA was unsuccessful, since it did not discriminate between those who were and those who were not considered to need TJR by the orthopaedic surgeon (Gossec et al, 2011*).

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SUMMARY POINTS

- Osteoarthritis (OA) is the most common joint disorder representing a socio-economic burden.
- The natural history of OA varies widely according to the affected joint and the OA subtype (ie, erosive or non-erosive OA).
- Pain on usage clearly related to activity is the hallmark of OA symptoms.
- Risk factors are obesity, female sex, oestrogen deficiency, ageing, family history, active subarticular bone remodelling, joint laxity, playing sports or occupational joint overload, prior injury with damaged ligaments and meniscectomy and misalignment.
- The pathological features of the osteoarthritic joint are erosion of the articular cartilage, subchondral sclerosis, osteophyte formation, synovitis and alterations of the joint capsule.
- OA is characterised by an imbalance between catabolism and anabolism of the extracellular cartilage matrix.
- Soluble key mediators leading to cartilage disruption are the matrix metalloproteinase family (aggrecanases) and collagenases responsible for breakdown of proteoglycans and collagen.
- Inflammation involving cytokines such as IL-1, IL-6 and TNF α is increasingly recognised as an important factor in OA development and progression.
- Adipocytokines are soluble mediators involved in the degradation of cartilage that can account for OA in non-weight bearing joints in obese patients.
- Low-grade synovitis is a crucial factor in the pathogenesis of OA, producing proinflammatory cytokines and a vicious cycle between cartilage degradation and synovial inflammation.
- Plain radiographs are the gold standard for diagnosis and are useful to establish the knee joint compartment involved as well as the degree of disease progression, although the radiographic findings correlate poorly with pain severity.

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module

EULAR on-line course on Rheumatic Diseases

Osteoarthritis: pathogenesis, clinical aspects and diagnosis

Augustin Latourte, Pascal Richette, Rik Lories

A previous version was co-authored by Rik Lories, Barbara Neerinckx, Francis Berenbaum, Rani Liu, Margreet Kloppenburg, Jérémie Sellam, Gabriel Herrero-Beaumont



IN-DEPTH DISCUSSION I

Erosive osteoarthritis (OA)

Definition

Erosive OA is regarded as a subset of hand OA. The term ‘erosive OA’ was first used by Peter et al. in 1966 to describe 6 women with OA in interphalangeal joints (IPJs) with the presence of inflammation and development of erosive and osteoarthritic signs on radiographs (Peter et al, 1966). Although earlier, Kellgren and Crain (Kellgren and Moore, 1952; Crain, 1961) had already described the clinical and radiographic features. Erosive OA is a radiographic subset of OA that is based on the presence of central erosions and collapse of the subchondral bone plate. Erosions can be detected in several hand joints, such as the IPJs and the first carpometacarpal joint (CMCJ), but also in the knees, the shoulders, and the metatarso-phalangeal joints (Zhang et al, 2002; van Saasse et al, 1989). However, the term “erosive OA” specifically relates to hand OA with erosions in the IPJs. Subchondral erosions in other joint sites, such as the knees and the first CMCJ, seem not to be related to erosions in the IPJs (Haugen et al, 2011; Kwok et al, 2011).

Prevalence

The prevalence of erosive OA, when compared to non-erosive hand OA is relatively low. In large-scale population-based studies the prevalence of erosive OA among participants with symptomatic hand OA was around 10% (Kwok et al, 2011; Haugen et al, 2011). Erosive OA tends to be more prevalent in females than in males. The prevalence of erosions in first CMCJ (thumb base) is lower than in IPJs, and the co-occurrence of erosions in both sites at the same time is relatively rare (Kwok et al, 2014).

Aetiology

Whether erosive OA comprises a separate disease entity with specific risk factors and pathogenesis or a more severe stage of hand OA is until now unclear (Zhang et al, 2009). Several underlying mechanisms have been suggested to be implicated in erosive OA, both systemic and local ones. The role for underlying systemic mechanisms is supported by the finding that new erosions develop especially in patients who already had erosions (Bijsterbosch et al, 2011).

A potential systemic factor is inflammation. The clear signs of inflammation present in some forms of hand OA lead Ehrlich in 1972 to the use of the term ‘inflammatory OA’ for the subset that is now referred to as erosive OA. He described this as a “nodose form of arthritis which begins abruptly and painfully with dramatic redness overlying the involved joints” (Ehrlich et al, 1972). The role of inflammation was further demonstrated by histology of synovial biopsies of erosive DIPJs and PIPJs in an inflammatory stage, showing intense proliferative synovitis indistinguishable from rheumatoid arthritis (Peter et al, 1966). In hand OA, soft tissue swelling is associated with erosive progression (Meersseman et al, 2015). The higher levels of high-sensitivity C-reactive protein in patients with erosive OA compared to patients with non-erosive OA are in line with these

observations (Punzi et al, 2005). During the last few years, ultrasound studies have been performed and reveal that power Doppler signal, as signal of active inflammation, is frequently seen in patients with erosive OA (Vlychou et al, 2009; Kortekaas et al, 2015), especially in the phase that erosive activity is taking place (Wittoek et al, 2010). Moreover, synovial inflammation, as assessed by ultrasound or MRI, may be an important predictor of incident erosions in hand OA (Mancarella et al, 2015; Kortekaas et al, 2016; Haugen et al, 2016).

Genetic predisposition could play a role in the pathogenesis of erosive OA (Stecher et al, 1953). In a sibling pair study, familial aggregation for evolution of erosions was seen, suggesting that heritable factors play a role. Several genetic factors have been reported to be associated with erosive OA. Remarkably, genetic factors were found to be associated rather with erosive OA, than with non-erosive hand OA. However, before definite conclusions can be drawn, further replication studies have to be performed.

The role of metabolic comorbidities and cardiovascular risk factors in the pathogenesis of erosive OA is currently debated (Marshall et al, 2015; Magnusson et al, 2015; Stand et al, 2017). Local joint factors, such as joint pain and joint space narrowing, can also play a role in erosive evolution (Bijsterbosch et al, 2011).

Imaging

Established criteria for erosive OA do not exist. Erosions on radiographs can be defined by different scoring methods (Altman and Gold, 2007; Kallman et al, 1989; Verbruggen and Veys, 1996), but whether one or more erosive joints have to be present to define erosive disease is not yet established (Gazeley et al, 2017).

Radiographic features of erosive OA are central subchondral erosions, joint space narrowing, collapse of the subchondral bone and subchondral sclerosis (Kidd and Peter, 1966; Martel et al, 1980) (Figure 1). The central erosions can appear like typical 'sea-gull wing' or 'saw-tooth lesions' (Martel et al, 1989). Whereas both the OARSI method and the method developed by Kallman et al. score the presence or absence of a central/subchondral erosion or collapse in the interphalangeal joints, the Verbruggen-Veys method is based on scoring osteoarthritic joints in progressive, consecutive phases (Verbruggen and Veys, 1996). Five anatomical phases are distinguished, being the normal (N), stationary (S), joint space loss (J), erosive (E) and remodelled (R) phase. The sequence of evolution from N to S to J to E to R phase is proposed to reflect the natural history of erosive OA (Verbruggen and Veys, 1996). Only the OARSI method displays an example to score erosions in the first CMCJ (Altman and Gold, 2007).

Recently, ultrasound (US) and MRI are available to detect erosions. Erosions on US are defined as a cortical break seen in both longitudinal and transverse scans. First, US was shown to be less sensitive for erosions than radiographs (Iagnocco et al, 2005) and erosions were therefore not included in a US scoring system for hand OA (Keen et al, 2008). However, in recent US studies erosions could be detected, and US was even more

sensitive than radiography (Vlychou et al, 2009; Wittoek et al, 2010; Wittoek et al, 2011). Moreover, US was validated with MRI as a reference method (percentage of agreement between MRI and US for erosions was 78%, kappa= 0.55). Grainger et al. reported that erosions, especially marginal erosions, in patients with hand OA were more often present on MRI than on radiography (Grainger et al, 2007). Marginal erosions resembled those seen in inflammatory arthritides. Using MRI, 80% of joints examined showed one or more erosions compared with 40% using radiographs. The characterization of erosions on MRI and the association between erosions and other structural abnormalities, such as bone marrow lesions, will be facilitated by a recently developed scoring method (Haugen et al, 2011; Haugen et al, 2014).

Figure 1: Erosive osteoarthritis in multiple DIPJ and PIPJs, with signs of osteophytes



Clinical burden

Erosive OA is considered to have a higher clinical burden and worse outcome than non-erosive hand OA (Kwok et al, 2013). The structural damage that can affect the IPJs can eventually lead to instability of the joint and ankylosis (Patrick et al, 1989). As a consequence, people with erosive hand OA have three times more pain and two-and-half times more hand disability than persons with non-erosive hand OA. However, research in detail revealed that the high clinical burden does not only depend on the presence of erosions. Patients with erosive OA also have more nodes, which are determinants of clinical outcome as well. Taking the number of nodes into account, hand mobility and patient satisfaction regarding function and aesthetics are worse in patients with erosive OA compared to patients with non-erosive hand OA. Although, pain, disability, mobility and grip strength are not. In a French study, aesthetic discomfort, which was especially reported by women with erosive OA with a high clinical burden, was also associated with depression, anxiety and poor health related quality of life (Hodkinson et al, 2011).

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module

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Osteoarthritis: pathogenesis, clinical aspects and diagnosis

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IN-DEPTH DISCUSSION II

Models of osteoarthritis

Models of osteoarthritis: A more extensive discussion of this topic can be found in Thysen S, Luyten FP, Lories RJ. Targets, models and challenges in osteoarthritis research. Dis Model Mech. 2015 Jan;8(1):17-30. doi: 10.1242/dmm.016881.

In vivo models aim to recapitulate OA disease processes and associated lesions. Understanding mechanisms of disease and assessing the clinical response to potential therapies are important conditions for the translation of genetic or *in vitro* data towards therapy in patients. Animal models of OA include naturally occurring OA by (accelerated) aging, transgenic animals, as well as surgically or chemically induced models. Unfortunately, there is no animal model that completely reproduces the signs and symptoms of human OA, a group of diseases with very different presentations. Each model and species used has distinct advantages and disadvantages and the impact of preclinical research depends largely on the choice for the most appropriate preclinical model of OA.

For example, the spontaneous development of OA in transgenic animals can give very useful information about the effect of a gene of interest. Long term strategies such as MMP inhibitors or nutraceuticals may also be studied in such long-term set-ups. In contrast, short-term surgical models show less variability and may be more cost-effective. The relative disadvantage is that these induced models may reflect more post-traumatic OA and not be entirely representative of spontaneous developing human OA that is typically a fairly slow process. In general, small animals (mice, rats, rabbits and guinea pigs) are most often used in the search for specific disease mechanisms and in initial drug screenings for reasons of cost-effectiveness, ease of handling and housing and opportunity for genetic manipulations. Large animal models show more similarity to humans based on their cartilage morphology, joint anatomy and biomechanics and provide therefore more clinically relevant data. However, these models are higher in cost and have heightened ethical concerns and a poor genetic characterization. Nevertheless, they are a crucial and necessary step in the safe and cost-effective development of new therapies. Most models specifically assess the knee joint as this is the predominant joint for natural OA to occur and it is sufficiently large in all animal models for intra-articular manipulations.

Outcome measures

The assessment of joint damage, in particular cartilage loss is an essential part of the animal model discovery or preclinical work. Pioneering work in the histopathologic assessment of OA was established by Collins (Collins, 1939), who based his grading system (Grades I-IV) on the degree of fibrillation of articular cartilage. In 1971, Mankin et al. (Mankin, 1971) developed a microscopic Histologic Histochemical Grading system (HHGS) (14 point scoring system) based on a combination of cellular changes, extracellular matrix staining with Safranin O and structural changes. Although these scoring systems are still used, they have many limitations, particularly in the assessment of early OA. The OARSI histopathology initiative developed a standardized scoring system for the most important small and large animal models that assesses joint degeneration by

‘staging’ and ‘grading’ systems. Ideally, macroscopic and microscopic evaluation of OA requires a more holistic approach given the importance of the non-cartilaginous structures for the disease process. The OARSI histopathology initiative fills in the shortcomings from previous scoring systems and provides additional scoring parameters to explore alterations in the synovium, subchondral bone, menisci, tendons and ligaments (Cook et al., 2010; Gerwin et al., 2010; Glasson et al., 2010; Kraus et al., 2010; Lavery et al., 2010; Little et al., 2010; McIlwraith et al., 2010).

As an alternative for the time-consuming and tissue-destructive histopathology, non-invasive imaging techniques such as MRI and microCT are increasingly used in animal studies. Non-invasive in vivo imaging can be used for longitudinal follow-up in the same animal to monitor the disease progress and treatment monitoring in drug trials. Standard clinical MRI (1.5 and 3T) is being used in large animal models (dogs, goats/sheep, horses) (Galindo-Zamora et al., 2013; Ley et al., 2013). Rodents and rabbits are too small to undergo standard in vivo MRI. Recently, high-resolution micro-MRI (>7T) has been performed on rats and rabbits to monitor cartilage lesions of surgically induced OA (Batiste et al., 2004; Goebel et al., 2010). This area of imaging needs further optimization and is challenging because, among other reasons, imaging of small rodent joint requires specific magnetic coils. μ CT is preferably used for high-resolution imaging of bone architecture alterations. Due to its low soft-tissue contrast, direct imaging of the cartilage is impossible. Contrast agents such as ioxaglate or hexabrix permit visualization of cartilage.

Small animal models

Mouse

Mice are widely used as an animal model because of the easy management, low costs, and the availability of genetically modified animals. Spontaneous OA occurs in aged C57Bl/6 and BALB/c mice (Stoop et al., 1999), but is much more pronounced in the STR/ort mouse strains and therefore this strain is more often used in screening studies (Mason et al., 2001). The possibility to induce genetic modifications (transgenic, knock-out and knock-in, inducible, tissue specific) made the mouse model an extremely useful tool for replicating genetic defects and elucidating the molecular pathogenesis of OA.

Acute enzymatic-, chemically- or inflammation-induced OA models (e.g. intra-articular injection of collagenase (van der Kraan et al., 1989), methylated bovine serum albumin (mBSA) (Stanton et al., 2005) and papain (van der Kraan et al., 1989)) and destructive surgical models (e.g. (partial) medial meniscectomy ((P)MM), medial collateral ligament transection (MCLT) and anterior cruciate ligament transection (ACLT) (Clements et al., 2003)) lead to severe OA pathology in mice (Glasson et al., 2007). Currently, the Destabilization of the Medial Meniscus (DMM) surgical model is frequently used as a clinically relevant OA model. Transection of the medial meniscotibial ligament leads to altered mechanical loading and induces cartilage damage that more closely resembles some aspects of the slowly progressive human disease (Glasson et al., 2007).

When studying the effects of biomechanics in OA, the mouse is not an ideal model due to its small size compared to humans. Additionally, mouse knee cartilage has relatively few cell layers and less of a zonal tissue organization when compared to the larger species, which make it difficult to induce small lesions that extend slowly through the different depths of the non-calcified cartilage over-time (Glasson et al., 2010).

Rat

Rat models are relatively similar to mouse models, as they are relatively inexpensive and easy to house and handle. Natural occurring OA is extremely uncommon and transgenic models of OA are not yet available, but the technology to generate transgenic overexpression and knockout rats is increasingly used in other fields (Huang et al., 2011). Consequently, chemically- (e.g. i.a. injection of iodoacetate (Guzman et al., 2003)) and surgically induced (e.g. medial meniscal tear (MMT) or ACLT (Hayami et al., 2006)) models are frequently performed in rats. The thicker cartilage with zonal structure makes direct surgically-created partial- and full-thickness cartilage lesions possible (Gerwin et al., 2010). Rats are therefore attractive animal models to study cartilage repair by gene therapy, stem cell transplantation, chondrocyte implantation and local growth factor stimulation. Rat models have also been used for the assessment of OA-related pain (Bove et al., 2006) and to study the outcome of novel pain therapies (Ahmed et al., 2012; Cowart et al., 2012; Schuelert and McDougall, 2006).

Rabbit

Like rodents, rabbits are easy to handle and have relatively low housing costs. The rabbit knee joint has some anatomical similarities with the human knee. However, the biomechanics are different and therefore, the rabbit is less suitable for functional studies. The rabbit is used frequently in cartilage regeneration experiments, as large quantities of cells can be extracted from rabbit tissues. A disadvantage is that young rabbits have a high potential for spontaneous healing of cartilage or osteochondral defects. Articular cartilage of rabbit femorotibial joints matures at approximately 3 months (Lavery et al., 2010).

Guinea pig

The spontaneous occurring OA in the Hartley guinea pig is a frequently used model because it displays progressive degenerative changes that closely resemble the development of OA in humans. The spontaneous guinea pig OA model has clear advantages to large animals because the time to reach skeletal maturity is much shorter (Kraus et al., 2010).

Large animal models

A major advantage of using large animals is that their macroscopic and microscopic anatomy is similar to the human situation and the opportunity to undertake topographical analysis of joint cartilage by arthroscopy and

serial aspiration of synovial fluid for biomarker analysis. A disadvantage is that histology of large animal joints is more difficult because the whole joint can't be captured on a single microscopic section.

The canine model is a very good translational model for biomarker studies. Most frequently used models in dog are the ACLT model (a.k.a. Pond/Nuki model) (Kuroki et al., 2011) and the groove model (Intema et al., 2008). Additionally, dogs, like horses (McIlwraith et al., 2010), are also prone to develop natural occurring osteoarthritis with overuse or age and undergo similar treatments as humans (Cook et al., 2010; Tirgari and Vaughan, 1975).

Goats and sheep, however, do not appear to develop spontaneous OA (Little et al., 2010). Another disadvantage is that these animals are ruminants and so the bioavailability of oral therapies needs to be tested before starting animal studies. Surgically-induced models for goats and sheep are partial or total meniscectomy. The ACLT model only induces very mild cartilage damage (Little et al., 2010).

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Osteoarthritis: treatment

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LEARNING OBJECTIVES

- Define the principles of evidence-based practice and the three main sources of evidence that need to be considered
- Specify the objectives of management of patients with osteoarthritis (OA)
- Apply the principles of management of patients with OA
- Apply three core non-pharmacological aspects of management that should be considered in every patient with OA and justify their central role in management
- Justify and apply an initial trial of simple safe analgesia for pain control
- Select appropriate adjunctive treatments from at least 10 recommended treatment options that may be considered for patients with OA
- Discuss the indications, benefits and side effects of intra-articular injection of glucocorticoid for symptomatic OA
- Specify the benefits and principles of strengthening and aerobic exercise for patients with large joint OA
- Critically evaluate the research evidence for management of OA
- Review quality care for OA
- Consider models of OA care
- Consider the role of the multidisciplinary team in primary care
- Consider the role of the rheumatologist in the care of patients with OA

1 Introduction

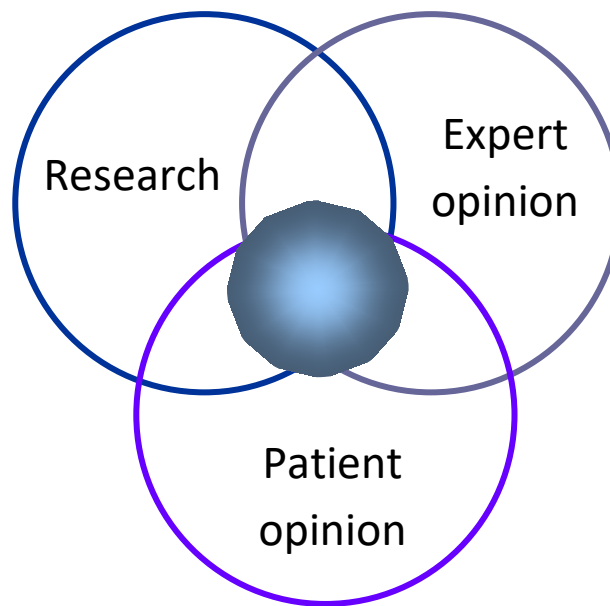
Osteoarthritis (OA) is by far the most prevalent joint disease and a leading cause of disability in older adults. Unsurprisingly, OA-related pain and limitation of activity is one of the most common causes for adult consultation in primary care. In recent years a number of international evidence-based clinical practice (EBP) recommendations for OA have been published to help guide clinical decision making (Jordan et al., 2003; Zhang et al., 2005*; Zhang et al., 2007a*; Zhang et al., 2007b*; Zhang et al., 2008; Zhang et al., 2010*; NICE, 2008*; NICE, 2014a*; Fernandes et al., 2013*; McAlindon et al., 2014*). However, there is evidence that OA is given a low priority by health professionals and patients and that recommendations are not translated into practice. This overview will address the following areas:

- the principles of EBP and the level of agreement between recent guidelines developed by different methodologies
- the management objectives for OA
- the agreed core set of treatments that everyone with OA should receive
- the other recommended treatment options that are available for incorporation into the central management plan for patients with OA and the possibility of using structure-modifying drugs
- the caveats and omissions with respect to the clinical research base for management of OA
- the indicators of quality care in OA
- the rheumatologist's role in OA management.

2 Evidence-based recommendations for OA

The philosophy of EBP is to make rational clinical decisions in light of available evidence and to integrate the best research evidence with clinical expertise and patient values (Sackett, 2000). The three main forms of evidence for clinical management that need to be examined critically and with common sense are: (1) research (mainly clinical trials and observational studies); (2) expert practitioner experience and opinion; and (3) patient acceptability, experience and opinion. Misguidedly, many people consider EBP to be focused predominantly on research evidence, but all three are equally weighted (figure 1). It is only when all three concur that we can truly approach 'best practice' (Sackett, 2000).

Figure 1 The three types of evidence to consider for evidence-based management. All three are equally weighted.



There is an accepted hierarchy with respect to research evidence for the efficacy of clinical treatments, the highest level being meta-analysis of randomised controlled trials (RCTs) (box 1). For uncommon or rare side effects of treatments, however, RCTs are less sensitive than large observational studies, which may be considered a higher category in this respect.

Box 1 Level of evidence according to source

Category of evidence from:

- Ia: Meta-analysis of randomised controlled trials (RCTs)
- Ib: RCT
- IIa: Controlled study without randomisation
- IIb: Quasi-experimental study
- III: Non-experimental descriptive studies, such as comparative, correlation and case–control studies
- IV: Expert committee reports or opinion or clinical experience of respected authorities, or both

For some interventions, especially surgery and physical interventions, there may be very few or even no RCTs to examine. This may result from ethical issues (e.g., inability to undertake a sham joint replacement) or the impossibility of blinding an intervention (e.g., spa therapy). Although this may result in a low level of research evidence, if observational studies and expert and patient opinion strongly support the use of such interventions (e.g., joint replacement surgery), these can still be strongly recommended. Recommendation of a treatment is not just based on efficacy and safety. Cost, the logistics of delivery, and patient acceptability all need consideration. Such multifaceted decision-making may result in different guideline groups giving different strengths of recommendation for the same treatment, especially when they vary in terms of

composition (specialists, general practitioners, allied health practitioners, patients, etc) and the methodology employed to derive consensus. Therefore all types of evidence, including EBP guidelines, need to be examined with care and common sense. Estimation of efficacy in OA clinical trials is usually presented as effect size (ES) and 95% CI in comparison to placebo (or active control) for outcomes such as pain relief and improvement in function. The effect size is the standardised mean difference: the mean difference between treatment and control divided by the standard deviation of the difference. It has no units and is comparable across interventions. Clinically, an ES of 0.2 is considered small, 0.5 is moderate, and 0.8 is large (Zhang et al., 2005*; Zhang et al., 2007a*).

EULAR has produced separate EBP recommendations (combining both research evidence and expert opinion) for the management of knee OA (Jordan et al., 2003), hip OA (Zhang et al., 2005*) and hand OA (Zhang et al., 2007a*) in recognition that treatment options may differ according to the joint affected. The Osteoarthritis Research Society International (OARSI) has produced similar recommendations for hip and knee OA (Zhang et al., 2007b*; Zhang et al., 2008*; Zhang et al., 2010*; McAlindon et al., 2014*). Most recently, the National Institute for Health and Care Excellence (NICE) in collaboration with the Royal College of Physicians UK has published guidelines for OA in general, taking into account multisite OA (NICE, 2008*; NICE, 2014a*). The Ottawa panel has guidelines also for the management of hip (exercise) and knee OA (Brosseau et al., 2016, 2017a, 2017b, 2017c). EULAR has also published recommendations for non-pharmacological therapies (Fernandes et al., 2013*). Although there are differences in detail between these guidelines, as with previous guidelines published worldwide, there is good overall agreement on the treatment objectives, the principles of management, and the selection of main treatment options.

2.1 Knowledge mobilisation

There is evidence that patients do not receive treatments with proven clinical and cost effectiveness despite being recommended by international guidelines, and there is large variation in practice (Porcheret et al., 2007a; Porcheret et al., 2007b, Hagen et al., 2016). Healthcare professionals often feel that they have little to offer in consultations for OA. Patients want their condition to be taken seriously, but in routine consultations in primary care there is often limited time to address joint pain. For example, written information is a core requirement of a consultation for OA (NICE, 2014a*) and yet in usual practice only a small percentage of patients consulting their general practitioner (GP) will have a record of having received this. In recent years it has been recognised that in order to bridge the gap between evidence and quality clinical care, something else needs to happen. Different terms have been used to describe this activity, such as knowledge brokering, knowledge transfer, knowledge exchange and knowledge mobilisation. Knowing the evidence is not the same as using it in day-to-day consultations. The following sections reflect current recommendations and guidelines, although important differences in advice will be mentioned, and suggest ways in which they can be used in clinical practice.

3 Management objectives

The agreed objectives are:

- Patient education and information access
- Pain relief
- Optimisation of function
- Beneficial modification of the OA process.

4 Management principles

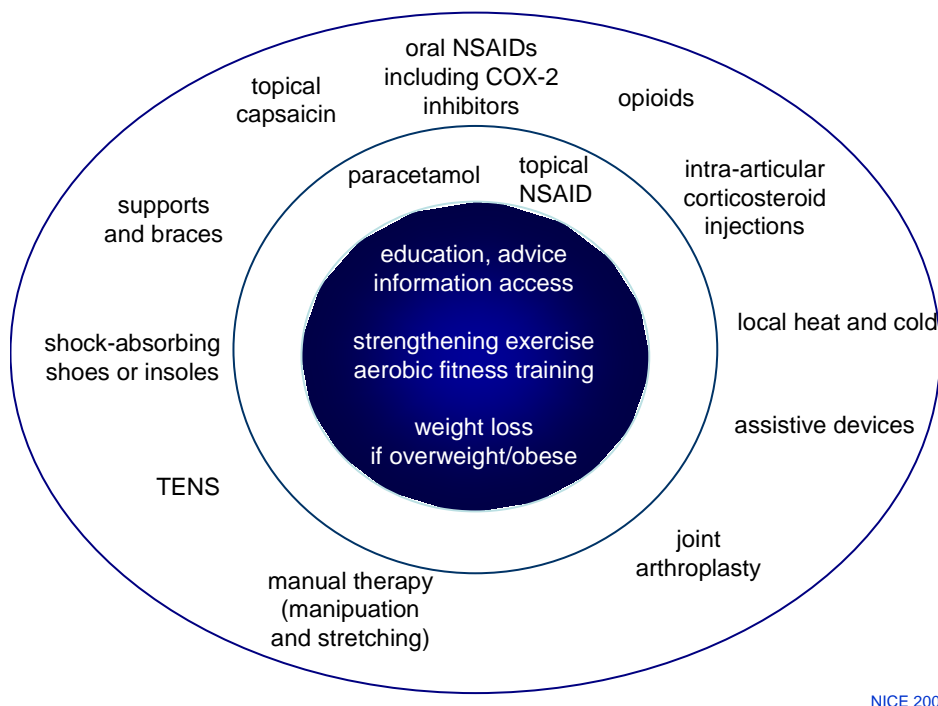
Although there is widespread expert consensus for the key principles of management emphasised in this section, guidelines do diverge in some respects (Nelson et al., 2014). Furthermore, the research evidence to support the management principles is often derived from relatively short-term studies that cannot necessarily reliably inform the ongoing management of a long-term condition (LTC). Management needs to be individualised and patient centred. This is only possible after a thorough, holistic assessment and competent examination. Making, giving and explaining the diagnosis in positive terms is a valuable starting point (Porcheret et al., 2014). Numerous factors influence treatment selection—for example, OA-related factors such as the joint involved, whether more than one joint is affected, the degree of structural damage, and the level of pain intensity. Person-specific factors, such as age, required daily activities (occupation, leisure), patient expectations, number of joints affected and perceptions of OA all modify the approach that is taken.

OA often exists with comorbidity, such as cardiovascular and metabolic diseases (Violan et al., 2014). Consequently, as well as the development of a shared management plan to manage OA, attention to concurrent medication is important. Such comorbidity may influence treatment selection for OA. For example, cardiovascular or renal disease might prevent the use of a particular modality such as a non-steroidal anti-inflammatory drug (NSAID)/coxib (COX-2 selective inhibitor). Anxiety and depression often co-exist with OA (Stubbs et al., 2016) but may go unrecognised in primary care (Memel et al., 2010). Importantly, however, recognition and treatment of comorbidity such as non-restorative sleep or depression, can alleviate the symptoms of OA and reduce the need for analgesia (Fernandes et al., 2013*).

There is a wide selection of treatment options for OA. However, except for intra-articular (IA) glucocorticoid or surgery, the effect sizes of the majority of OA treatments are only modest. Therefore, successful management may require the use of multiple components, both non-pharmacological and pharmacological, rather than a monotherapeutic approach. Evidence for packages of care per se is limited; furthermore, for sites such as the foot there is a paucity of evidence for specific approaches despite high prevalence estimates (Roddy et al.,

2013). Management should always contain the core elements of education and information access, exercise, and reduction of adverse mechanical factors (e.g., weight loss if overweight), together with any adjuncts that are thought appropriate. Such a 'core-plus option' approach has been emphasised, particularly by NICE (2008*) (figure 2).

Figure 2 The National Institute for Health and Care Excellence concept of OA treatment: the central core treatments every patient with osteoarthritis should receive. Additionally, treatments from the middle and outer circle should be selected for the individual patient according to manifestation, severity and functional limitations as well as the time course of disease (NICE, 2008*). *NICE highlighted that paracetamol is less effective than previously considered. COX-2, cyclo-oxygenase 2; NSAID, non-steroidal anti-inflammatory drug; TENS, transcutaneous electrical nerve stimulation. (Source: NICE, 2014a*, <http://www.nice.org.uk>)



NICE 2008

For pain control, an additive rather than substitutive approach is advised. Where no benefit is experienced from a particular type of agent, it should be discontinued to avoid unnecessary polypharmacy. Otherwise, if the first option analgesic gives some relief but is insufficient, then a second agent with a different method of action is added (e.g., a topical NSAID could be added to oral paracetamol (acetaminophen)). If this is still insufficient, then a third agent (e.g., topical capsaicin or oral opioid) and eventually a fourth agent may be added. Such an approach recognises the complex nature of pain processing and the relatively modest effect of any individual pharmacological agent used as monotherapy for chronic pain. In case of improvement, therapy may be reduced in the reverse manner.

After initiation of management, the patient should be reassessed to judge the effectiveness of the plan, and the treatments modified or altered according to the degree of success obtained. This has been highlighted by the recent NICE 2014 update (NICE, 2014a) and supplemented by the NICE Quality Standards (NICE, 2015)

which suggests that patients should be offered an annual review for their osteoarthritis if they have more than one joint affected, comorbidities, troublesome joint pain, or are taking medication for their joint pain.

Consensus shows that review of self-management plans, pain relief and analgesia are considered important by patients, GPs, allied health professionals and nurses (Finney et al., 2013; Porcheret et al., 2013).

The non-specific beneficial effects of treatment should not be under-rated (figure 3). The magnitude of such non-specific (placebo) effects for pain relief in RCTs is far greater than the additional effect obtained by individual drugs such as oral or topical NSAIDs, opioids or nutraceuticals (Zhang et al., 2008). The patient will particularly capitalise on these effects if they are given a thorough assessment by an interested practitioner, if positive messages are reinforced, and if they are reassessed to determine the outcome (Doherty and Dieppe, 2009). Although non-specific effects are considered a major hindrance in RCTs, they are an integral and inevitable component of best clinical practice (Doherty and Dieppe, 2009).

Figure 3 Thorough patient assessment and a positive practitioner–patient encounter. Patient consent obtained.



5 Core treatments to consider for every patient with OA

With an ageing population and increasing risk factors for poorer health such as obesity and reduced physical activity, musculoskeletal conditions such as osteoarthritis will be the main cause of physical disability in older adults. Support for self-management is therefore a priority and the use of core treatment in the management of OA is a key implementation objective. Patients may prefer non-pharmacological approaches and support for self-management over analgesia, but healthcare professionals feel uncertain about and lack confidence in giving such interventions (Paskins et al., 2014).

The core approaches include: access to written information and advice; support for self-management; healthy eating and maintenance of a healthy weight; and advice on exercise and physical activity. These core management principles for OA are the same as those for other LTCs and the knowledge and skills for delivering these key approaches are transferable across a range of LTCs. They may be supplemented with simple analgesia and joint protection techniques.

5.1 Education and information access

It is a professional responsibility to inform patients of their diagnosis and prognosis, to explain tests, and to discuss in detail the advantages and disadvantages of treatment options. This enhances understanding of OA and its management, and counters misconceptions—for example, that OA inevitably progresses and cannot be treated. In addition, access to such information beneficially influences outcome and can be regarded as treatment (figure 4). When studied in OA, access to information has been shown to reduce pain and disability, improve self-efficacy and coping skills, and reduce the frequency of primary care consultation and (in the US system) health costs. It is unclear how this works but it is not only explained by better adherence to other aspects of management like regular exercise. Educational techniques and motivational interviewing can be effective, for example individualised education packages, regular telephone calls, group education, patient coping skills, and spouse-assisted coping skills training. Education does not necessarily require therapist contact but can also use written literature, videos or internet tools. Information sharing and reinforcement should be an ongoing, integral part of management rather than a single event at time of presentation. Information written by patients and healthcare professionals for patients has been shown to be beneficial (Grime and Dudley, 2014).

Figure 4 Positive benefits from information concerning osteoarthritis and its management. Patient consent obtained.



5.2 Advice on exercise and activity

Joints are built to move, and the health of all integral components of the joint depends on regular movement. If a joint is compromised by OA, it is even more important to maintain movement. Two types of exercise can reduce pain and disability long-term and both should be prescribed to anyone with large joint OA, irrespective of age: (1) aerobic exercise (fitness training) and increased activity which improves wellbeing, encourages restorative (delta) sleep and benefits common comorbidities such as obesity, diabetes, chronic heart failure and hypertension; and (2) local neuromuscular training, strengthening, and range of motion exercises for quadriceps and gluteal muscles (figure 5) (Fernandes et al., 2013*). This can greatly improve the detrimental physiological accompaniments of large joint OA, specifically reduced muscle strength, reduced knee proprioception, impaired standing balance, and increased tendency to fall. Such benefits are modest but long lasting if adherence is maintained, giving effect sizes (ES), for example, of 0.39 (95% CI 0.30,0.47) for pain relief and 0.31 (95% CI 0.23,0.39) for functional improvement (Fernandes et al., 2013*). Cochrane reviews of exercise in hip and knee OA identified maintenance of the benefits of exercise on pain and function for two to six months after exercise trial treatment ended, though at a lower effect sizes than during the trial periods (Fransen et al., 2014, 2015). The American College of Rheumatology (ACR) 2012 recommendations for the management of knee OA and hip OA also include aquatic exercises, medially-directed patellar taping, manual therapy, tai chi and psychosocial interventions (Hochberg et al., 2012*). A network meta-analysis comparing different packages of exercises for lower limb OA, predominantly knee OA, demonstrated that combinations of exercise to increase strength, flexibility and aerobic capacity are likely to be the most clinically effective (Uthman et al., 2013). In a recent study, hand exercises delivered in classes by occupational therapists were found to be cost-effective (Oppong et al., 2014), and a systematic review of benefits of hand exercise for OA identified low- to moderate-quality evidence of small-to-moderate beneficial effects on pain (ES 0.27), function (ES 0.28), and stiffness (ES 0.36) (Østerås et al., 2017).

Patients should be advised to balance activity and rest, breaking up long periods of activity (such as shopping, housework and gardening) with frequent, short rest periods—so-called ‘pacing’ of activities. Although this means that specific physical tasks take longer to do, they are more likely to be completed successfully and with less mechanically-induced pain as a result. Patients should be informed that the physical training should be done on a continuous, regular basis.

Figure 5 Simple initial quadriceps strengthening exercise (straight leg raise) being taught to a patient with knee osteoarthritis. Patient consent obtained.



5.3 Reduction of adverse mechanical factors

Obesity is a common comorbidity and an important modifiable risk factor for knee OA, and to a lesser extent hip and hand OA. The principles of education about weight management are detailed in the recent EULAR recommendations (Fernandes et al., 2013*). There are limited numbers of RCTs of weight loss in obese/overweight patients with large joint OA, but these show clear improvement in function, and modest improvements in pain in those who successfully lose weight. Weight loss is advised for many other health reasons and reduction in obesity has obvious face validity with respect to both primary and secondary prevention of knee and hip OA (figure 6). Successful weight loss programmes recommend an individualised programme that contains: frequent self-monitoring; both diet and exercise; regular eating (three times daily); good food variety but reduced portion size; low (saturated) fat and sugar and high fruit and vegetable content; nutritional awareness through education; and modification of eating triggers (e.g., stress). Bariatric surgery may be considered as part of a comprehensive weight management programme in morbidly obese people with hip or knee OA (Fernandez et al., 2013*).

Figure 6 Weight loss in obese and overweight patients is advised for many health reasons, including improved outcome for osteoarthritis. There is evidence from randomised controlled trials that in the short term this improves function more than pain.



Patients with knee and hip OA should be advised about appropriate footwear. Shoes with thick but soft (e.g., air-filled) soles and no raised heels minimise rebound upward force transmission and adverse knee, hip and back alignment when walking (figure 7). This recommendation is primarily supported by expert opinion, but due to high levels of satisfaction and low cost, such shoes should be advised for all patients with knee and hip OA.

Figure 7 The worst shoe (left) for the health of feet, knees and hips, having a thin hard sole, narrow raised heel, narrow forefoot and shallow uppers. The better shoe on the right has a thick soft sole, no raised heel, a broad forefoot and a deep soft upper.



Review of the effectiveness of the use of lateral wedged insoles in patients with medial knee OA found no significant benefit on pain or function (Fernandes et al., 2013*). Historically, medial wedged insoles have been recommended for patients with lateral tibiofemoral OA or mild valgus malalignment. However, there is no clear evidence to support the use of one type of insole over another, and adverse effects including foot sole pain, low back pain and popliteal pain have been reported; as a result the recent EULAR non-pharmacological guidance document did not recommend the use of wedged insoles (Fernandes et al., 2013*).

Prefabricated foot orthoses and rocker-sole footwear can both improve foot pain in people with OA of the first metatarsophalangeal (MTP) joint, though insoles may be preferable as adherence and side effect profiles are better (Menz et al., 2016).

6 Simple analgesia and topical NSAIDs for pain control

The above core treatments can improve pain long term. However, in addition many patients benefit from the use of pharmacological agents for pain control.

6.1 Paracetamol (acetaminophen)

Paracetamol is an antipyretic analgesic with a central, although ill defined, mechanism of action. Paracetamol is relatively insoluble and is available in many different formulations, including dispersible for those who have difficulty swallowing tablets. The main potential for drug interactions is with warfarin. However, it does have some peripheral prostaglandin inhibition and although previously thought to not cause gastrointestinal (GI) or cardiovascular toxicity, there is growing evidence to associate paracetamol with many of the side effects recognised to occur with NSAIDs, especially GI bleeding (Zhang et al., 2010*; Hinz and Brune, 2012; Roberts et al., 2016). The combination of paracetamol and an NSAID particularly appears to increase the risk of GI events. Furthermore, paracetamol has to be used with caution as it has a narrow therapeutic to toxicity ratio, and at only several times its maximum recommended dose it can cause severe life-threatening hepatic failure, particularly in combination with alcohol intake. It should be mentioned that the tradition for the use of paracetamol in patients with OA differs significantly throughout European countries. The effect size for paracetamol in OA RCTs is only small and the main reason that it has been previously recommended so strongly as a first choice analgesic is because of its perceived safety (Jordan et al., 2003; Zhang et al., 2005*; Zhang et al., 2007a*; Zhang et al., 2007b*; Zhang et al., 2008*; NICE, 2008*), in addition to its low cost and ready availability. However, with the growing concerns over its safety and its recognised small effect size for chronic pain relief, paracetamol recommendations have recently changed. In 2014, OARSI declared its benefits ‘uncertain’ for patients with knee OA associated with comorbidity, although they have continued to recommend paracetamol for patients without comorbid conditions (McAlindon et al., 2014). They also recommend it is used with ‘conservative dosing and duration’. NICE (2014a*) has not changed its

pharmacological recommendations, pending an MHRA review of paracetamol safety, but it has drawn attention to the limited clinical effectiveness of paracetamol in the updated guidance.

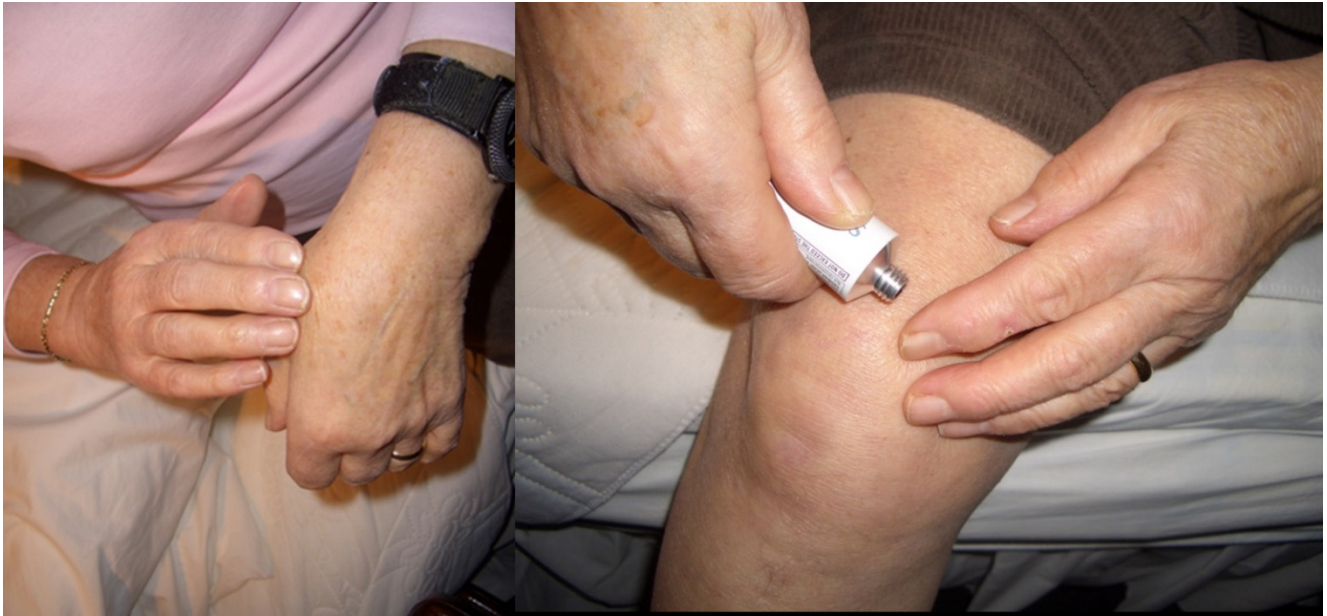
6.2 Topical NSAIDs

Topical preparations are extremely popular with patients and associated with good adherence. It makes eminent sense to patients to apply a medicine directly to the painful site, and given that patients with OA usually only have only one or very few symptomatic joints at any one time, such an approach is feasible and well suited to OA. However, the benefits of topical NSAIDs are less clear for patients with multi-site OA.

Topical NSAIDs are strongly recommended for pain relief for hand OA and knee OA (figure 8) (Jordan et al., 2003; Zhang et al., 2007a*; NICE, 2008*; NICE, 2014a*). NICE recommend that topical NSAIDs should be considered as a first line drug option. When directly compared, topical NSAIDs have been shown to be as effective as the oral equivalent NSAID or coxib, but are associated with a lower incidence of GI and systemic side effects (equivalent to placebo) (NICE, 2008*). Topical NSAIDs produce <15% of the plasma levels of NSAID compared to oral administration, and one large case–control study has shown no increased risk of serious GI outcomes from topical NSAIDs (Evans et al., 1995). Topical NSAIDs vary greatly with respect to the active drug, carrier base and physical state (creams, gels, sprays), so they need to be considered as separate agents and the evidence for efficacy examined for each. This may explain the heterogeneity of systematic reviews that combine data from different agents. The two topical NSAIDs with the best research evidence for efficacy are diclofenac and ketoprofen. In general, there is moderate quality evidence of benefit, and very low quality evidence relating to harms; after 6 to 12 weeks, 6 out of 10 people with OA had much-reduced pain compared with 5 out of 10 for people treated with the topical placebo (the carrier agent) (Derry et al., 2016). Conaghan et al. (2013) have previously shown that the carrier agent can result in pain relief beyond that expected by an oral placebo, though the mechanism is not known.

Although reasonable synovial fluid levels of NSAIDs can be detected following their topical application, this largely relates to secondary blood-borne delivery rather than direct vertical penetration from the surface. However, in many patients with OA the origin of their pain may be periarticular rather than intracapsular, so this may not be crucial. Topical NSAIDs usually require application three times daily; they are smeared or sprayed onto the skin and do not need to be ‘rubbed in’ (this was a common misconception used to explain any efficacy observed).

Figure 8 Topical non-steroidal anti-inflammatory drug (NSAID) being used for thumb base osteoarthritis (OA) (left) and for knee OA (right).



Although reasonable synovial fluid levels of NSAIDs can be detected following their topical application, this largely relates to secondary blood-borne delivery rather than direct vertical penetration from the surface. However, in many patients with OA the origin of their pain may be periarticular rather than intracapsular, so this may not be crucial. Topical NSAIDs usually require application three times daily; they are smeared or sprayed onto the skin and do not need to be 'rubbed in' (this was a common misconception used to explain any efficacy observed).

7 Additional treatment options to consider for individual patients

A wide range of additional options are available. These are broadly divisible into pharmacological agents for pain control, biomechanical aids and appliances, and surgical interventions. They are listed here by group rather than in any order of priority.

7.1 Pharmacological agents

7.1.1 Topical capsaicin

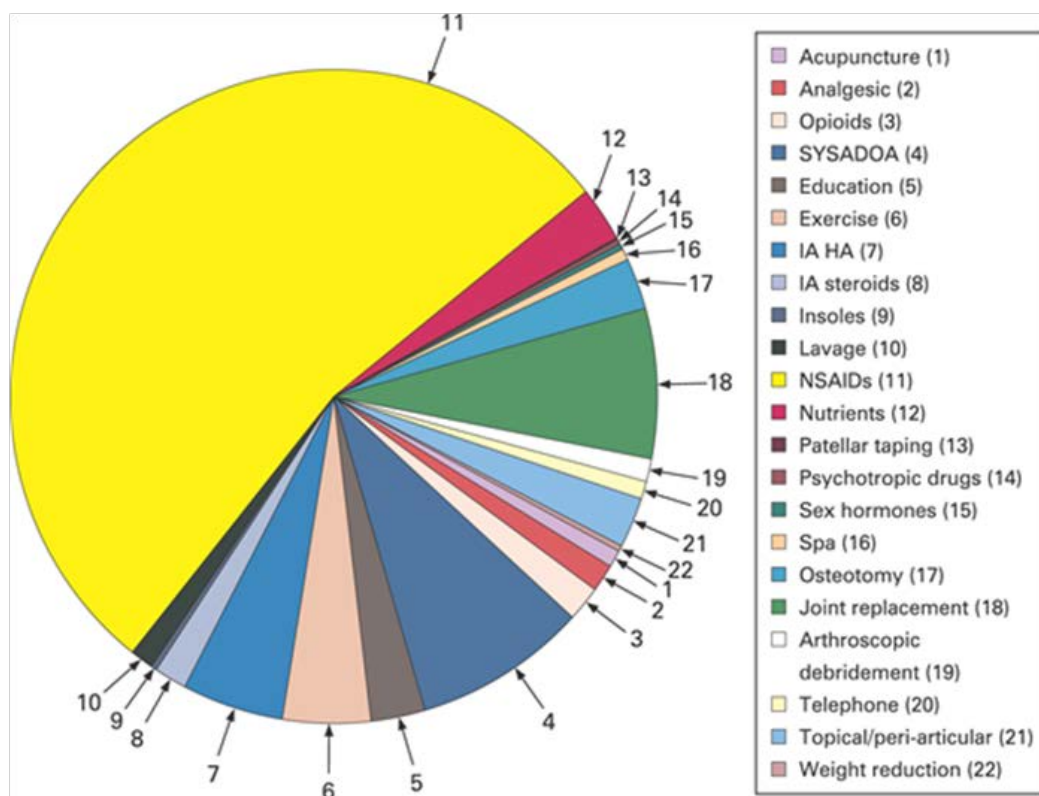
This is a lipophilic alkaloid derived from chilli peppers. Capsaicin selectively binds to the protein TRPV1 (transient receptor potential vanilloid type 1), a heat-activated calcium channel on the surface of peripheral type C nociceptor fibres. When capsaicin binds to TRPV1, it lowers its threshold and activates the channel at lower than body temperature, giving a burning sensation. Prolonged activation of these neurons by repeated application of capsaicin gradually depletes presynaptic substance P, a key neurotransmitter for pain and heat, thus reducing the transmission of painful stimuli. Topical capsaicin applied four times daily can reduce pain associated with hand or knee OA (Jordan et al., 2003; Zhang et al., 2007a*; NICE, 2008*). It shows a

progressive effect that is usually maximal between 1 and 2 weeks. An initial burning sensation which wears off after the initial few days of application is very common, making it impossible to fully blind this agent in RCTs. It is available at concentrations of 0.025–0.075%. At the higher dose, over one third of patients are troubled by local burning, stinging or erythema and discontinue the treatment. It is therefore sensible to initially start at the lower dose. Patients should be warned to wash their hands carefully after application and to avoid contact with their eyes and mucosal membranes. The specific licensing arrangements for capsaicin vary between countries.

7.1.2 Oral NSAIDs (including selective COX-2 inhibitors)

Oral NSAIDs may be considered in patients who are unresponsive to acetaminophens. Numerically there are more RCTs of NSAIDs, including both non-selective and selective COX-2 inhibitors (coxibs), than all other OA treatments combined, producing a skewed research evidence base towards this one modality (figure 9).

Figure 9 The epidemiology of clinical trials in knee osteoarthritis showing a large bias towards randomised controlled trials of oral non-steroidal anti-inflammatory drugs (NSAIDs). IA HA, intra-articular hyaluronan; NSAIDs, non-steroidal anti-inflammatory drugs; SYSADOA, symptomatic slow acting drugs for osteoarthritis. (Reproduced from Pendleton et al., *Ann Rheum Dis* 2000;59:936–44.)



There is clear RCT evidence for efficacy of oral NSAIDs above placebo, and data to show superior efficacy of NSAIDs compared to paracetamol, but no consistent data supporting superior efficacy of one NSAID or chemical class over another (on the contrary, most RCTs show equivalence between NSAIDs and coxibs in OA

at different sites). In general terms, however, NSAIDs are not very potent analgesics for OA. As with many other analgesics, discontinuation rates for oral NSAIDs are high (40–50% at 2 months, over 80% by 12 months), and substitution studies have shown ease of withdrawal of chronic NSAIDs from patients with OA, in place of simple analgesia and lifestyle advice, without any worsening of OA symptoms.

The main concern with NSAIDs, of course, is life-threatening toxicity. NSAIDs can cause serious GI complications such as peptic ulcers, perforations and obstructions as well as bleeds. This risk increases especially with age and concurrent use of other medications, such as warfarin, platelet aggregation inhibitors or SSRIs (selective serotonin reuptake inhibitors). Current European recommendations for prescribing NSAIDs in patients at increased risk of GI toxicity are to use a COX-2 selective agent or a non-selective NSAID plus a proton pump inhibitor (PPI) or misoprostol for gastro-protection. Unfortunately, the reduced GI risk associated with the use of COX-2 selective agents is largely lost when low-dose aspirin is co-administered. It is important to note that non-selective NSAIDs cannot substitute for low-dose aspirin treatment for cardiovascular indications, as aspirin is the only irreversible inhibitor of COX-1.

As a group, patients with OA are predominantly in the category of increased GI risk through being over 65 years of age and/or having comorbidity, including cardiovascular disease, justifying prophylaxis with gastro protection. Because of this, and for cost effectiveness reasons, NICE (2008*) guidelines recommend co-prescription of a PPI with both non-selective and COX-2 selective agents for any patient with OA. Such an approach additionally reduces the incidence of less serious but troublesome dyspepsia that can occur with both NSAIDs and COX-2 selective inhibitors. For any NSAID, the lowest dose should be given first and only increased if there is insufficient benefit. In any case, NSAIDs should be administered at the lowest effective dose for the shortest time necessary.

In addition to GI toxicity, there is considerable concern over cardio-renal safety. There is growing evidence that this risk is common to both unselective NSAIDs and COX-2 selective agents, although the degree of risk may vary between individual drugs. For example, the estimated increase in risk of serious cardiovascular events (mainly myocardial infarction or stroke) with ibuprofen (relative risk (RR) 1.51, 95% CI 0.96,2.37) is similar to diclofenac (RR 1.63, 95% CI 1.12,2.37), but the risk may be lower from naproxen (RR 0.92, 95% CI 0.67,1.26). The current advice from the European Agency for the Evaluation of Medicinal Products (EMA) is that COX-2 selective NSAIDs are contraindicated in patients with ischaemic heart disease or stroke and that prescribers should exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia, diabetes and smoking, as well as for patients with peripheral arterial disease. This again includes a high proportion of older patients with OA. Direct renal toxicity, especially in the elderly, and multiple drug interactions (especially with diuretics and antihypertensive medication) are further major safety concerns in the OA population. Therefore, this group of drugs is commonly contraindicated in the

majority of patients with OA, and increasingly as they age. A further, though less well studied, concern is possible musculoskeletal safety. For example:

- There are animal data that suggest that NSAIDs can inhibit bone repair and may have adverse effects on cartilage metabolism, especially OA cartilage.
- One RCT has suggested that an oral NSAID (indomethacin) may cause more rapid joint space loss in patients with knee OA (that is, it is a negative disease-modifying agent) (Huskisson et al., 1995).
- Several NSAIDs given at normal doses following hip replacement surgery can prevent heterotopic new bone formation (figure 10), raising concerns over possible effects on bone remodelling and osteophytosis in OA.

Figure 10 Heterotopic new bone formation followed this patient's right total hip replacement, causing pronounced hip restriction. This complication was prevented when the patient underwent subsequent left hip replacement followed by 6 weeks of postoperative oral non-steroidal anti-inflammatory drug treatment.



7.1.3 Opioids

Although opioids are widely recommended and used, there are very few RCTs (all short-term) in patients with knee, hip or hand OA, and little data to suggest that dose escalation is effective (Jordan et al., 2003; Zhang et al., 2005*; Zhang et al., 2007a*; Zhang et al., 2007b*; Zhang et al., 2008*; Zhang et al., 2010*; NICE, 2008*). Side effects largely limit their use and are more common in the elderly, the most troublesome being nausea, constipation, dizziness, confusion, somnolence and itching, with a number needed to harm (NNH) of 5. Dependence and possible addiction from long-term use for non-cancer pain are further limiting factors. Nevertheless, the use of opioids increased dramatically in the USA and some other countries following the withdrawal of rofecoxib and the growing concerns about the safety of NSAIDs. Most guidelines recommend

that if paracetamol and topical agents are ineffective, then the addition of ‘weak’ opioids (e.g., codeine, dihydrocodeine, tramadol) should be considered. Stronger opioids (e.g., oxymorphone, oxycodone, fentanyl, morphine sulfate) should only be used for severe OA pain in exceptional circumstances, predominantly as a short-term interim measure before surgical intervention.

7.1.4 Amitriptyline and antidepressants

Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has been recommended by OARSI for patients with knee OA and patients with multisite OA, following RCT evidence demonstrating that it has beneficial effects on pain (McAlindon et al., 2014*). Side effects include nausea, dry mouth, somnolence and fatigue among others, but it is usually reasonably well tolerated. OARSI have given it an ‘uncertain’ recommendation for patients with knee only OA and comorbidities due to the availability of other more targeted therapies and its side effect profile.

There are scant data (mainly for imipramine) to support the use of low-dose tricyclic antidepressants as analgesics in OA. However, low-dose amitriptyline may be considered for refractory pain in patients with OA who also have non-restorative sleep (as amitriptyline can improve delta sleep). Depression is a common comorbidity, and in patients with OA and depression, successful treatment of their depression can improve pain and disability associated with OA, reinforcing the requirement and success of holistic assessment and management in OA (Fernandes et al., 2013*).

7.1.5 Nutraceuticals

‘Nutraceuticals’ is a term used to cover a wide range of natural products and foods that are thought to have health benefits. For OA there are numerous nutraceuticals that claim either pain relieving benefits and/or retardation of joint damage that are available for self-purchase in pharmacies, health food stores and supermarkets, and these are sometimes referred to as SYSDOA (symptomatic slow-acting drugs for OA). Being food products there are no strict regulations concerning the validity of such claims and no compulsory quality control. Nevertheless, such products are extremely popular and have huge sales worldwide. The rationale for the use of glucosamine and chondroitin is that they are basic components of cartilage glycosaminoglycans and that dietary supplementation will improve the integrity of the hyaline cartilage matrix. There is no clear rationale, however, for any mechanism of pain relief in OA.

The mode of action and both in vitro and in vivo effects of these compounds remain highly controversial, although their safety is rarely disputed. Overall, the RCT evidence for slow onset symptom benefit is best for glucosamine sulfate at a single dose of 1500mg/day. A network meta-analysis found no benefit from glucosamine salts (Wandel et al., 2010).

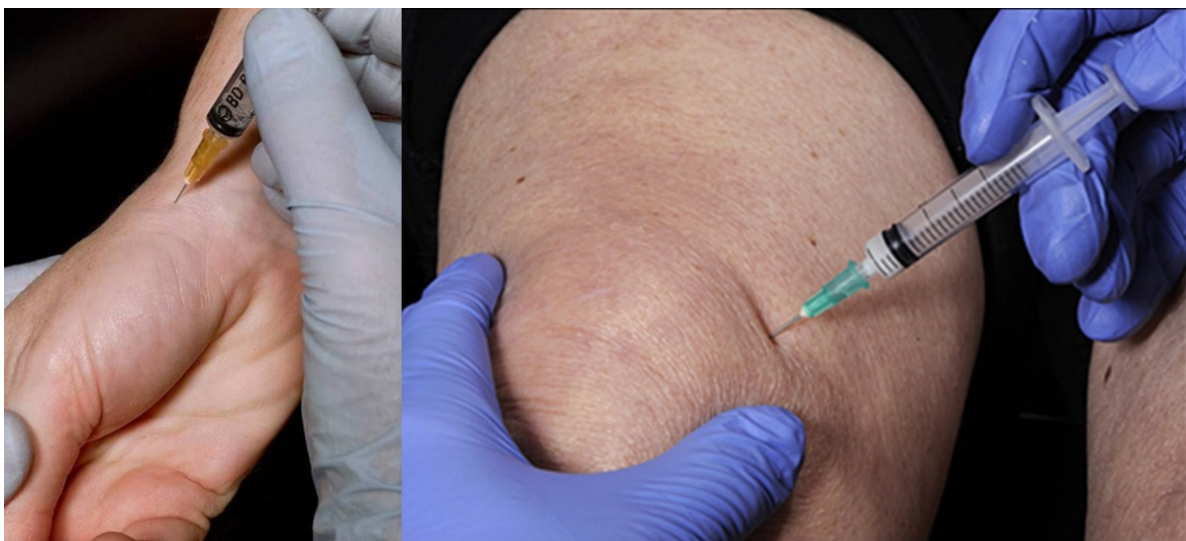
There is meta-analytical evidence from mainly low-quality studies that chondroitin sulfate can give small-to-moderate pain relief effects in OA (Singh et al., 2015). There is low-to-moderate evidence that diacerin has minimal effects on pain and only a small benefit on joint space narrowing (Fidelix et al., 2014.). It has been associated with a high rate of adverse events such as diarrhoea, with restrictions placed on its prescription in Europe. A systematic review and meta-analysis comparing Avocado Soybean Unsaponifiables (ASU) with placebo in patients with knee and hip OA demonstrated a small benefit for pain in favour of ASU (Christensen et al., 2008).

Data on these products is heterogeneous, possibly prone to publication bias, and most guidelines do not support the use of nutraceuticals for pain reduction in OA. NICE, considering cost-effectiveness, have recommended not to use nutraceuticals.

7.1.6 Intra-articular glucocorticoid

There is RCT evidence to justify IA injection of long-acting glucocorticoid for pain relief in knee and hip OA (figure 11). This intervention is quick and simple to do and has a large effect size (ES 1.27 at 7 days post-injection for pain relief against placebo for knee OA). It produces relatively rapid relief of severe pain within a few hours to a few days. This benefit is relatively short lasting in RCTs; in knee OA, small to moderate effects on pain relief are seen at 4-6 weeks post injection with small effects seen at 13 weeks and similarly in hip OA, pain relief has been demonstrated 8 weeks post injection. However, individual patients may derive benefit for longer. In knee OA, there are no clear clinical predictors of response such as presence of effusion, synovitis or degree of structural damage. However, some studies in hip OA suggest that low body mass index (BMI), radiographic severity and synovitis may be predictors of outcome (Hirsch et al., 2013).

Figure 11 Intra-articular injection of glucocorticoid is helpful for quick control of pronounced pain from thumb base OA (left), knee osteoarthritis (OA) (right), and other joints.



There is less trial evidence for OA at other sites, but this treatment is recommended in all guidelines, being well supported by expert opinion. Other joints affected by OA that are commonly injected include the trapeziometacarpal, acromioclavicular and first metatarsophalangeal joint.

Although sepsis is a theoretical concern, as long as sensible sterile precautions are observed, IA steroid injection is a very safe, easily undertaken and well tolerated procedure (Courtney and Doherty, 2005). The main side effects encountered in practice in a minority of patients are:

- temporary pain exacerbation or post-injection 'flare' (this can follow any joint aspiration or injection, even when saline is injected)
- post-injection facial flushing, which is mostly limited to women and may last for 24–72 h post-injection; this is a constitutional reaction that is likely to recur with subsequent injections
- worsening of blood and urine sugar values in diabetic patients for 24–48h, occasionally requiring adjustment of diabetic treatment.

IA steroid injection is a very useful treatment to instil confidence and optimism in a patient. It helps them realise that their pain can be helped and may encourage a more positive approach to other elements of their management plan. It is particularly helpful at providing a temporary respite to allow the patient to commence physical interventions such as neuromuscular training, or to tide the patient over an important event such as a family wedding or holiday.

7.1.7 IA hyaluronan

Hyaluronic acid (HA), also known as hyaluronan or hyaluronate, is a large molecular weight glycosaminoglycan that is a constituent of many tissues including both the synovial and cartilage extracellular matrix. The viscoelastic properties of HA aid joint lubrication and maintain tissue hydration, but HA also has many other biological actions including interaction with other extracellular macromolecules and cell receptors, including CD44. HA is the major non-protein component of synovial fluid and it is cleared from the joint via the lymphatic circulation and degraded by hepatic endothelial cells. Synovial lining cells are the main source of articular HA, and serum HA measurements have been investigated as a biomarker of synovial reactivity. The initial rationale to use HA in OA was to correct the reduced HA molecular weight and concentration observed in OA synovial fluid and to improve joint lubrication—so-called 'viscosupplementation' (figure 12). A range of HA preparations is now available, varying in terms of molecular weight, degrees of cross linkage and polymerisation, and source of manufacture.

There are RCTs in knee OA to support pain relief from various HA preparations that is superior to placebo at 3 months post-injection, but improvements are small (pooled ES 0.21, 95% CI 0.10,0.32) (Richette et al., 2015). RCTs in hip OA have shown similar results.

Figure 12 In osteoarthritis there is reduction in hyaluronic acid (HA) concentration, molecular weight and polymerisation, leading to reduced viscosity of synovial fluid. The rationale of 'viscosupplementation' by injection of HA was to correct these physicochemical abnormalities to aid joint lubrication.



Most preparations require a course of three to five weekly injections to demonstrate symptom benefit, which poses logistical and cost disadvantages. A single injection preparation is available but has limited clinical trial data at present. Post-injection flares are infrequent but can be more florid than those seen with steroid or saline injections. Most guidelines, with the exception of NICE (2008*), give guarded recommendation for consideration of HA in OA.

7.2 Biomechanical aids and appliances

7.2.1 Sticks and walking aids

Walking aids (figure 13) can reduce pain in patients with hip and knee OA, and reduction of impact loading theoretically might reduce the rate of structural progression of OA.

Patients should be given formal instruction in the optimal use of a cane or crutch in the contralateral hand (Jones et al., 2012). Frames or wheeled walkers are often preferable for those with bilateral disease and are particularly helpful for certain tasks requiring walking and carrying—for example, when out shopping. There is a sound biomechanical rationale for the use of a walking stick and observational evidence that use of a stick in the contralateral hand reduces the adduction moment across the medial tibiofemoral compartment and mechanical loading through the hip. The magnitude of the adduction moment has been demonstrated as a risk

factor for structural progression of knee OA, so it is feasible that use of a stick could have more than immediate benefits on pain reduction. Use of a stick or walking aid is recommended in all guidelines for knee and hip OA (Jordan et al., 2003; Zhang et al., 2005*; Zhang et al., 2007b*; Zhang et al., 2008; Zhang et al., 2010*; NICE, 2008*; NICE, 2014a*; Fernandes et al., 2013*). Non-use is often associated with negative perspectives of walking aids so, as always, a detailed discussion with the patient and a clear explanation of benefits is required.

Figure 13 (A) There is a wide range of walking sticks and walking aids to suit the individual. These can all reduce mechanical loading across a knee or hip that is compromised by osteoarthritis. (B) Nordic walking poles.



7.2.2 Braces, splints and other biomechanical approaches

In patients with knee OA and mild to moderate varus or valgus instability or malalignment, a knee brace can reduce pain, improve stability and diminish the risk of falling. A Cochrane review (Duivenvoorden et al., 2015) indicates that the evidence base is inconclusive (low-quality evidence suggests a lack of benefit) for the effects of knee braces on pain, function, and quality of life for people with OA of the medial compartment of the knee.

For patients with severe symptomatic thumb base OA, splints are recommended for pain relief and to correct lateral angulation and flexion deformity. Two small RCTs comparing the effects of a full splint (covering both thumb base and wrist) versus a half splint (only protecting the thumb base) in patients with first carpometacarpal OA have shown that inclusion of a wrist component gives better pain relief (ES 0.64, 95% CI 0.02, 1.96; number needed to treat (NNT) of 4 for improvement of patient daily life activity). As part of core

management, patients should be advised on pacing of hand usage, and to avoid repetitive power grip, pinch and twisting movements.

For patients with pronounced symptoms and functional difficulties from hand, hip or knee OA, adjunctive assistive devices may be required to modify the patient's environment in a way that reduces mechanical loading and facilitates specific actions. Examples for hand OA include enlarged grips on pens or cutlery, non-slip mats to assist opening objects, and electric can-openers in the kitchen (Zhang et al., 2007a*; Fernandes et al., 2013*). International guidelines recommend the use of joint protection as an effective intervention for medium-term outcome in hand OA. In the first large-scale randomised trial to investigate the clinical effectiveness of two self-management programmes for community-dwelling adults aged 50 years and over with hand OA (Dziedzic et al., 2015), occupational therapists delivered an intervention targeting the following joint protection principles:

- distributing the weight of what you lift over several joints (e.g., spread the load over two hands)
- avoiding putting strain on the thumb and repetitive thumb movements
- avoiding prolonged grips in one position
- using as large a grip as possible
- reducing the effort needed to do a task (e.g., use labour-saving gadgets, avoid lifting heavy objects, and reduce the weight of what you lift)
- energy conservation (activity pacing and planning).

At 6 months, 33% assigned joint protection were responders compared with 21% with no joint protection ($p=0.03$). While differences in most secondary outcomes for joint protection were not statistically significant, improvement in pain self-efficacy was noted at each step (3-month $p=0.002$; 6-month $p=0.001$; 12-month $p=0.03$).

For knee or hip OA, replacing a bath with a walk-in shower or using raised toilet seats and chairs may be beneficial (Fernandes et al., 2013*). For patients with problems undertaking activities of daily living, it may be helpful to seek expert advice from occupational therapists or from disability equipment assessment centres.

7.3 Other non-pharmacological treatments

7.3.1 Acupuncture

Acupuncture is an ancient treatment with multiple potential mechanisms of action including release of endogenous opioid. It is practised by many allied health professionals, but although there is an extensive

research base examining the efficacy of acupuncture, interpretation is difficult because of variability both in delivery and in controls. A typical treatment involves six or more needles inserted near the painful joint and sometimes at more distant sites, which may then be manipulated to produce a 'needle sensation', stimulated electrically (electroacupuncture) or warmed by burning a dried herb (moxa) on the needle end. A course of treatment usually involves six or more such sessions. In RCTs clearly it is impossible to blind the practitioner and difficult to blind the patient, but placebo 'sham acupuncture' has been attempted by inserting needles into the wrong place and not stimulating them or by using blunt retractable needles that cause pressure but not skin penetration. However, there is concern over whether such sham controls are a completely inactive placebo. Unsurprisingly, there is heterogeneity of results from RCTs. Some meta-analyses do report pain relief from acupuncture compared to placebo, however the effect size is small and any benefit appears relatively short, lasting from 2 to 6 weeks, and in the recent update of NICE recommendations (2014a) acupuncture was not recommended for use.

7.3.2 Thermotherapy

Thermotherapy is locally applied heat or cold. There is little research evidence but it is used widely by patients with OA. Heat can be applied in various ways such as by application of heat packs, by immersion in warm water or wax baths or by diathermy, while local cold is usually administered by ice packs or by massage with ice. Heat and cold are recommended in most guidelines as a simple and safe adjunct to the self-management of pain (Fernandes et al., 2013*; NICE, 2014a*).

Balneotherapy is a popular modality in some European healthcare systems (defined as the use of baths containing thermal mineral waters) and includes practices such as Dead Sea salt or mineral baths, sulphur baths and radon-carbon dioxide baths (McAlindon et al., 2014*). In the OARSI guidelines for the non-surgical management of knee OA, balneotherapy was considered appropriate only for the sub-phenotype with multiple-joint OA and comorbidities, due to paucity of treatment alternatives for that group (McAlindon et al., 2014*).

7.3.3 Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) may give safe and effective pain relief in some patients with OA (NNT 3; 95% CI 1,5), and is recommended as a safe adjunctive modality in the majority of guidelines. TENS produces pulsed currents via electrodes placed on the skin; the rationale for its use is selective electrical stimulation of peripheral sensory fibres that then cause inhibition of nociceptive nerve transmission via gating at a segmental cord level (figure 14). If used, patients should receive training and written instruction with respect to selection of stimulation intensity and appropriate placement of electrodes, and be reassessed after an initial trial period. Patients should be encouraged to experiment with different intensities and duration of application if the desired relief is not achieved initially, allowing control of symptoms as part of self-

management. In one RCT, even a single TENS treatment increased the pressure pain threshold in people with knee OA. On the other hand, subjective pain ratings at rest and during movement were similarly reduced by active TENS, suggesting a strong placebo component to the effect of TENS (Fernandes et al., 2013*; NICE, 2014a*).

Figure 14 One of many commercially available compact and portable transcutaneous electrical nerve stimulation devices. (Source: Five Star medical Supply, <http://www.fivestarmedicalsupply.com>)



7.3.4 Therapeutic ultrasound

A double blind, randomised, placebo controlled pilot study to determine the feasibility of conducting an RCT assessing the effect of low intensity pulsed ultrasound therapy on cartilage repair in participants with mild to moderate knee OA, showed an increase in medial tibial cartilage thickness in the active ultrasound therapy group. On the other hand, a randomised double blind controlled clinical study showed that therapeutic ultrasound has no further significant effect on symptoms in people with knee OA, so evidence remains equivocal. Previously, European recommendations for the management of hand OA recommended ultrasound in combination with warmth, but this was based mainly on consensus opinion (Zhang et al., 2007a*).

7.3.5 Behavioural interventions

Cognitive behavioural therapy can improve sleep for people with OA but there is no evidence that this has a beneficial effect on pain itself or on pain coping (Smith et al., 2015). An internet-delivered combination of exercise advice and training plus pain coping strategy training (PainCOACH) was found to improve pain and function for at least six months (Bennell et al., 2017).

7.4 Surgery

For patients with severe hip or knee OA, total hip arthroplasty (THA) and total knee arthroplasty (TKA) are widely recognised as reliable and appropriate surgical procedures to control pain, restore function and improve quality of life (figure 15). Evidence for their efficacy is based on numerous uncontrolled observational studies and several large cohort studies as well as a wealth of expert and patient opinion. Successful outcomes require: careful selection of patients most likely to benefit; thorough preparation in terms of optimising general health and patient information; well performed anaesthesia and surgery; and appropriate rehabilitation and domestic support for the first few postoperative weeks. Skou et al. (2015) found that, in patients eligible for knee replacement who were randomised to total knee replacement plus 12 weeks of subsequent nonpharmacological management (exercise, education, dietary advice, insoles, analgesia) or the 12 weeks' nonpharmacological management only, there was a greater improvement in pain and function in the surgical group (adjusted mean difference of 15,8 points in the KOOS score, favouring surgery) but most patients in the nonsurgical group did not undergo subsequent arthroplasty within the 12-month follow-up period; the surgical group had a higher incidence of serious adverse events (48% vs. 12%). An abstract reporting the two-year follow-up (Skou et al., 2017) identified that nearly two-thirds of patients eligible for surgery but randomised to nonsurgical treatment postponed surgery for at least two years after randomisation. Continued use of a nonsurgical approach may therefore be a reasonable strategy, coupled with appropriate ongoing clinical review.

Recovery from TKA is slower than from THA, but with appropriate rehabilitation from the first postoperative day most patients resume normal activities within 6–12 weeks. All studies show substantial improvements in pain and function, although generally THA is more effective than TKA in restoring function to normal; quality of life indices 1 year after THA have been shown to be comparable to age and gender matched non-OA controls. Over 95% of joint replacements continue to function well into the second decade after surgery, and most provide lifelong pain-free function. However, approximately one in five patients is not satisfied with their replacement and a minority gets little or no improvement in pain following joint replacement.

All guidelines agree that referral for consideration of THA or TKA should be considered in patients with hip or knee OA who experience persistent pain, stiffness and reduced function that are refractory to non-surgical treatments and which impact significantly on their quality of life (Jordan et al., 2003; Zhang et al., 2005*; Zhang et al., 2007b*; Zhang et al., 2008*; Zhang et al., 2010*; NICE, 2008*; NICE, 2014a*). Joint replacement is very effective at relieving these symptoms and carries relatively low risk both in terms of systemic complications and suboptimal outcomes for the joint itself. Importantly, referral should be made after core treatments have been tried, but before there is prolonged and established functional limitation and severe pain, since this may compromise a good outcome following surgery. Orthopaedic scores and questionnaire-based assessments are available to assess pain, functional impairment and X-ray damage (e.g., the New

Zealand score and the Oxford hip or knee score), but these have not been validated to assess appropriateness of referral. As there is no common consensus on when joint replacement should be carried out, a shared decision, between doctor and patient, on when surgery should be performed should be based on an individualised risk/benefit estimation.

Figure 15 A total hip arthroplasty. Joint replacement involves removal of the articular surfaces and replacement with synthetic materials, usually metal and plastic (sometimes ceramic), with or without use of bone cement to stabilise the implanted components.



The decision to refer for surgery is individual and ultimately it is the patient who must decide based on their own risk/benefit calculation depending on their symptom severity, their general health, their expectations of lifestyle and activity, and the effectiveness of the non-surgical treatments they have tried. Patient-specific factors such as age, gender, smoking, and presence of obesity or other comorbidity should not be barriers to referral for joint replacement. Some patients will have higher risks of postoperative complication or higher risk of long-term prosthesis failure, but there is no evidence to support these as reasons to deny treatment. Specifically, there is no evidence to support poorer outcomes from THA or TKA in patients who are obese, have multiple comorbidities or are of advanced age, and these factors should not be barriers to referral (NICE, 2014a*). On the contrary, there is evidence that these patients can have greater benefit than other groups.

Patients with involvement of just one tibiofemoral compartment may be considered for unicompartmental knee arthroplasty (figure 16) (NICE, 2008*; Zhang et al., 2008*). If this lesser procedure fails, it does not preclude subsequent consideration of a TKA. Tibial osteotomy for medial compartment knee OA has also been identified to be beneficial in a Cochrane review (Brouwer et al., 2014), though it is not known how this compares to nonsurgical treatment or to a unicompartmental arthroplasty.

Figure 16 A unicompartmental joint replacement for medial tibiofemoral osteoarthritis.



Because the risk of subsequent implant failure, predominantly from loosening, is greater in younger, more mobile patients and in those who practise sports, corrective osteotomies and joint preserving procedures (e.g., hip resurfacing) may be considered in such patients.

Due to lack of evidence to support arthroscopic lavage and debridement for knee OA, these invasive procedures should not be offered as part of treatment for OA itself, but should be considered in a patient with knee OA if, in addition to their OA symptoms, there is a clear history of mechanical locking, but not just for stiffness, ‘giving way’ or X-ray evidence of osteochondral ‘loose’ bodies (NICE, 2008*). In a systematic review, arthroscopic surgery for knee OA has been found to have an “inconsequential” benefit that is short-lived, disappearing within one to two years (Thorlund et al., 2015).

Surgery should also be considered at other joint sites for severe symptomatic OA refractory to other measures. The specific surgical options will vary according to each joint. For example, several procedures are available for thumb base OA including arthrodesis, trapeziectomy alone or with synthetic or biological interpositions, osteotomy and total joint replacement. Two systematic reviews suggest that there are no benefits but more

complications from combined procedures, so simple trapeziectomy is generally recommended (figure 17) (Zhang et al., 2007a*).

Figure 17 *Trapeziectomy for first carpometacarpal joint osteoarthritis, in this patient resulting in a successful outcome in terms of pain relief and functional improvement.*



7.5 Disease-modifying OA drugs

Although there is considerable interest in the possibility of drugs that may beneficially modify the biochemical and structural changes of OA, currently no guidelines recommend any drug for this purpose. RCTs to investigate slowing of radiographic cartilage loss in patients with knee OA have been undertaken with glucosamine, chondroitin, diacerein, doxycycline, risedronate, strontium and hyaluronan. Two placebo controlled RCTs of glucosamine sulfate 1500 mg/day have reported a reduction in radiographic medial tibiofemoral joint space loss at 3 years with a pooled ES of 0.24 (95% CI 0.04,0.43); and a meta-analysis of five placebo controlled RCTs of chondroitin sulfate 800 mg/day has reported a small difference of 0.16 mm (95% CI 0.08,0.24 mm) in medial compartment minimum joint space after 2 years. A single RCT of diacerein in patients with primary hip OA has demonstrated slowing of joint space loss after 3 years, but no effects were observed in a 1-year study of diacerein for knee OA. A single study of doxycycline, in obese women with knee OA, demonstrated less reduction in medial joint space after 30 months in the index knee of patients on doxycycline (0.30 ± 0.6 mm vs 0.45 ± 0.70 mm), but paradoxically no effects on the contralateral knee. Evidence from two relatively short-term studies of hyaluronan and risedronate in knee OA are inconclusive. Reginster et al. (2013) investigated the use of strontium in knee OA and identified that both 1g and 2g daily doses were associated with less joint space loss than placebo (0.23mm for the 1g/day dose, 0.27mm for the 2g/day dose, compared to 0.37mm for placebo); pain and function were also better in the 2g/day dose group. Strontium treatment for osteoporosis has previously been the subject of a safety warning (<https://www.gov.uk/drug-safety-update/strontium-ranelate-cardiovascular-risk>). Vitamin D has recently been investigated for its role in

improving the health of cartilage, bone and muscle in OA but found not to improve knee pain nor cartilage volume loss (McAlindon et al., 2013).

There are a number of caveats and issues with such studies, including the small effect sizes and the lack of clear evidence for any significant improvement in patient centred outcomes (pain, function, quality of life) for any apparent slowing of cartilage loss. Such therapies predominantly target one joint tissue, specifically cartilage (glucosamine, chondroitin, doxycycline, diacerein) or bone (risedronate), and because all joint tissues are involved in OA, it may be unrealistic to expect overall improvements by influencing just one of the component tissues.

7.6 Possible new therapeutic options

Two disease-modifying anti-rheumatic drugs (DMARDs) used in the treatment of inflammatory arthritis are currently being investigated for their role in OA. Hydroxychloroquine has been evaluated in two small RCTs in knee and hand OA, with improvements in symptoms and function reported (Kingsbury et al., 2013). An abstract (Kingsbury et al., 2017) of results from the UK HERO trial evaluating hydroxychloroquine identified no benefit over placebo. Methotrexate has also been the subject of one RCT in knee OA, but the associated publication was withdrawn in 2016. Methotrexate is currently being evaluated in larger multi-centre RCTs in hand OA and knee OA, respectively.

Targeting nerve growth factor as a therapeutic option showed promise when the monoclonal antibody, tanezumab, demonstrated marked analgesic efficacy in OA of the knee; however, development of this drug is still on hold after increased rates of joint replacement were reported in the treated arm of this phase II trial.

IL-1, a main inflammatory cytokine in the pathophysiology of OA, represents one of the possible treatment targets. Although pre-clinical studies have suggested benefit from IL-1 blockade on activity and progression of OA, clinical studies have thus far failed to demonstrate similar results in humans with systemic or intra-articular drugs (Chevalier et al., 2011). TNF α blockade (administered systemically and intra-articularly) has also been evaluated in three small RCTs in hand and knee OA; these studies did not demonstrate any impact on clinical outcomes, although reduction in radiographic erosion rate was reported in swollen proximal interphalangeal joints (PIPs) in a study of hand OA (Verbruggen et al., 2012). Other agents under current investigation include nitrous oxide, protease inhibitors and inflammatory cytokine intracellular signalling cascades (Pulsatelli et al., 2013).

The injection of autologous platelet-rich plasma has some limited data on effectiveness in reducing pain and improving mobility in knee OA; in theory, cartilage repair may be enhanced by injection of the patient's own blood products. Although RCTs have demonstrated some improvement in clinical outcomes, none have demonstrated visual evidence, arthroscopically, of cartilage repair. NICE have reviewed this intervention and

concluded there is insufficient evidence to recommend this treatment; however, the procedure is considered safe and may be conducted under special arrangements for clinical governance, consent and audit or research (NICE, 2014b).

A food supplement or nutraceutical that has some limited clinical data to support short-term symptom relief is an extract from *Scutellaria baicalensis* and *Acacia catechu* (otherwise known as UP446), thought to be a leukotriene and prostaglandin inhibitor (Sampalis and Brownell, 2012).

Finally, studies of intra-articular cellular therapy injections for osteoarthritis and focal cartilage defects in the human knee have suggested positive results with respect to clinical improvement and safety. However, the improvement was modest, a placebo effect cannot be disregarded and the methodological quality of the literature was poor (Chahla et al., 2016).

8 Caveats to the research base for OA management

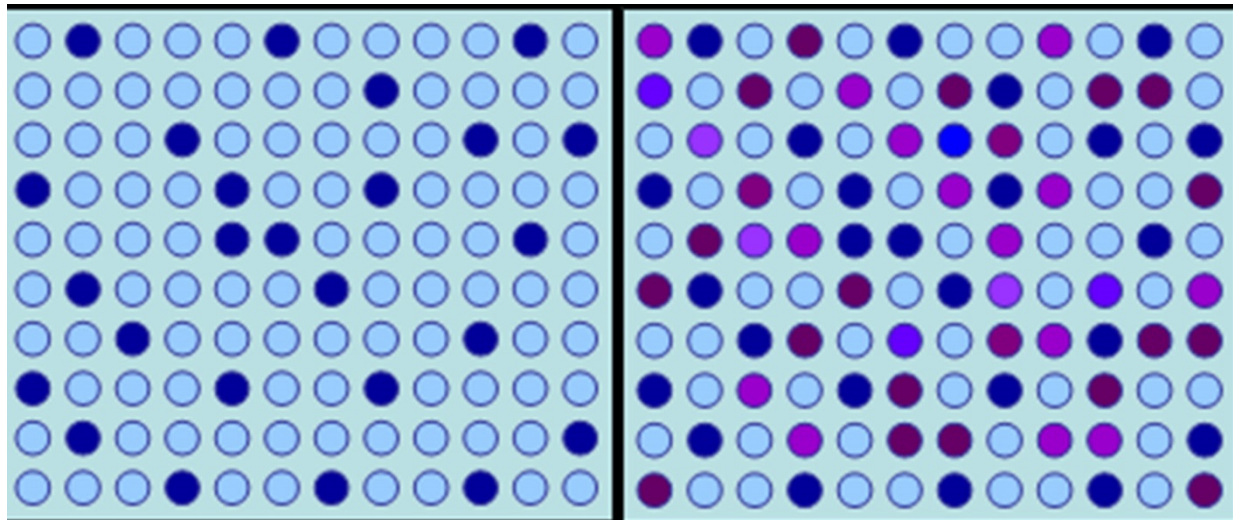
RCTs can play an important role in showing whether an individual treatment can be effective in a carefully controlled setting—that is, whether a treatment has clinical efficacy. However, many RCTs have limitations and caveats that reduce the generalisability of the trial findings to the varied population of people with OA encountered in everyday clinical practice. It is therefore common for the more important clinical effectiveness of the treatment outside of a trial setting to be less impressive than the effect size demonstrated in an RCT. The most common limitation to any RCT is bias, and the most common form of bias is selection bias. Although a large number of RCTs have investigated the efficacy of a range of treatments in OA, there are important limitations to the research base in OA. For example:

- The majority of OA trials focus on knee OA and there are relatively few RCTs for other joints targeted by OA. However, OA at sites such as the knee, hand and hip differs in terms of prevalence and incidence, the profile of risk factors for development and progression, and prognosis for clinical outcome. In addition, there are limited data to suggest that the same treatment, such as an oral NSAID, may have a bigger effect size at the knee than at the hip, and that even the placebo effect in OA may vary between sites, being greatest at the hand, lower at the knee, and least at the hip. Therefore, RCT results gained at one site cannot necessarily be extrapolated to another site of OA—each requiring study in their own right.
- A common selection bias in most RCTs is that patients with OA are recruited from secondary care, yet the majority of patients with OA are managed solely in primary care.
- The majority of RCTs are relatively short term, from a few weeks to a few months, and very few last 1–2 years or more. This results in a paucity of data regarding long-term benefits of treatments in OA and possible emergence of long-term side effects.

- The majority of trials in OA are of drug treatments, giving undue emphasis to pharmacological agents in the research base.
- Many RCTs of drug treatments for pain require patients to 'flare' (that is, show a certain degree of worsening of symptoms) on stopping their current medications before entering a study. Such flare designs have a bias towards patients who respond to medication, and thus tend to inflate the treatment response.
- Most studies investigate the efficacy of a single intervention even though multiple treatments are given in practice. Very few studies examine the benefits of two or more combined treatments and whether there is interaction, above simple addition, between treatments. Factorial designs that randomise patients to either (1) treatment A, (2) treatment B, (3) treatment A + B, or (4) placebo, are uncommonly used for OA trials yet give clinically informative results.
- Patients with OA recruited for RCTs are usually subject to a large number of exclusions, such as being elderly, having comorbidity, being on certain medications, having a knee effusion or having severe radiographic change. This tends to make the study sample homogeneous and medically robust. This has advantages in terms of reducing the numbers needed for the trial, reducing the likelihood of side effects and minimising costs, but such a sample may not be representative of patients with OA in general (figure 18). Results of such studies often have poor generalisability and lack information concerning clinical predictors of response—for example, do certain patients with pronounced X-ray change, a knee effusion or gross obesity do less well than those without such features? A better study design would be to reduce exclusion criteria, including people with comorbidities. This heterogeneity is more representative of the whole population with OA, but has the disadvantages of requiring more patients to be randomised and of increasing costs. However, results of such studies have good generalisability and can answer what most practitioners want to know: which patient is likely to do best with this particular treatment?

Such multiple caveats reduce the usefulness of many trials in terms of guiding clinical decision making. However, the quality, both of design and of reporting of RCTs, continues to improve and is aided by publication conventions such as CONSORT which require inclusion of key elements such as a flow diagram showing the number of participants at each stage of the study (from those eligible to those that complete), the method of recruitment and the exact randomisation procedure, using a check list to ensure full inclusion of essential information. Nevertheless, it is important to examine each study critically, especially in terms of the common intrinsic biases listed above, and to judge the possible relevance of the trial results to your own patient population with OA.

Figure 18 Randomised controlled trials in osteoarthritis usually study a small sample of homogeneous patients (dark blue), subject to the same exclusions, from the whole population of osteoarthritis (left). Studies with little exclusion require more participants (heterogeneity requires greater numbers for randomisation to distribute variation equally) (multi-coloured) but produce more generalisable data and, because of variation between participants, can examine predictors of response to the treatment.



9 Quality of care in OA

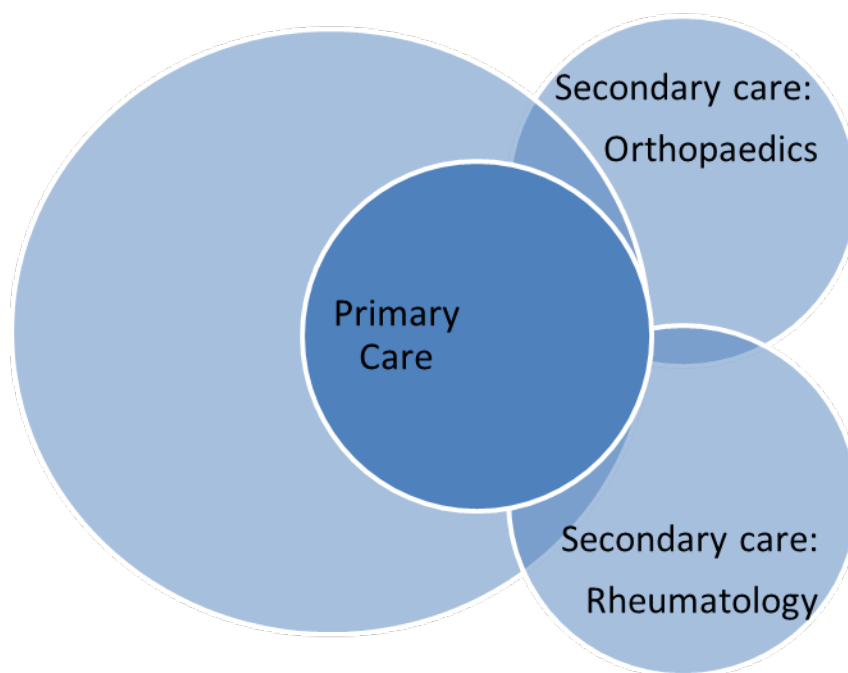
Despite the existence of concordant evidence-based guidelines for the management of OA, whenever the care of patients with OA has been audited in recent years, it is apparent that the standard of care is often suboptimal. In the community, the core elements (education, exercise prescription, reduction of adverse mechanical factors) are often omitted and the most common treatment approach hinges around drug treatments, predominantly NSAIDs.

Routine audit of and feedback on clinical care for OA is needed to improve the quality of that care and has prompted an interest in measures of quality of OA care. Such indicators are defined as a 'measurable [element] of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality, of care provided' (Lawrence and Olesen, 1997). A systematic review identified that there are a number of well-validated indicators that could be used to capture processes of care for primary care (Edwards et al., 2013). Edwards et al. (2014) tested quality indicators in an electronic pop-up template in primary care consultations and demonstrated that use of computer prompts helps to improve the uptake of first line analgesia with an increase in use of topical NSAIDs with template use. The EUMUSC.net project (<http://www.eumusc.net/>) is a European initiative to develop standards of care and has also suggested a set of indicators for OA. Østerås et al. (2013) have generated a patient self-report measure of quality indicators which has been replicated by primary care researchers in the UK (Dziedzic et al., 2014).

10 Models of care

OA is one of the most common long-term conditions and as such needs to be centrally managed in primary care. Indeed, the care of patients with OA starts even before they consult a healthcare practitioner and the ARMA standards of care for OA highlight the importance of community services in health promotion and supporting self-management (figure 19). Joint problems are the most common cause of restriction in daily life in most countries and healthcare for such problems is frequently provided in primary care settings.

Figure 19 The care of patients with osteoarthritis.



10.1 OA in primary care: the role of the multidisciplinary team

Although the biomedical model has contributed to major advances, a model that embraces chronic pain management and its psychological and social components is needed. Primary care is the ideal arena to achieve high-impact prevention strategies such as healthy eating, healthy weight, physical activity and exercise. Joint pain itself reduces physical activity. The multidisciplinary team including general practitioners, practice nurses, physical therapists, occupational therapists, podiatrists and community pharmacists, is in a crucial position to provide support for self-management, especially for interventions related to exercise and behavioural change (Dziedzic et al., 2009). These interventions are complex and need to be embedded in the patient's own experiences, informed by lay knowledge of living with joint pain, and discussed as part of all consultations (Morden et al., 2011; Grime and Dudley, 2014).

10.2 OA in secondary care: the role of the rheumatologist

Only a small proportion of patients with OA may be referred to secondary care, and ultimately see a rheumatologist, with the majority of patients being managed in primary care. Furthermore, patients referred because of complex OA to rheumatologists in Europe may only be seen on one occasion, with therefore no implementation or initial monitoring or adjustment of a suggested management plan. Regular review of patients with OA is clearly important and recommended among others by NICE. With this in mind, what is the role of the rheumatologist for the patient with OA? We would suggest the following:

1. Work with primary care colleagues to suggest local guidelines for referral, such as management of 'complex cases', patients with diagnostic uncertainty, or patients in need of specialist adjunctive services such as occupational or physical therapy that are not available in the community.
2. Rheumatologists are experts in musculoskeletal medicine. It is unrealistic to expect all primary care practitioners to know about the range of treatments listed in this module and the evidence behind them. Use opportunities to support primary care colleagues in the treatment of patients with OA. This might include, but not be limited to:
 1. Education and update sessions for primary care. It is of particular importance to highlight the range of, and evidence base for, non-pharmacological treatment options available.
 2. Detailed plans for individual patients. If local policies do not permit follow-up of patients with OA in secondary care, suggest monitoring and adjustments to the management plan in correspondence with primary care.
3. Consider OA patient pathways in your region. To what potential services might patients with OA be referred? Are all services connected and offering consistent messages about OA care? Are any third sector agencies involved or being utilised?

OA is a leading cause of morbidity and disability and rheumatologists have the skills and expertise to manage these patients effectively. This may be regarded as the real challenge for rheumatologists in the future. As rheumatologists may only see a small proportion of these patients in practice, it remains the rheumatologist's responsibility to act as an advocate for patients with OA.

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SUMMARY POINTS

- Recent evidence-based guidelines concur with respect to the objectives and principles of management of patients with knee, hip or hand osteoarthritis (OA) and on the core therapy that should be considered for anyone with OA. The guidelines also agree, with only minor variation, on the many adjunctive options that should additionally be considered and advised for individual patients.
- There is research evidence to support many of the recommended treatments for OA, but expert and patient opinion are equally important forms of 'evidence', especially given the caveats and limitations of most RCTs and the difficulty of blinding and/or using placebo/sham interventions of physical treatments or surgery. In determining the strength of recommendation for any treatment, many factors other than efficacy need to be considered, including safety, cost, logistics of delivery, acceptability and the individual patient's preferences.
- A multifaceted, individualised package of care should be devised with the patient and subsequently monitored and adjusted as necessary. The non-specific benefits of treatment should not be ignored or underrated, but fully optimised.
- The objectives of management are: (1) patient education and information access; (2) pain relief; (3) optimisation of function; and (4) beneficial modification of the OA process.
- The core treatments that should be considered for every patient with OA are: (1) patient education and information access; (2) exercise— both generalised aerobic fitness training and local neuromuscular training, strengthening and range of motion exercise; and (3) reduction of adverse mechanical factors—for example, weight loss if overweight/obese, appropriate footwear, pacing of activities. Recent audits suggest that these core aspects of management are often omitted.

- Topical NSAIDs are recommended as a first line analgesic. Paracetamol may be used at conservative dosing and duration, although it is less effective and has greater risk than previously thought.
- Other pharmacological adjuncts for pain control include topical capsaicin, oral non-steroidal anti-inflammatory drugs (including COX-2 selective agents) and opioids. An additive rather than substitutive approach is recommended, with due regard to problems of polypharmacy.
- Intra-articular injection of glucocorticoid is recommended for short-term control of pronounced pain. There is much less support for intra-articular injection of hyaluronan.
- Other biomechanical approaches that are recommended include walking aids, braces, splints and assistive devices.
- Other physical treatments that are recommended include thermotherapy and use of TENS (transcutaneous electrical nerve stimulation).
- Currently no drug is recommended for disease modification of OA. Glucosamine sulfate, chondroitin, diacerein and others are regarded as relatively safe but have limited support for adjunctive pain relief. Hydroxychloroquine cannot currently be recommended and methotrexate remains under evaluation.
- Treatment of comorbidity, such as depression, is important. Low-dose amitriptyline at night is recommended in patients with pain and non-restorative sleep. Duloxetine has beneficial effects on pain.
- Surgery, including total joint replacement, should be considered for patients who have persistent pain, stiffness and reduced function that are refractory to non-surgical treatments and which impact significantly on their quality of life. Patient-specific factors such as age, obesity or other comorbidity should not be barriers to surgery, and referral should be made before there is prolonged and established functional limitation and severe pain, though continued nonsurgical management with appropriate ongoing clinical review can also be considered.
- Many patients with OA will not ultimately see a rheumatologist and rheumatologists should consider opportunities to support primary care in the management of these patients.

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module

EULAR on-line course on Rheumatic Diseases

Osteoarthritis: treatment

John Edwards, Zoe Paskins, Krysia Dziedzic

A previous version was co-authored by Zoe Paskins, Krysia Dziedzic, Burkhard Leeb

IN-DEPTH DISCUSSION I

Exercise for OA

Exercise is a central core component of OA management. Here we will consider:

- the general benefits of regular activity
- the decline in muscle function in OA
- evidence for exercise in management of OA
- practical considerations relating to delivery of exercise

General benefits of exercise and regular physical activity

There are many health reasons to promote regular physical activity (Fig. 20). For example, it associates with increased life expectancy and reduces risk of cardiovascular disease, diabetes, obesity, osteoporosis and certain cancers (Fentem, 1994). In the elderly, regular exercise may slow or even reverse age-related changes such as decline in muscle bulk and strength (Beudart et al., 2017), balance (Howe et al., 2011) and is one component of falls prevention (NICE, 2013). Furthermore, regular exercise in people with OA improves mental health and encourages restorative sleep, well-being and quality of life (O'Reilly and Doherty, 2001; Tanaka et al., 2015), though the effects on mental health in the wider population are less clear (Penedo and Dahn, 2005).

Fig. 20. Regular physical activity has many health benefits



Rationale for exercise for OA - decline in strength and fitness in OA

People with knee OA often show reduced quadriceps and hamstring strength, impaired balance and proprioception and a tendency to fall. Weakness in OA may result from muscle atrophy (predominantly type II fibres), reflex spinal cord inhibition or voluntary inhibition due to pain. Quadriceps weakness associates with severity of pain and disability in knee OA and may be a predictor of adverse outcome. Also, symptomatic medial compartment knee OA is associated with reduced strength in all muscle groups at the hip (Hinman et al., 2010). Although most data relate to knee OA, in principle reversible decline in muscle health is a therapeutic target for OA at any joint. In addition to impairments in motor and sensory function, people with

OA have reduced cardiovascular fitness compared to age- and sex-matched controls. Therefore, there is a clear logic to support both neuromuscular training/strengthening and aerobic exercise as a treatment for OA (Zhang et al., 2008; Zhang et al., 2007; Fernandes, 2013; McAlindon, 2014; NICE, 2014) although referral for exercise is offered in only 39% consultations (Hagen et al., 2016).

Evidence for exercise in OA

Exercise may slow the progression of OA in several ways and moderate daily exercise does not increase risk of hip or knee OA (Lefèvre-Colau et al., 2016). Moderate to high quality evidence shows that land-based exercise offers short term benefits for knee pain and function sustainable 2-6 months after cessation (Fransen et al., 2015).

Exercise increases glycosaminoglycan content in cartilage of patients at risk of knee OA (Roos and Dahberg, 2005), increases the chondroprotective cytokine IL-10 both intra- and periarticularly in symptomatic knee OA (Helmark et al., 2010) and promotes muscle protein synthesis in old individuals with knee OA (Petersen et al., 2011). The benefits of exercise for knee OA are supported by a systematic review and meta-analysis of 13 RCTs undertaken in 2005 (Roddy et al., 2005a) and by a review of systematic reviews (Jamtvedt et al., 2008). Pooled effect sizes (ES) for pain relief are moderate for both aerobic (ES=0.52, 95% CI 0.34, 0.70) and strengthening exercises (ES=0.32, 95% CI 0.23, 0.42) and ESs for self-reported disability are 0.46 (95% CI 0.25, 0.67) for aerobic and 0.32 (95% CI 0.23, 0.41) for strengthening exercise (Roddy et al., 2005a). In symptomatic knee OA, both weight bearing and non-weight bearing exercises associates with improvement in physical function (Bruyere, 2009). The mean (95%CI) decline in WOMAC 3 days after completing an 8 week exercise regime was -10.3 (-8.5 to -12.2) for the weight bearing and -17.2 (-14.6 to -19.8) for the non-weight bearing group (Bruyere, 2009). The benefits of exercise are substantially greater than the small (clinically insignificant) benefits of paracetamol, long recommended as a first-line pharmacological treatment for OA, as reported in a systematic review and network meta-analysis (Machado et al., 2015) and also greater than oral NSAIDs (Zhang et al., 2010) .

Exercise in knee OA can improve the amount of time spent walking, gait speed and distance walked (Tanaka et al., 2016) and Tai Chi, balance and proprioceptive exercises are also beneficial (Anwer et al., 2016). Compared with surgery, exercise therapy and meniscectomy showed comparable results but exercise after meniscectomy showed benefit on function in the longer term (Swart et al., 2016).

Aquatic therapy can also be an effective and safe adjunctive treatment for knee OA (Lu et al., 2015). Well-structured water based exercises with appropriate intensity and control of overload can be effective in improving physical function and increasing muscle strength (Mattos et al., 2016). There are less data for hip and hand OA (Valdes and Marik, 2010), although two RCTs of water-based exercise for hip OA report pain relief (ES=0.25, 95% CI 0.02, 0.47) and reduced stiffness (ES=0.17, 95% CI 0.05, 0.39) (NICE, 2008; Zhang et al.,

2008). A meta-analysis of RCTs showed that even land based exercise regimens show a small treatment effect for pain (standardized mean difference= -0.38, 95% CI -0.09 to -0.67) but not for physical function in hip OA (standardized mean difference= -0.02, 95% CI -0.31 to 0.28) (Fransen et al., 2010). The Ottawa panel has recommended land based therapeutic exercise strength training for hip OA (Brosseau et al., 2016).

A network meta-analysis comparing different packages of exercises for lower limb OA, predominantly knee OA, demonstrated that combinations of exercise to increase strength, flexibility, and aerobic capacity are likely to be the most effective (Uthman et al., 2013). A recent study of hand exercises delivered in classes by occupational therapists demonstrated that hand exercises were cost effective (Oppong et al., 2015), though a Cochrane review of exercises for hand OA determined that the quality of evidence was generally low but that benefits of exercise were small for pain in hand OA and the effect on quality of life was uncertain (Østerås et al., 2017).

As mentioned above, knee OA is associated with weakness in hip muscles. It may therefore be advisable to encourage hip muscle strengthening exercises in individuals with knee OA. In a pilot study, hip abductor muscle strengthening reduced knee pain and knee load (measured as the external adductor moment at the knee) (Thorp et al., 2010). However, in a RCT of hip abductor and adductor strengthening in individuals with varus knee OA, there was a significant reduction in knee pain and improvement in knee function, but no change in knee load, suggesting the presence of other mechanisms (Bennell et al., 2010). Limitations in interpreting the research evidence include the short duration of RCTs (only two have gone to 18 and 24 months); variability in type, frequency and intensity of exercise regimens; and variation in delivery (e.g. home versus hospital, individualised or group-based). When compared directly, strengthening and aerobic exercise show equivalent benefits (Roddy et al., 2005a).

Despite heterogeneity of RCT interventions, current guidelines strongly support both strengthening (neuromuscular training) and aerobic fitness exercise for OA, especially knee or hip OA (Roddy et al., 2005b; Zhang et al., 2007; Zhang et al., 2008; NICE, 2014). Exercise appears safe, with no reported pain exacerbation in patients with OA (Roddy et al., 2005b). Long term (three to 30 months) low-impact therapeutic exercise has been found, in a systematic review, to be safe for older adults with knee pain; there was no evidence of increase in pain or decrease in physical function, radiological progression of OA, nor an increase in total knee replacements (Quicke et al., 2015).

Provided trauma is avoided, moderate exercise does not lead to acceleration of knee OA, whether or not there is evidence for pre-existing disease (Bosomworth, 2009; Quicke et al., 2015). There is not complete consensus on conditions that represent a clinical need to restrict exercise or form an absolute contraindication. Aerobic activity benefits comorbidities commonly occurring with OA. A helpful starting

point to consider exercise restriction or contraindication is the narrative review by de Rooij et al. (2013), who list various cardiac and metabolic conditions as absolute contraindications and additional reasons for restriction of exercise.

Considerations relating to the practical delivery of exercise to people with OA

As with OA management overall, a key principle is to individualise the exercise programme. Delivery methods vary in terms of local availability or quality and some patients enjoy group activities whereas others do not, so both local factors and patient choice require consideration. Any programme should start at a low frequency, duration and intensity appropriate to the patient's capabilities, and then slowly increase to allow physiological adaptation. "Small amounts, often" is appropriate and mirrors the principle of pacing of general activities. There is a helpful introduction to the health benefits of exercise and, specifically, advice about the principles involved in starting exercise (Chapter 16) at the (UK-focussed) Motivate2Move website (<https://gpcpd.walesdeanery.org/index.php/welcome-to-motivate-2-move>).

A systematic review by Juhl et al. (2014) identified that programmes with exercises of a single type were more effective than those with mixed types (effect size for pain reduction 0.61 in trials examining a single exercise type compared to 0.16 for mixed types).

For muscle strengthening it is common to start with isometric exercises which tighten the muscle without moving the joint, thus avoiding impact loading.

Straight-leg raising while sitting or lying (Fig. 21) or pushing the knee into extension on the bed are common starting quadriceps exercises (Fig. 22).

Fig. 21. Patient being instructed on a straight-leg raise, keeping the foot dorsi-flexed to focus contraction on the quadriceps.



Fig. 22. Patient being instructed to push the knee down hard onto a soft object on a bed, again with foot dorsi-flexed.



Each manoeuvre is held for 5-10 seconds before relaxing, and then repeated after a short rest. These exercises are easily done while watching television or lying in bed and can be gradually progressed in terms of numbers of contractions in each cycle and numbers of cycles/day, or by putting weights (e.g. a cushion) on the foot. 'Range of motion exercises' are useful for "warm-up" prior to isometric exercise.

More dynamic exercises, which strengthen muscles while moving the joint, can be added in, for example, step-ups (Fig. 23), walking, cycling, swimming, dancing, or exercising on a variety of machines in the home or at a gym. Resistance training is beneficial in reducing pain and stiffness and improving function in knee OA (Li et al., 2016).

Fig. 23. Stepping up and down a stair – this has an aerobic component if prolonged.



Patients who enjoy cycling should use a raised seat so the knee is not too flexed when pushing down (to avoid undue patello-femoral stress). Such dynamic exercises increase the efficiency of co-ordinated movement (neuromuscular training) and often merge with aerobic exercise. Aerobic exercise causes the heart and lungs to work harder than at rest and is recognized by an increase in pulse, increased respiratory rate and sweating.

The ESCAPE-PAIN programme integrates education about self-management and coping strategies with an individualised exercise regime. Benefits on function from this programmes have been identified in a randomised controlled trial (Hurley et al., 2007).

Adherence to exercise regime is important to pain relief and physical function at 5 years (Pisters et al., 2010). Clearly, it helps adherence if the patient selects an activity that they enjoy. It is also useful to link home exercise to a regular activity (e.g. prior to a morning shower) so it becomes part of the daily routine. A meta-analysis with high heterogeneity offers some evidence for no difference between outpatient versus home exercises in short term improvement in physical function and knee ROM (Florez-García et al., 2016; Jansons et al., 2016). Other strategies to improve adherence include keeping a diary, telephone monitoring, and involvement of spouse and friends (Roddy et al., 2005b). Trained therapists and practitioners (e.g. physiotherapists, occupational therapists, practice nurses, swimming bath and health club trainers) can advise on appropriate exercises, starting levels and rates of progression, and often give important positive feedback. Therapist-delivered pain coping skills training can also augment exercise (Bennell et al., 2015). A recent systematic review of adherence interventions in people with arthritis concluded that there was only limited evidence for any such intervention (Ezzat et al., 2015), though an earlier, Cochrane, review identified positive benefits to adherence from the use of specific strategies to enhance adherence (such as the use of goal-setting, feedback, reinforcement, diaries, pedometers); supervision; the use of refresher or 'booster' sessions; additional tools such as audio- or video-tapes to supplement supervision; and incorporation of exercise into self-management programmes (Jordan et al., 2010).

There is no agreement over the minimum effective "dose" of strengthening or aerobic exercise for OA but benefits from land-based therapeutic exercises for knee OA can be sustained for at least 2-6 months after cessation of formal treatment (Fransen et al., 2015). In general, the more the better but the frequency and intensity depend on the individual. Juhl et al. (2014) identified that better results were obtained in programmes that were supervised and had at least three sessions per week with at least 12 supervised sessions. Once exercise has been successfully adopted by the patient, enquiry concerning ongoing exercise should occur at each patient review to reinforce the importance of exercise maintenance (Bennell et al., 2014), and the safety of this long term (Quicke et al., 2015).

Further resources:

- Arthritis Research UK *Everyday exercises for everyday lives*
www.arthritisresearchuk.org/everydayexercises.aspx
- ESCAPE-PAIN
<http://www.escape-pain.org/>

- Motivate2Move
gpcpd.walesdeanery.org/index.php/welcome-to-motivate-2-move
- NHS Exercise: getting started
www.nhs.uk/Livewell/getting-started-guides/Pages/getting-started-guides.aspx

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doi:10.1016/j.joca.2010.01.013.

31

module

EULAR on-line course on Rheumatic Diseases

Osteoarthritis: treatment

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A previous version was coauthored by Zoe Paskins, Krysia Dziedzic, Burkhard Leeb

IN-DEPTH DISCUSSION II

Intra-articular injection of corticosteroid in OA

Intra-articular (IA) injection of corticosteroids is widely recommended for short-term control of marked pain in OA. Here we will consider:

- the evidence for efficacy of IA corticosteroid in OA
- pharmacology of injectates and possible mechanisms of action
- predictors of response, and
- indications, contraindications and possible side-effects

Evidence for efficacy of IA corticosteroid in OA

IA injection of corticosteroid, first proposed by Hollander over 50 years ago, is a widely used and valued therapy for OA. Although current guidelines recommend use of IA steroid for knee, hip and hand OA, relatively few RCTs have examined this treatment. Historically, the support in guidelines has reflected widespread clinical confidence in this treatment. Universal experience suggests that benefit from IA steroid can appear very quickly, usually within 24 hours, and that in some individuals benefit may last several weeks or even a few months.

A Cochrane systematic review undertaken in 2015 examined 27 randomised or quasi-randomised controlled trials that compared IA corticosteroids with sham injection or no treatment in people with knee osteoarthritis (Juni et al. 2015). This review reported a modest effect of IA corticosteroid on pain 1 to 2 weeks after treatment (Standardised Mean Difference SMD -0.48, 95% CI -0.70 to -0.27), small to moderate effect at 4 to 6 weeks (SMD -0.41, 95% CI -0.61 to -0.21), small at 13 weeks (SMD -0.22, 95% CI -0.44 to 0.00) with no evidence of an effect at 26 weeks. Similar results were found for physical function, although no effect was seen at 13 weeks. However, the review concluded that the benefits of IA corticosteroids were unclear due to low methodological quality and heterogeneity of the included studies.

There are five RCTs of IA corticosteroid for hip OA, three of which used fluoroscopic guidance (Lambert et al. 2007, Kullenberg et al. 2004, Flanagan et al. 1988) and two of which used ultrasound guidance (Qvistagard et al. 2006, Atchia et al. 2011). The two most recent studies demonstrated significant relief of both pain and function at eight weeks post injection (Lambert et al. 2007, Atchia, et al. 2011). Qvistagard et al. (2006) measured outcomes at three months but found no significant difference in pain or function at this point. However, two other studies have demonstrated difference in outcomes at 3 months; Kullenberg et al. (2004) reported significant pain reduction at 12 weeks and Lambert et al. (2007) reported significantly more WOMAC20 responders in the steroid treated group at 3 months.

Individual RCTs comparing IA corticosteroid injection vs placebo for thumb-base trapeziometacarpal (TMC) OA have not demonstrated any difference in outcomes at time points from 4 to 26 weeks (Meenagh et al. 2004, Heyworth et al. 2008). However, data from a randomised trial comparing IA triamcinolone with HA did

demonstrate beneficial effects of IA corticosteroids on pain, grip strength and hand function, persisting for 6 months (Bahadir et al. 2009). A more recent systematic review and meta-analysis of placebo controlled studies reported no effect on pain relief at 24-26 weeks (Kroon et al. 2016). This review also identified one study comparing IA corticosteroid with placebo for painful interphalangeal OA, which has a low risk of bias and reported beneficial effects on pain during movement and swelling. The acromioclavicular joint and first metatarsal-phalangeal joint are further examples of commonly injected sites where evidence of efficacy is largely anecdotal.

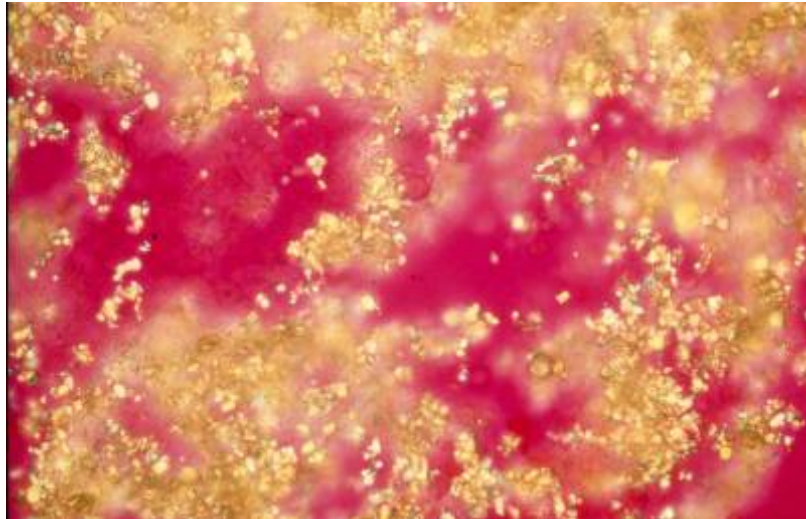
There are many caveats to the interpretation of studies of IA corticosteroid injection in OA. All the studies generally have low numbers of participants; for example, the hip trials mentioned above recruited between 36 and 104 patients with just 12 to 40 participants receiving steroid injections. The control groups for these studies also vary with some using saline injection as control, and others using local anaesthetic alone. Some RCTs have an additional intervention group of hyaluronan injections; in these studies the steroid treated groups have had additional 'sham' injections (Qvistgaard et al. 2006, Heyworth et al. 2008). Studies vary in their use of imaging to guide injections and the population that have been recruited, with most studies recruiting from secondary care where patients may have more severe disease. Furthermore, the dose of steroid varies between studies and may not reflect usual practice.

Pharmacology of injectates

Commonly used preparations for IA injection are long acting hydrophobic steroids such as methylprednisolone acetate, betamethasone acetate, triamcinolone hexacetonide and triamcinolone acetonide. All may be detected in synovial fluid 1-2 weeks after injection (Fig. 24), triamcinolone products possibly persisting the longest. A Cochrane review suggests that IA triamcinolone hexacetonide is twice as effective as IA betamethasone for pain relief at 4 weeks (RR 2.00 95%CI (1.10 to 3.63)) (Bellamy, 2006) with a further systematic review suggesting triamcinolone hexacetonide has a quicker onset of action than methylprednisolone (Garg et al. 2014). The dose of injectate is also important: Robinson and colleagues demonstrated marked difference in outcomes relating to stiffness and disability at 12 weeks when comparing 40 mg with 80 mg of IA methylprednisolone for hip osteoarthritis (Robinson et al. 2007).

There is no general consensus regarding the frequency of administration but in general the longer the interval between injections the better. One RCT comparing safety and efficacy of IA steroid versus IA saline given every 3 months for two years showed no apparent detrimental effects (Raynauld et al. 2003).

Fig. 24. Steroid particles in knee synovial fluid identified one week after injection.



Mechanism of action

Although there is little research data, experience suggests that aspiration of a swollen joint may quickly relieve pain by reducing intra-articular hypertension and that injection of a long acting steroid may prevent re-accumulation of fluid and reduce synovial inflammation. The precise mechanisms are incompletely understood, but the most relevant effects of IA steroid are likely to be on synovial membrane, with reduction of lymphocyte and macrophage activity, decrease of inflammatory mediators such as prostaglandins, collagenases and cytokines and limitation of vascular permeability. The latter may be in keeping with the observed reduction of effusion. IA steroid may also diffuse into peri-articular tissues and give additional symptom benefit at these sites.

Predictors of response

Predictors of response may be considered in terms of disease or patient specific characteristics or treatment specific characteristics. First, we will consider the specifics of treatment.

Various studies have evaluated the accuracy of blinded injections and concluded that accuracy associates with efficacy (Jones, 1993). In recent years, as the use of musculoskeletal ultrasound has become more common, a number of studies have evaluated the impact of ultrasound on both accuracy and efficacy. Ultrasound guidance increases the accuracy of IA corticosteroid injections, although blinded injections of the knee using the superolateral patellar approach have been reported as having accuracy of 87% (Maricar et al. 2013a). For IA in OA, there is, as yet, limited evidence demonstrating superior clinical efficacy and cost effectiveness to support the use of ultrasound guided injections; however, a recent systematic review suggests a short term benefit in injections of the knee (Maricar et al. 2013a).

Other treatment specific predictors of response include the type and dose of steroid which have been discussed in the sections above.

In terms of disease specific predictors, it would seem logical to consider that patients with a marked inflammatory component to their OA would have better outcomes with IA corticosteroid. Correct intra-capsular placement can influence the benefit obtained and knees with effusions may be easier to aspirate and associate with more accurate injections. However, studies that have evaluated the role of synovitis and effusion in predicting response in knee and hip OA have shown conflicting results. A systematic review of predictors to response in knee injections included studies that had evaluated the association of effusion, synovitis, structural damage, and aspiration with outcome, and concluded that there were no consistent predictors (Maricar et al. 2013b).

In studies evaluating predictors of outcome following hip injection, radiographic severity of disease and lower BMI have been associated with improved outcomes (Desmukh et al. 2011, Robinson et al. 2007,). The presence of synovitis and has been associated with improved outcome in one study (Atchia et al. 2011), but the presence of effusion was not predictive of outcome in two other studies (Qvistgaard et al. 2006, Robinson et al. 2007).

Most studies of IA have not been designed to evaluate predictors of response, and it is perhaps not surprising that the studies have yielded conflicting results, given the small numbers of participants. Hirsch et al. (2013) reviewed the evidence for predictors of response in knee and hip injections and concluded that important psychological predictors had been infrequently studied; ongoing studies are aiming to evaluate the role of psychological factors such as the presence of anxiety and depression in predicting outcomes in OA corticosteroid injections.

Indications and clinical application

The main indication for IA steroid injection is to control moderate to severe pain. In clinical practice such quick control of significant pain is very useful. It can also give the patient confidence and optimism concerning their OA and increase adherence to other OA treatments. Although some guidelines emphasise possible better benefit in patients with an effusion or an inflammatory “flare”, IA injection should not be restricted to such patients. Two additional indications for IA steroid injection are: [1] for the florid inflammation of acute calcium pyrophosphate crystal arthritis (CCPD, formerly: pseudo gout), which can associate with OA, especially knee OA in older patients; and [2] for an associated popliteal cyst to temporarily reduce synovial fluid production (usually administered by the anterior route rather than directly into the cyst).

Contraindications

The main contraindication to IA steroid injection is local infection or cellulitis. As with venepuncture, anticoagulation therapy is not a problem as long as anticoagulation is within the therapeutic range, the procedure is as non-traumatic as possible, and more prolonged pressure is placed over the puncture site following needle withdrawal. IA steroids are not recommended for haemarthrosis complicating OA or for complications such as true locking or internal derangement.

Side-effects

In general, IA steroid injection is a very safe treatment, assuming that basic aseptic precautions are observed (Courtney and Doherty 2005). Although septic arthritis is a serious potential side-effect this appears to be extremely rare. In practice, the more common side-effects are:

- Uncomfortable **facial flushing**, observed in about 10% of patients, mainly women, the day after the injection and lasting just 24-72 hours. It may be more common with triamcinolone but is largely constitutional and likely to recur with repeat injections.
- **Post-injection flares** (<5%), usually beginning shortly after injection and subsiding within several hours. These may reflect crystal-induced inflammation from corticosteroid ester crystals but also occur following injection of saline placebo.
- **Subcutaneous atrophy**, sometimes with depigmentation or telangiectasia, at the site of steroid injection (< 1%). This is mainly limited to injection of steroid into small joints or superficial periarticular structures. Triamcinolone is the main culprit and non-fluorinated steroid is recommended for small joint and periarticular injections.
- **Temporary worsening of diabetic control**, usually for just 24-72 hours. As long as the patient is forewarned this is not usually a clinical problem.

A theoretical risk to consider with multiple injections is the risk of steroid induced atrophy of cartilage and bone; a recent trial examining the effect of three monthly IA corticosteroid injections in knee OA, over a two year period, did report significant reductions in cartilage volume in the corticosteroid treated group (McAlindon et al. 2017). There is more evidence to suggest chondrotoxicity as a result of intraarticular local anaesthetic which is often coadministered with corticosteroid: lidocaine-induced chondrotoxicity arises from intra-articular infusions of local anaesthetic in a post-surgical setting, and there is evidence of a chondrotoxic effect from a single injection in animal studies (Gulihar et al. 2015). Finally, there has been concern that injections prior to joint replacement surgery may predispose to post-operative infection but this risk has not been confirmed by a recent systematic review (McMahon et al. 2013).

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Low back pain and associated syndromes

David Walsh

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LEARNING OBJECTIVES

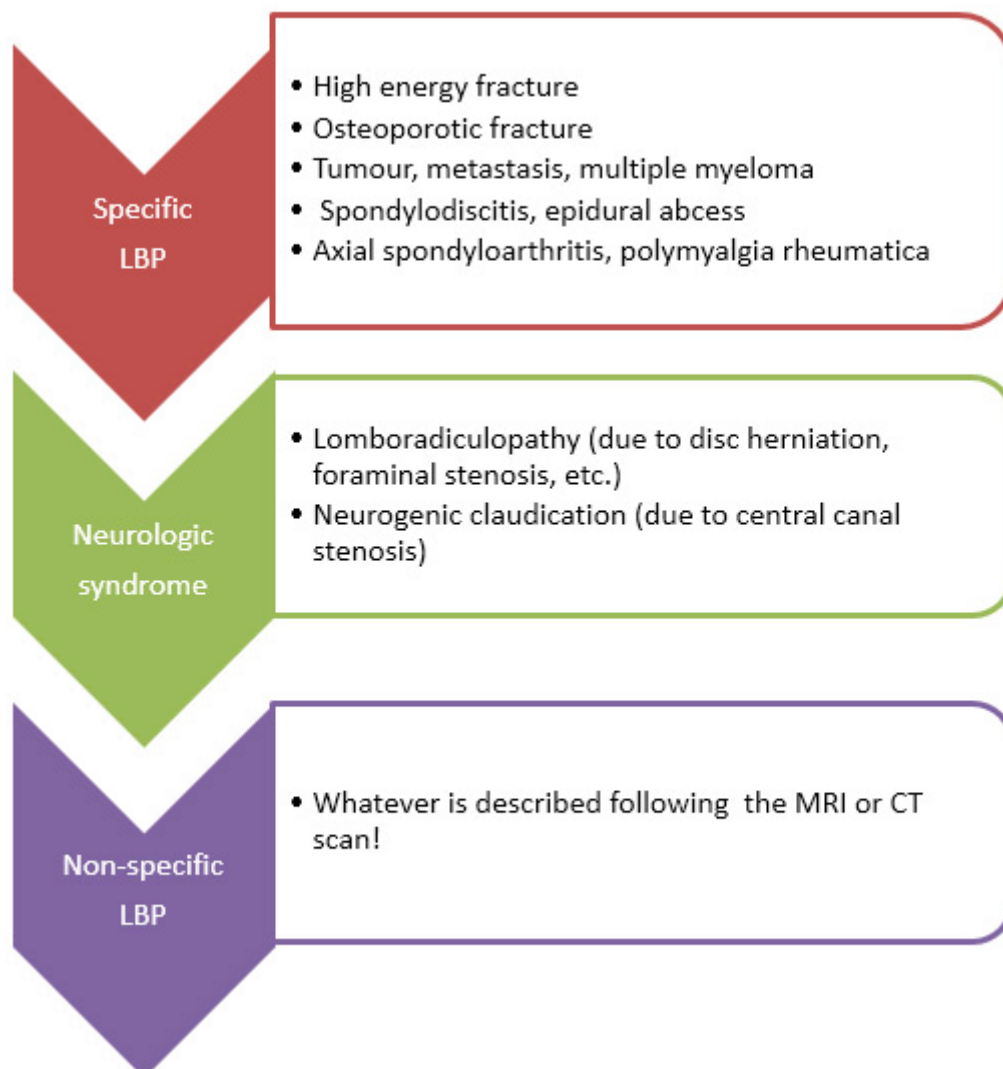
- Identify patients at risk of specific low back pain (LBP) and act accordingly
- Demonstrate knowledge of the current view of the epidemiological data and evolution of LBP
- Display a basic understanding of current theories related to non-specific LBP
- Recognise how chronicity develops in LBP and the associated main factors
- Describe the specificities related to the evaluation of patients with LBP
- Manage acute and chronic LBP based on an evidence-based approach
- Understand the value and limitations of radiological imaging in managing LBP (eg, idiopathic scoliosis, Scheuermann's disease, spondylolysis, etc)
- Identify and manage neurological syndromes originating in the spine (cauda equina syndrome, radiculopathy and neurogenic claudication)
- Discuss the benefits and limits of surgical intervention, depending on the syndrome

1. DEFINITION AND EPIDEMIOLOGY OF LOW BACK PAIN

Low back pain (LBP) is defined as pain related to the area between the lower ribs and the gluteal folds, with or without non-neuropathic leg pain, and is traditionally considered to affect a vast number of people (70–80%) at least once in their life (Balagué et al, 2012*). It affects people of all ages.

LBP is primarily a symptom encompassing several subgroups of diseases. It may be due to specific medical causes (<5%) or neurological syndromes (10%), but it is usually classified as non-specific LBP in most patients (figure 1). Non-specific low back pain has been defined as that which is not due to cancer, fracture, infection or an inflammatory disease process (*Ward et al, 2016), and the term 'non-specific' is not intended to indicate a lack of understanding of underlying pain mechanism.

Picture 1: Classification for low back pain (LBP)



The annual incidence of non-specific LBP (defined as a first episode in subjects reporting no previous symptoms or as incident pain after a pain-free period) is about 25% (Taylor et al, 2014). The figures were

similar in community-based or occupational populations. A longitudinal study based on SMS Track reported that almost two-thirds of subjects had LBP during a 1-year follow-up (Leboeuf-Yde et al, 2013).

The global burden of LBP is substantial, due to its impact on quality of life (Hoy et al, 2014). Despite limitations in the evidence, LBP ranked first out of 291 conditions studied for the number of years lived with disability, and sixth for disability-adjusted life-years. These elements explain the tremendous socioeconomic impact of LBP. Relationships with occupational activities are far from straightforward (Driscoll et al, 2014). Many people with non-specific LBP also report pain in several other musculoskeletal sites, as well as more or less non-specific symptoms unrelated to the musculoskeletal system—for example eczema, constipation, diarrhoea, dizziness, sleep problems, tiredness (Hartvigsen et al, 2013).

LBP is usually classified as acute, subacute and chronic according to its duration. LBP is considered 'acute' when it lasts from 1 day to <6 weeks, 'subacute' if it is present for 6 to <12 weeks, or 'chronic' when it is present for ≥ 12 weeks (van Tulder et al, 2006). Relapses are frequent, and 'recurrent' LBP has been defined as a new episode after a symptom-free period of 6 months (Balagué et al, 2012*). An alternative classification of LBP depends on pain trajectory; those who recover, those with a fluctuating pattern, and those with persistent back pain (Axén and Leboeuf-Yde, 2013). Improvement generally occurs during the first month following new onset LBP, but only a minority of people with persistent pain at 1 month might be pain free at 1 year. Factors that predict worse pain prognosis include higher disability, psychological characteristics such as catastrophizing, anxiety or depression, and more widespread pain (radiating into the legs, or also experienced in neck or shoulder) (*Hill et al., 2011). Almost half of people suffering an episode of LBP might not seek medical care (Ferreira et al, 2010) and public information might be equally important as is professional advice to ensure that people manage their LBP optimally.

2 Source of pain in non-specific LBP

The pathophysiology of non-specific LBP is largely unknown. Multiple spinal tissues might contribute to LBP, and heterogeneity between and within individuals makes diagnostic sub classification challenging. Treatments directed at a specific pathology should be of greatest benefit to those whose pain is caused by that pathology, and people with more severe symptoms have greater potential to benefit from an effective treatment. Stratification of patients according to pathology or severity is therefore logical, although treatment effects that clearly differentiate between classification groups have been difficult to prove, and many treatments for LBP (e.g. analgesic drugs and cognitive behavioural therapy) are generally applicable.

Since the discovery of disc herniation in 1934, back pain has been mainly related to lesions of the spine. This straightforward and common sense theory gained much acceptance during the 1970s and 1980s with the development of imaging technologies, such as computed tomography (CT scan) and magnetic resonance imaging (MRI), which emphasised the range of pathology occurring in the spine. However, neither acute nor

chronic LBP can be clearly related to these radiographic findings. A prospective study in an asymptomatic population showed that MRI repeated at the time of the first acute episode was identical to MRI performed at inclusion in the study, even in patients with severe episodes of pain and disability (Carragee et al, 2006). Numerous studies highlight the extremely high percentage of 'pathological' findings in the normal asymptomatic population (Takatalo et al, 2012; Steffens et al, 2014*), including discopathy (eg, reduced signal on T2 weighted MRI images; black disc, reduced disc height, marginal osteophytes, bulging discs, disc herniations, facet joint osteoarthritis, spondylolisthesis and annulus fibrosus tears. This clearly reduces the specificity of imaging studies. In a meta-analysis, the authors concluded that although some of these imaging findings were statistically more common among patients with chronic LBP, there was no clinical significance at the individual level since the frequency in the normal population was so high compared with the difference between the two populations (Steffens et al, 2014*).

Discs, facet joints and sacroiliac joints are each considered possible discrete sources of LBP. However, clinical tests and imaging have not definitively been shown to predict outcome from specific treatments directed at these structures (Hancock et al, 2007, Mars et al., 2015). Malik et al (2013). Anatomical classification of LBP with refined tools might yet be appropriate, and the current sparsity of supporting evidence might reflect the frequently mixed pathology in LBP, lack of specificity of clinical tests, and disappointingly low efficacy of interventions.

'Spinal instability' has been proposed as a mechanism for LBP (Panjabi et al., 1989). Gross instability due to major structural lesions (eg, fractures, tumours or infections) might certainly benefit from surgical stabilisation. Clinicians report symptoms and signs of spinal instability, radiologists describe signs of spinal instability on X-ray and MRI reports, physiotherapists use techniques to increase spinal stability and surgeons operate on patients because of spinal instability. However, many studies have highlighted the lack of a relationship between these different uses of the same concept. For example, patients with clinical signs of spinal instability do not have the features that the radiologists describe as associated with spinal instability, and neither one nor the other have ever been related to a modification of the neutral zone (Reeves et al, 2007*). Irrespective of whether 'spinal instability' is a major source of LBP, increased pain during spinal movement clearly indicates a biomechanical component. However, prevention of movement in a spinal segment by surgical fusion does not necessarily lead to pain relief, possibly suggesting other causes of pain.

Many patients can identify a specific moment or activity that initiated their LBP, but in most cases, acute LBP resolves spontaneously, regardless of the treatment. The mechanisms by which LBP might become chronic are incompletely understood, but chronic pain does not inevitably indicate persistent damage. Current evidence suggests that, far from damaging the back, maintaining activity during an acute episode of LBP facilitates effective repair. Bed rest is believed to be counterproductive. Maintaining activity might help restore strength and proprioceptive reflexes, reducing the risk of re-injury.

Inconclusive evidence from attempts at diagnostic classification based on imaging need not necessarily preclude a structural origin for LBP. Structural or biomechanical changes that cannot be easily imaged might mediate the weak associations between radiographic findings and LBP. Biomechanical factors such as sub failure magnitude loads might contribute (Rainville et al, 2011*). A non-injury model of LBP has been proposed (Indahl et al, 1998; Sorensen et al, 2010; Rainville et al, 2011*). In this model, pain arises from a complex interaction between the nerve receptors within the connective tissues of the spine and abnormal paraspinal muscle function or tension might be sufficient to explain symptoms. Lumbo-pelvic kinematics—range, speed and precision of movement, and proprioception—are modified in patients with LBP. Slight disorganisation of muscle function, demonstrated by surface electromyography during repetitive standing tasks, might predict the development of LBP in previously pain-free individuals (Holm et al, 2002*), and might be reduced after successful rehabilitation programmes.

If classification of LBP is to have clinical value, it should be matched to effective treatment. Each of the many proposed classifications is intended to predict benefit from a specific form of treatment. Classification should help explain why treatments work, complementing evidence from randomised controlled trials that they do indeed work. Analgesia following medial branch block should predict benefit from denervation. Exercise might improve strength and proprioception where they are deficient, even though pain might occur during the exercise. Helping patients to make sense of the benefit of treatments such as exercise will help them to accept and adhere to it.

3 Chronicity

3.1 Peripheral sensitisation

Despite the only weak association between imaging findings and reported pain, several observations point to peripheral mechanisms in chronic LBP. Pain is typically dependent on position and movement and blockade of afferent input (e.g. by nerve block or radiofrequency denervation) can reduce pain severity at least in some patients. Mechanisms in the periphery might drive pain even in the absence of ongoing injury, due either to structural or functional changes in the spine. Inner regions of intervertebral discs are not normally innervated. When nerves have grown into these structures as a part of the repair process (Freemont et al., 1997), it might be expected that they will become sensitive to normal biomechanical loads. Altered biomechanics in the spondylotic spine, for example increased forces transmitted through vertebral end plates due to changed properties in the intervertebral disc, might also lead to neuronal activation during normal activities. Peripheral sensitisation produces increased afferent signalling in response to a standard stimulus, and may be mediated by altered ion channel expression in primary afferent neurones. Nerve growth factor (NGF) has emerged in recent years as a key driver of peripheral sensitisation in a variety of chronic musculoskeletal conditions. Significant and clinically important pain reduction in placebo-controlled trials of blocking antibodies directed at

NGF strongly implicates this pathway in chronic low back pain, and raises hope of novel pharmacological treatments in the future (Gimbel et al., 2014).

3.2 Central sensitisation

For several decades, central sensitisation and altered central pain processing have been suggested as a unifying underlying mechanism responsible for symptoms in patients with different pain conditions—particularly, chronic LBP. In this hypothesis, enhanced pain transmission leads to a chronic state of pain in the absence of peripheral tissue injury after an initial noxious stimulus. Several mechanisms have been proposed, demonstrating participation in this increased response to peripheral stimulation affecting both the ascending and descending pain pathway. Electrophysiological constructs underpinning the ‘gate control theory’ of pain, and ‘wind-up’ parallel clinical constructs whereby barriers to afferent signals might be deficient in the central nervous system, and repetitive stimulation might lead successive stimuli to cause increased pain (temporal summation). Inadequate descending inhibitory pathways, or augmented facilitation from the brainstem might lead to the same effect. Shared pathways within the brain might link cognitive and emotional processing to pain, such that emotional components are not only essential to the definition of pain, but adverse emotional factors increase pain’s sensory component and vice versa.

The relative contributions of peripheral (in the spine or peripheral nerves) or central (spinal cord or brain) mechanisms to chronic LBP remains difficult to establish, both in populations and individuals (Roussel et al, 2013*). Widespread reduced pain thresholds, suggestive of central sensitisation overlap substantially with non-pain populations and evidence from more objective indices such as spinal RIII reflexes (RIII) have been inconclusive. However, increasing evidence suggests an alteration of brain structure, brain function and brain chemistry in chronic LBP. In comparison with pain-free controls, subjects with chronic LBP have reductions in cortical grey matter in the bilateral dorsolateral prefrontal cortex, thalamus, brainstem, primary somatosensory cortex (S1) and posterior parietal cortex. Reductions in grey matter have been reported in areas associated with inhibitory pain control. Neuroimaging using functional MRI studies provides supportive evidence for augmented central pain processing in these patients, with enhanced activity in the right insula, posterior cingulate cortices and supplementary motor area. A lack of activation of the sensory modulation system was seen in patients with chronic LBP who displayed a high degree of fear-avoidance behavioural changes. Interestingly, these cortical or subcortical changes (in the volume of grey matter and functional activity) have been shown to be reversible (neuroplasticity) and to normalise with successful treatment. It remains unclear, therefore, to what extent these changes might cause rather than merely result from (or reflect) chronic LBP.

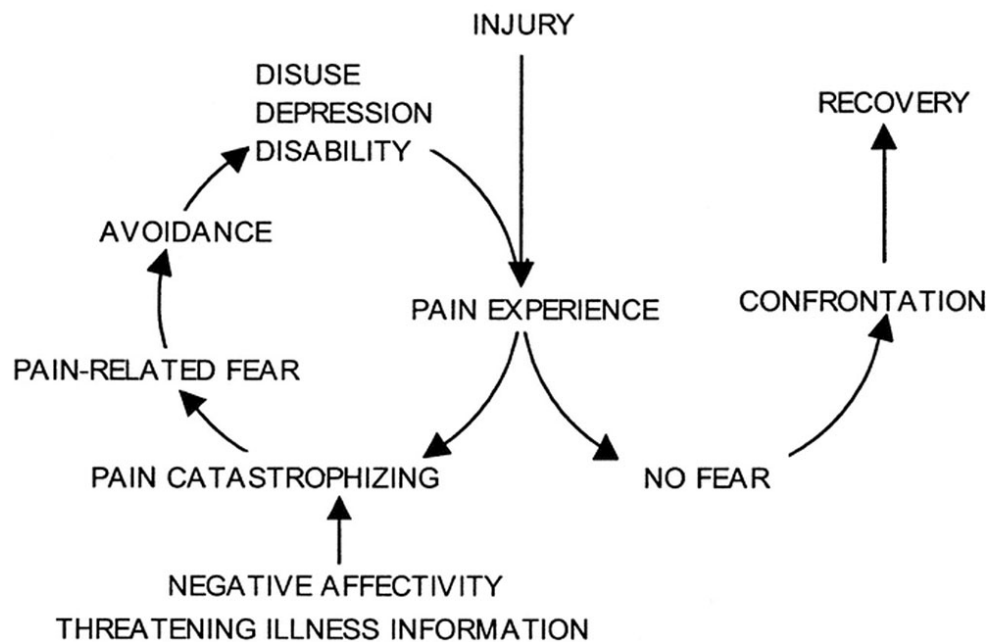
3.2 The biopsychosocial model

In 1987, Gordon Waddell, a Scottish orthopaedic surgeon, published a seminal article in the journal *Spine* (Waddell, 1987). After analysing the epidemiological evidence, he pointed out that the traditional biomedical model alone failed to explain the sharp increase in costs occurred during the past 10–20 years. He argued that a biopsychosocial perspective was more appropriate to understanding this condition because for many people the problem was not the pain itself, which is often transient, but rather their own and society's perceptions and reactions to pain. He then compared rest and active rehabilitation for LBP. Although rest was commonly prescribed, it was based on a doubtful rationale and little or no evidence of a lasting benefit, whereas harm could be expected from prolonged bed rest. By contrast, clinical studies confirming the benefit of active rehabilitation were already available. Unhelpful reactions to LBP include unnecessary avoidance of physical activity and social interaction, resulting in increased absenteeism from work and increased healthcare use. He concluded by advocating a change from the negative philosophy of rest for pain to a more active restoration of function.

Thanks to this model, many studies have confirmed that pre-existing psychological constructs (eg, depression, anxiety, fear-avoidance beliefs) are predictive of poorer outcome, as measured by pain and disability, and that these same constructs are major determinants for the transition from an acute to chronic pain state. Social and organisational factors influence the consequences of back pain, such as work absenteeism. Almost a decade later, new conceptualisations of the relationship between cognitive-behavioural factors, such as pain-related fear and avoidance and disability, and their respective role in the development of chronic pain have been developed (Vlaeyen et al, 1995). The cyclical process whereby pain produces fear, which leads in turn to behavioural avoidance, inactivity, disability and increased focus on pain avoidance, is well described in Vlaeyen's model of chronic pain pathogenesis (figure 2).

In the following years, the concepts of catastrophising (an exaggerated negative orientation towards noxious stimuli) and fear of pain and movement (also called kinesiophobia) have been largely confirmed as central to understanding why patients develop chronic LBP (Wideman and Sullivan, 2011; Parr et al, 2012; Wertli et al, 2014a; Wertli et al, 2014b). However, the description of a linear succession of events starting with pain catastrophising as the cognitive antecedent of pain-related fear, and pain-related fear as the emotional antecedent of depression and disability, may not be as simple as shown in the above model (Corbière et al, 2011). More recent studies seem to indicate that there are two parallel pathways (with some interconnections). On the one hand, there is a unique relationship between depression, pain catastrophising and long-term pain intensity and, on the other, self-efficacy (the beliefs a person holds about his or her power to affect situations), which is related to fear of movement, with both acting on long-term work disability.

Picture 2. Vlaeyen's cognitive-behavioural model of chronic pain pathogenesis. (Reproduced with permission from Vlaeyen et al, Pain 1995;62:363–72.)



Overall, there is no doubt that all these psychological dimensions are extremely important in patients with LBP. There is a large consensus that they should always be explored (see section 4.1.1.2) and present important targets for preventative measures in people with acute or subacute LBP, and for treatment in those with chronic pain (see section 5). Hence, the development of the biopsychosocial model is often reported as a turning point or even a revolution in the world of back pain. Despite this, there was a 45% increase of disability due to musculoskeletal problems between 1990 and 2010, with LBP accounting for nearly half of this figure (Driscoll et al, 2014). LBP is now a worldwide health problem affecting more than 600 million people and one of the leading causes of disability. This negative picture may reflect slowness in scientific, healthcare and occupational communities to adopt the model, rather than being a failure of the model itself.

4 Evaluation

Most guidelines recommend a triage approach for distinguishing between non-specific LBP, radicular syndromes and specific LBP cases after having ruled out vascular, abdominal or other non-musculoskeletal causes. For all patients with acute LBP, a thorough history and brief clinical examination are sufficient. The initial examination has two main purposes: first, to exclude an alternative diagnosis (hip pain, greater trochanteric pain syndrome, sacroiliitis); second, to attempt to identify any 'red flags' that may suggest a specific spinal diagnosis (van Tulder et al, 2006). Red flags are risk factors detected in the past medical history and symptoms of a patient with LBP and associated with a higher risk of a specific cause of LBP (box 1). Broadly, red flags might be classified as 'surgical' or 'medical'. Characteristics suggesting cauda equine compression (bilateral leg pain, bladder or bowel dysfunction, loss of perineal sensation or anal tone) require immediate action due to the potential for long term neurological deficit following delayed decompression.

Medical red flags merit urgent investigation to ensure appropriate treatment, but do not preclude concurrent symptomatic treatment.

Individual red flags do not necessarily link to a specific pathology, but they indicate a higher probability of a medically serious underlying condition. Multiple red flags need further investigation. In the absence of any red flags, no imaging or blood test should be performed. The validity and usefulness of red flag items have been questioned, due mainly to low specificity for treatable specific pathology. Owing to the low incidence of serious life-threatening diseases among patients with LBP, the presence of one red flag should not be over interpreted as being synonymous with infection, malignancy or fracture. Over-investigation of each benign episode of LBP imposes financial burden on health care systems, and might perpetuate diagnostic uncertainty and unhelpful healthcare-seeking behaviours. Reassurance is not necessarily reassuring because no investigation has 100% sensitivity. Repeated episodes of LBP frequently feel different to previous ones. Repeated testing might only reinforce beliefs that the initial tests might have missed something important, and, when negative, might only encourage the patient to seek a third opinion rather than accepting treatment for their problem.

Box 1: Red flag list

Age of onset <20 years or > 55 years
Recent history of trauma
Constant progressive, non-mechanical pain (no relief with bed rest)
Thoracic pain
Past medical history of malignant tumour
Prolonged use of corticosteroids
Drug abuse, immune suppression, HIV
Fever
Systemically unwell
Unexplained weight loss
Widespread neurological syndrome (including <i>cauda equina</i> syndrome)

4.1 Clinical evaluation

4.1.1 Key points from the patient history

During the first consultation with a patient with LBP, with or without leg pain, the physician has to rule out visceral disorders (abdominal, genitourinary, vascular, etc) as the main cause of symptoms or as a comorbidity, and consider several other musculoskeletal causes of pain before focusing specifically on back pain. The topography, characteristics, mode of onset, factors that increase or decrease the intensity of pain, functional

limitations and the results of previous treatments for the same kind of pain, form some of the information to be gathered to establish a diagnosis and develop a management plan.

4.1.1.1 Pain characteristics

These are frequently said to be key elements of the history and patients are often keen to describe their pain in detail. These characteristics might enable some classification into nociceptive pain, neuropathic pain and pain from central sensitisation, hence guiding future treatment (table 1) (Smart et al, 2012a; Smart et al, 2012b; Smart et al, 2012c). Current or previous pain at sites other than the low back, and other 'central' symptoms such as fatigue and psychological distress, might also suggest central sensitisation, but do not exclude local pathology in the spine. People with chronic LBP frequently satisfy classification criteria for fibromyalgia, although it is unclear whether fibromyalgia results as central consequence of chronic focal pain, or should be seen as a comorbidity which exacerbates the problem of LBP.

Table 1: Main characteristics related to three different types of back pain

Nociceptive pain	Neuropathic pain	Central sensitization pain
Pain localized in the area of injury/dysfunction.	Pain referred in a dermatomal or cutaneous distribution.	Disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors.
Clear, proportionate mechanical/anatomical nature to aggravating and easing factors.	History of nerve injury, pathology or mechanical compromise.	Pain disproportionate to the nature and extent of injury or pathology.
Usually intermittent and sharp with movement/mechanical provocation; may be a more constant dull ache or throb at rest.	Pain/symptom provocation with mechanical/movement tests (e.g., active/passive, neurodynamic) that move/load/compress neural tissue.	Strong association with maladaptive psychosocial factors (e.g., negative emotions, poor self-efficacy, maladaptive beliefs, and pain behaviour) and diffuse/non-anatomic areas of pain/tenderness on palpation.
Absence of pain in association with other dysesthesias, night pain/disturbed sleep, antalgic postures/movement patterns and pain variously described as burning, shooting, sharp or electric shock-like.		

4.1.1.2 Risk factors for chronicity (yellow flags and other flags)

Understanding the course of back pain from acute or recurrent to chronic is of paramount importance when treating people with LBP. On the one hand, most acute episodes will resolve spontaneously even without treatment but, on the other hand, chronic disabling back pain is one of the greatest health problems we are facing today. Investigating and modifying risk factors for chronic disabling LBP early in the course of an episode is a key task for clinicians. Once thought to be important, physical and radiological factors have been

repeatedly shown to have limited influence on chronicity, whereas major determinants of chronicity are psychological and social factors (Main et al, 2008). Following the idea of red flags as signals for specific back pain, these psychological and social factors have been recorded under several coloured flags. Yellow flags designate psychosocial barriers to recovery, whereas orange flags designate psychiatric comorbidities (eg, substance abuse, personality disorder, anxiety, etc). Blue flags refer to conditions in the workplace that may inhibit recovery, such as monotony, low degree of control, poor relationships or high work demands. Finally, organisational issues, such as financial reliance on disability benefits, workers' compensation problems or employer attitudes are examples of black flags. Table 2 summarises the strength of evidence and the predictive strength of the principal variables according to Main et al.

Table 2: Main factors for low back pain (LBP) chronicity

Variable	Strength of evidence [†]	Predictive strength [‡]	Flag assignment
Clinical history (LBP)	***	***	Red/yellow
Poor perceptions of general health	***	**	Yellow
Psychological distress	***	***	Yellow/orange
Depression	***	**	Orange/yellow
Fear avoidance	**	**	Yellow
Catastrophizing	***	**	Yellow
Pain behaviour	***	**	Yellow
Duration sickness absence	***	***	Yellow/blue/black
Employment status	***	***	Blue/black
Job dissatisfaction	***	***	Blue
Expectations for return to work	***	***	Blue
Physical demands of work	***	*	Black
Financial incentives	***	***	Black
Unemployment rates	**	***	Black

[†]Strength of the evidence: ***strong evidence: generally consistent findings in multiple, high-quality, scientific studies; **moderate evidence: generally consistent findings in fewer, smaller or lower-quality scientific studies; *weak, limited or conflicting evidence: one scientific study or inconsistent findings in multiple scientific studies.

[‡]Strength of the effect (the power of the predictor): ***strong predictor; **moderate predictor; *weak predictor.

Most of these factors have a direct impact on work status. Early in the course of chronicity, expectation of returning to work within the following months is an additional important measure since the longer the length of absence from work due to LBP, the lower the chances of ever returning to work. After more than 6 months' absence, the chances of returning to work are low, whatever treatment is given.

4.1.2 Key points from physical examination

Although the scientific validity of many clinical variables that contribute to the physical examination leading to diagnosis and treatment is limited, it is important to recall that patients consider history taking and a physical

examination part of a good 'back consultation'. Perhaps even more important to patients is communication and feedback (Laerum et al, 2006*). Information should be given in everyday language, consecutively and consistently during the clinical assessment and when evaluating imaging.

A brief physical examination is always an essential part of the assessment of acute LBP. Hip and sacroiliac pathologies must be excluded as both can mimic non-specific LBP. The passive straight leg raising (SLR) test is key to identifying lumbar radiculopathy due to disc herniation (figure 3). Although there is limited information in the primary care population, studies performed in patients requiring surgery show that a properly conducted SLR test (Lasègue test) is the most accurate for identifying nerve root pain. The SLR test has high sensitivity, while the crossed SLR test has high specificity. However, a review from the Cochrane Collaboration concluded that most physical tests have a poor performance when used in isolation (van der Windt et al, 2010) and it is a combination of tests that helps the clinician to make the diagnosis.

Picture 3: Passive straight leg raising test



The SLR test requires a firm level couch, with a supine, relaxed patient with trunk and hips without lateral flexion. The practitioner should ensure that the patient's knee remains extended, with the foot in the vertical

plane. The affected leg is supported at the heel and the limb gently raised (figure 3A). The angle of elevation at the onset of pain and the site of pain is recorded. The SLR test is positive if typical leg pain is reproduced. False positives due to pain on hip flexion should be excluded through hip examination. Neurological signs (myotomal or dermatomal motor or sensory deficits or reduced knee or ankle reflexes) might increase specificity, but even substantial nerve root compression can occur in the absence of reflex changes due to innervation through multiple nerve roots. Several additional techniques to increase sensitivity have been described but not validated: (a) the ankle dorsiflexed (figure 3B); (b) the hip medially rotated (figure 3C) and (c) the neck flexed (figure 3D). Reproduction of symptoms by one of these tests would be interpreted as a positive passive SLR outcome, suggesting increased root tension.

In addition to history taking and a passive SLR test, spinal palpation and motion tests are often used to verify the presence of muscle spasm, sub classify LBP mechanisms and/or to evaluate the effectiveness of an intervention. Specificity and sensitivity of these clinical tests have been difficult to determine in the absence of gold standards and incomplete benefit from specific treatments, although inclusion in the clinical examination might be important in providing a rational context for treatments which might be offered. Tenderness, unilaterally or bilaterally, on lumbar para-spinal palpation, plus increased LBP on extension (more than flexion), rotation, or combined extension/side or extension/rotation, might suggest pain originating from facet joints (Mars et al., 2015).

4.2 Subgroup classification

Heterogeneity amongst people with LBP might limit the apparent effectiveness of any single treatment in randomised trials, and provides a rationale for stratified or personalised care. Stratified care requires the identification of homogeneous subgroups of people with LBP in whom a specific treatment is likely to be effective. Personalised care requires customisation of treatment packages to the particular problems and needs displayed by the individual. Stratification based on underlying pain mechanisms remains the cornerstone of the scientific practice of medicine, but has been problematic due to the often multiple and overlapping pain mechanisms that might contribute to LBP and the uncertainty that surrounds identifying specific mechanisms in each individual. Stratification based on prognosis has benefits of empirical evidence for cost-effectiveness (*Hill et al., 2011). Groups of patients destined to do badly are likely to gain most benefit from treatment, and where poor prognosis is attributable to adverse risk factors, modifying those risk factors is most likely to be effective. One review identified 16 different diagnostic classification systems, seven prognostic systems and five treatment-based systems (Fairbank et al, 2011).

Imaging contributes little information on prognosis, and should only be used to identify specific mechanisms for which treatments might be effective, or to exclude pathologies that might pose unnecessary risk to the delivery of a treatment. Spinal surgery modifies spinal structure, and structural imaging is an appropriate

prerequisite for surgery. However, treatments offered by most primary care physicians, chiropractors, physical therapists, physiotherapists, rheumatologists, etc have effects which seem to depend little, if at all, on findings from spinal imaging (McCarthy et al, 2012; Wang et al, 2012; Widerström et al, 2012; Billis et al, 2013; Hall, 2014). A common perception that imaging is required to ‘see the cause of the pain’ before treatment can be planned is unjustified by evidence, can delay effective treatment (for example avoiding exercise until a scan has ‘shown it to be safe’), and can increase healthcare costs. Even in acute sciatica, imaging evidence of nerve root compression only weakly predicts outcome from epidural steroid injection (Ekedahl et al., 2017), although precise localisation of pathology might be important to ensure appropriate location of transforaminal injection.

The STarTBack screening tool is designed to be used by primary care physicians or therapists at the first point of contact for an episode of LBP, and has the best validation process, including randomised clinical trials and large, ‘real-life’, cohort studies (*Hill et al., 2011). It was developed as a ‘prognostic’ system, and focused on modifiable risk factors which inform treatments offered to high risk subgroups. It contains nine items: four deal with the pattern of pain and disability, four cover potentially modifiable psychological aspects (kinesiophobia, anxiety, depression, and catastrophism) and one scores the level of bothersomeness. The tool can be used to stratify patients into 3 groups with low, medium or high risk of chronicity. Providing early intensive treatment, incorporating both physiotherapeutic and psychological interventions, to the highest risk group improved outcomes, while limiting treatment to advice alone for those with good prognosis reduced healthcare costs (*Hill et al, 2011). STarTBack effectively stratified people with LBP with or without sciatica. People who have already failed first line treatments, however, have already identified themselves as being in a poor prognosis group, and STarTBack might have less utility as a stratification tool in secondary care settings.

4.3 Questionnaires, patient-reported outcomes

Patient-reported outcomes are data collected by self-administered questionnaires. Although they have been criticised for their lack of objectivity, they have shown a better correlation with clinical outcomes in patients with LBP than the results of physical examinations and imaging studies. This may be because pain is, by definition, an individual experience that cannot be objectively revealed. Moreover, patients’ self-perception is an important driver in their decision to seek or act on medical advice and, consequently, in costs generated. Once used mainly in clinical trials, these questionnaires are now advocated for use in the clinical setting. Given the multidimensional nature of pain, no single outcome measure is sufficient. Several validated tools exist, and the most popular have been cross-culturally adapted to several languages (table 3).

Table 3: The most frequent patient-reported outcomes in low back pain

Dimension	Examples of patient-reported outcomes
Pain	Visual analogue scale Numeric rating scale
Back-specific function	Oswestry Disability Index Roland and Morris Disability Questionnaire
Kinesiophobia	Tampa Scale Fear-Avoidance Belief Questionnaire
Anxiety and depression	Hospital Anxiety and Depression Scale Beck Depression Inventory
General health	Short Form Health Survey (SF-36, SF-12) Euroqol-5 Dimensions
Multidimensional	Core Outcome Measures Index Dallas Pain Questionnaire

The Core Outcome Measures Index, a brief multidimensional questionnaire, has been developed and validated in several languages (Mannion et al, 2005). This tool includes a series of questions about the domains of pain (back and leg/buttock pain intensity), each measured separately on a 0–10 numerical graphic rating scale, including function, symptom-specific well-being, general quality of life and social and work disability (each on a five-point Likert scale). It has gained wide acceptance and is at the centre of the evaluation forms used by the European Spine Registry (also known as Spine Tango).

4.4 Imaging in LBP

Diagnostic imaging tests (including X-ray examinations, CT and MRI) are not routinely indicated for LBP. They serve one major purpose: to identify specific pathology for which treatment would be considered (e.g. surgery for cauda equina or radicular pain, radiotherapy for metastatic cancer, medical treatments for ankylosing spondylitis). Imaging should be reserved for patients who are considering surgery or those in whom a serious disease (based on red flags) or radicular syndrome is strongly suspected. Patients might have high expectations that imaging will be instigated by the clinician, but inappropriate imaging in patients with LBP has several major drawbacks without improving outcome (Chou et al, 2009). Inappropriate imaging increases costs for society and might cause iatrogenic harm, leading to worse scores on back-specific functional and generic health-related quality of life questionnaires (Graves et al, 2012; Graves et al, 2014; Webster et al, 2014). Patient and public expectations from spinal imaging should be carefully managed both in the clinic and in society, in order to help optimise risks and benefits.

4.4.1 Plain radiography

The anteroposterior and lateral views demonstrate the general anatomy of the spine and allow a gross assessment of bone density and architecture, including the presence or absence of lumbosacral transitional

alignment and disc and vertebral body height. However, soft tissue structures are not properly evaluated by radiography. Oblique views show the pars interarticularis in profile and are useful for diagnosing spondylolysis when this is suspected. Other special views include flexion and extension views to assess instability, and an angled view of the sacrum to assess sacroiliac joints for ankylosing spondylitis.

4.4.2 Computed tomography

CT uses X-rays to generate cross-sectional images of the spine. Although spinal images can be obtained only in the frontal or slightly off-frontal plane, sagittal and coronal reconstruction can be produced. CT can accurately depict the foraminal and extraforaminal nerve root because surrounding fat provides natural contrast.

4.4.3 Magnetic resonance imaging

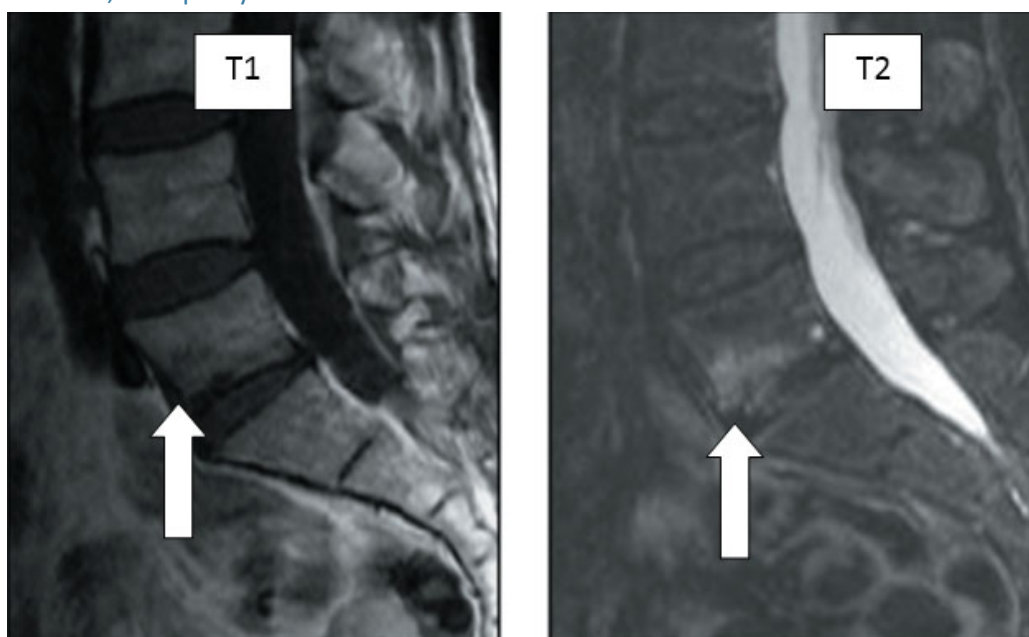
MRI has several advantages over CT for spinal imaging, including both visualisation of soft tissues and absent radiation risk, but claustrophobia can be problematic, as can be contraindications such as metallic implants. Different parts of the disc (nucleus pulposus and annulus fibrosus) can be distinguished from one another; ligaments can also be visualised. MRI offers better visualisation of the vertebral marrow and the contents of the spinal canal. A disadvantage of MRI is that it cannot be used to visualise cortical bone directly. In 1988, Michael T Modic, professor of radiology and neurology at Case Western University, Cleveland, USA, proposed a classification of MRI changes linked to disc disease and his name has been associated with these changes ever since. The 3 types of Modic changes, common observations in MRI (Takatalo et al, 2012), refer to signal intensity changes in endplates of affected discs (table 4). Type I represents oedema and the presence of an inflammatory reaction has been reported (figure 4A). Histological examination shows disruption and fissuring of the endplate and vascularised fibrous tissues within the adjacent marrow. Type II is the most common type of change, representing fatty degeneration of subchondral marrow (figure 4B). Histological examination shows endplate disruption with yellow marrow replacement in the adjacent vertebral body. Type III correlates with extensive bony sclerosis on plain radiographs (figure 4C). Histological examination shows dense woven bone and, thus, no marrow to produce a MRI signal. Progression from type I to type II has been frequently reported (as well as a mixed type combining types I and II) and may take several years. Changes from types I or II to type 0 (normal) or from type 0 to type II are also common.

Table 4: The three main forms of Modic changes

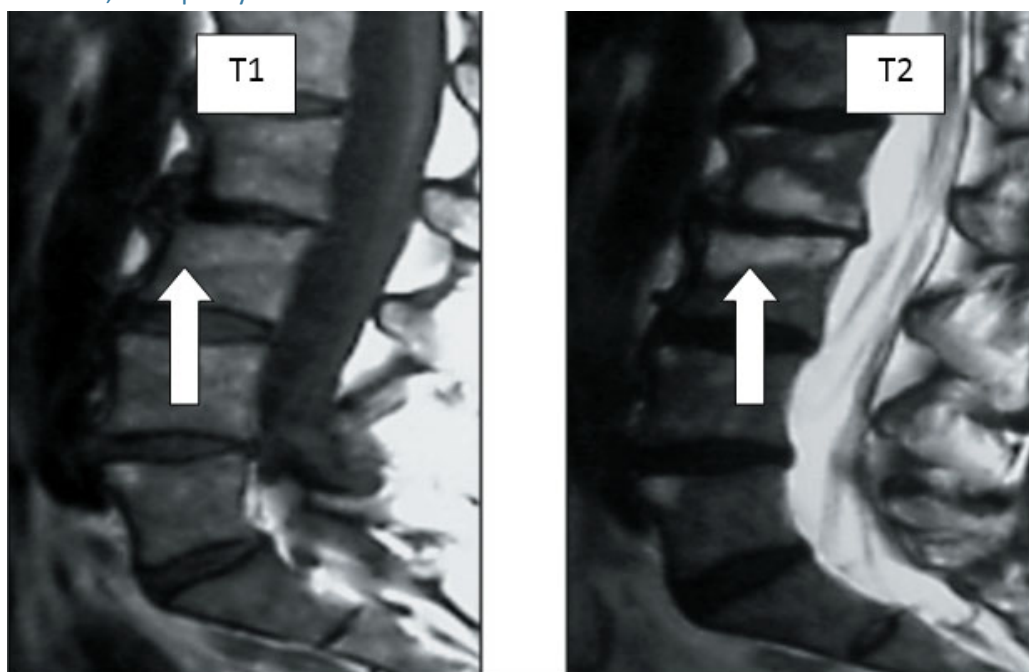
Type	T1	T2	Significance
I (Picture 4A)	↓	↑	Oedema Inflammatory reaction
II (Picture 4B)	↑	→ (or slight ↑)	Fatty degeneration
III (Picture 4C)	↓	↓	Bony sclerosis

Picture 4: The 3 main forms of Modic changes

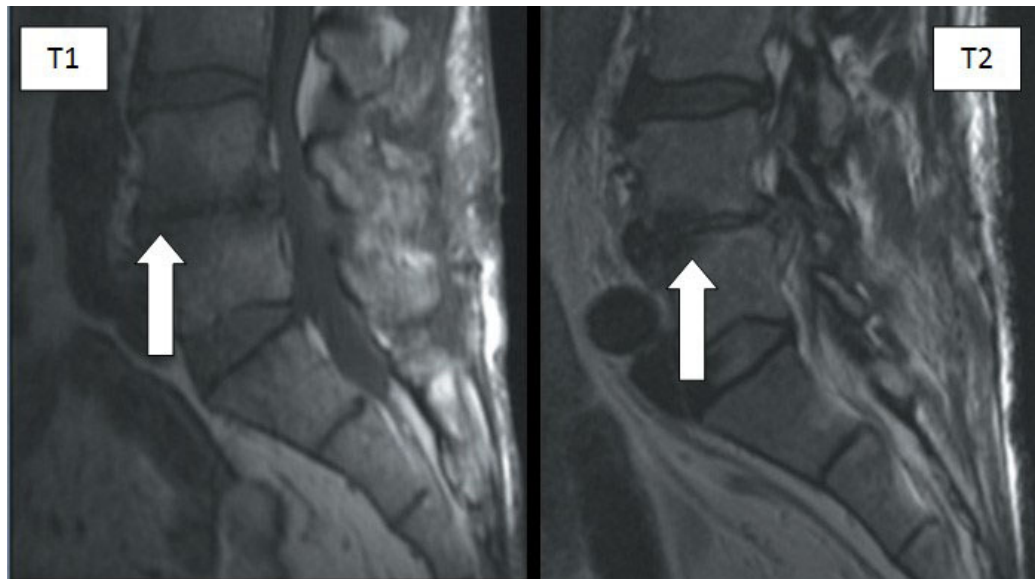
Picture 4A: MODIC 1, discopathy L5-S1



Picture 4B: MODIC 2, discopathy L2-L3



Picture 4C: MODIC 3, discopathy L4-L5



5 Treatment

It is important to recall that only a minority of patients with non-specific LBP seek medical attention. An economic study including a random sample of some 38 000 people with LBP showed that different clusters of healthcare system users can be identified. The vast majority ($n = 35\,675$) remain 'low users' with three other subgroups that changed from 'high' to 'low' care use ($n = 1272$), or from 'low' to 'high' ($n = 807$) and, finally, a small group ($n = 237$) that remained 'high' users of the healthcare system over the 2 years of the study (Ruetsch et al, 2013).

5.1 Guidelines

Over the past 15 years, many guidelines from different countries or societies have been published. Overall, there are few differences, except for some adaptations related to increased knowledge in some areas. Importantly, it has been shown repeatedly that compliance with guideline recommendations—by refraining from early imaging and other aspects of patient management—significantly reduces costs (Graves et al, 2014; Webster et al, 2014). Guidelines consistently recommend patient education and physical activity, advise against shoe insoles or orthoses and lumbar supports. Recommendations for or against spinal manipulation or mobilisation are less consistent. Differences between guidelines might in part reflect different perspectives and purposes. For example, the UK National Institute for Health and Care Excellence (NICE) adopted a health economic perspective (*Ward et al., 2016), which excluded costs to employers and social care. Health care costs, and the thresholds at which benefits might be considered value for money might vary between countries. Not all interventions are equally tested through randomised controlled trials, leaving scope for variation in expert opinions between guideline development groups.

The full NICE guidance (NICE CG173) lists 41 recommendations, plus additional links to other relevant guidance for the medical management of neuropathic pain (*Ward et al., 2016). Positive guidance recommends consider stratification (e.g. STarT Back at first point of contact), provide information and encouragement to continue normal activities and return to work, and consider a group exercise programme. Analgesic approaches should consider non-steroidal anti-inflammatory drugs or, if contraindicated, weak opioids with or without paracetamol. Combined physical and psychological programmes should be considered for people with persistent symptoms or earlier if there are adverse risk factors.

Qualified recommendations for manual or psychological therapies indicate that they should only be offered as part of treatment packages that include exercise. Paracetamol should not be offered alone, and opioids not routinely for acute LBP nor at all for chronic LBP. Important negative recommendations are to not offer foot orthoses, rocker sole shoes, belts or corsets, traction, acupuncture, ultrasound, percutaneous or transcutaneous electrical nerves stimulation, nor interferential therapy. NICE recommended that antidepressants, anticonvulsants or spinal injections should not be offered for LBP (as opposed to sciatica).

5.2 Additional comments

Previously mentioned treatments represent only a minority of even the 200 that were cited in a non-exhaustive review published in 2008. Although at times frequently prescribed, most have not been validated. It is important also to recall that the mean clinical benefit above placebo effects of most treatments reporting efficacy is small (about 10–15 points on a 0–100 scale for pain intensity reduction).

5.2.1 Information and advice

Great emphasis has been placed on information and reassurance, especially for acute and subacute LBP. Information can contribute to iatrogenic disability when it is based on pathological diagnosis for a work-related injury, a description of the anatomy and biomechanics of the spine, activity restriction or modification, and ergonomic advice (van Tulder et al, 2006). By contrast, advice to stay active and to continue ordinary activities as normally as possible, with an emphasis on advantageous coping strategies rather than being an ‘avoider’, produce a faster recovery, faster return to work and less disability. It has been shown also that physicians believing in the biomedical model of injury—rather than the biopsychosocial model—can have a negative impact on the future of their patients if they prescribe more bed rest and longer sick leave.

5.2.4 Spine surgery

Retrospective data from the USA between the mid-1990s and the first decade of this century showed a dramatic multiplication in the use of imaging, opiates and spinal injections, and also of the number of surgical procedures. These procedures are mainly spinal fusions, with a four- to fivefold increase over the past 15 years but without any clear benefit for patients. According to most guidelines, the role of surgery for LBP is very

limited. The rationale for surgery is weak as the demonstration of segmental instability (which might justify a segmental fusion) remains unclear.

Systematic reviews have shown that the results of surgery are comparable to those of structured multidisciplinary programmes (cognitive behavioural therapy and exercise rehabilitation) (Bydon et al, 2014). Long-term follow-up (9 and 11 years, respectively) have shown no differences in outcome between the surgical and the conservative arms in controlled trials. Moreover, there are no valid criteria for the selection of candidates who are most suitable for surgery. However, a pooled analysis of three randomised clinical trials showed that one-quarter of patients were able to stop analgesic treatment in the long term (Mannion et al, 2013*). Randomised controlled trials might be subject to selection biases (for example if participants were only recruited if their perceived need for surgery were in doubt), and it remains possible that there is a subgroup of patients with severe chronic LBP who might benefit from surgery. However, further research would be needed to enable any such responsive subgroups to be identified and to further justify the risks of surgery in clinical practice.

6 LBP entities possibly related to specific radiological findings

6.1 LBP in the adolescent

In past decades, the most prevalent theory for juvenile LBP could be summarised as almost the denial of the existence of non-specific pain. The corollary was aggressive investigations to rule out serious or even life-threatening diseases in these cases. There is now sufficient evidence to show that the most common diagnosis among adolescents with LBP is non-specific LBP, even though the probability of identifying a specific lesion (mainly spondylolysis or spondylolisthesis) is higher than among adults.

This section summarises some basic information about three spinal disorders often seen in adolescents

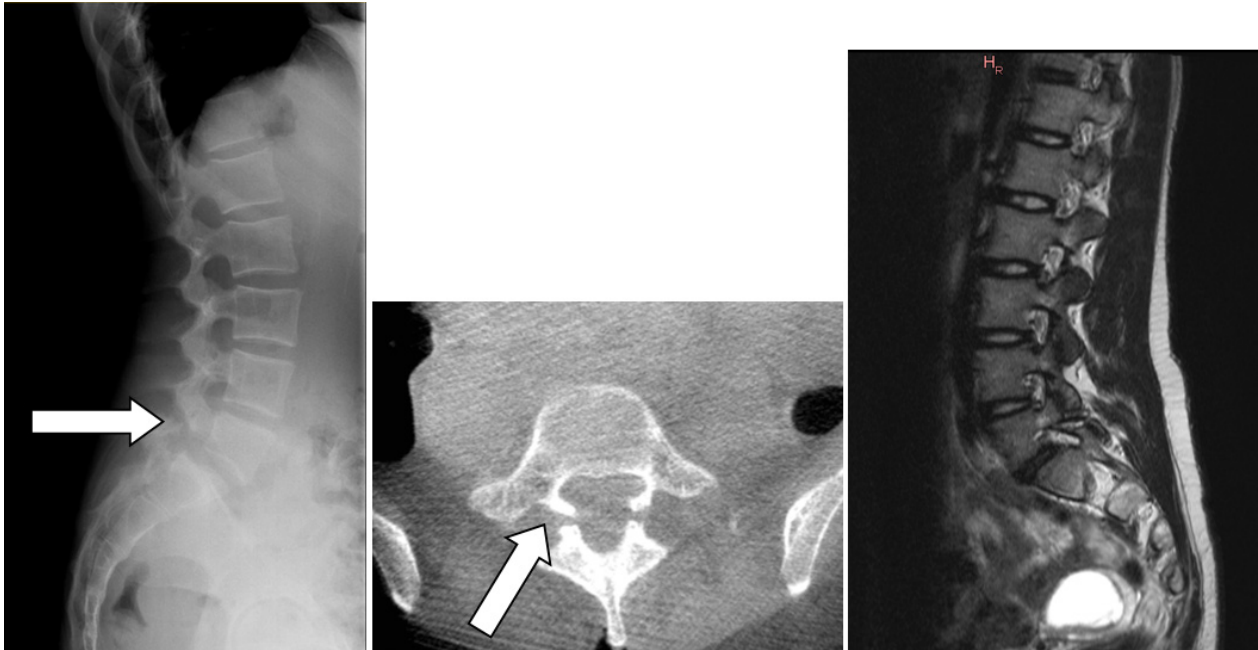
6.1.1 Spondylolysis/spondylolisthesis

Spondylolisthesis was described as early as 1782 by Dr Herbinaux, a Belgian obstetrician. Despite its long history and its prevalence (about 6% of the population), our understanding of the condition is still incomplete. It is generally admitted that spondylolysis or spondylolisthesis are not present at birth and probably appear when children can stand. L5 vertebrae are involved in the vast majority of cases. Familial clustering was identified by the first epidemiological studies more than 50 years ago. The main mechanism of injury (ie, lysis) of the pars interarticularis is usually a combination of repetitive flexion, extension or rotation of the lumbar spine. Acute traumatic injury is rare. An increased prevalence is found among adolescents with a high level of sporting activities (eg, gymnasts). In most series, there is a clear male predominance.

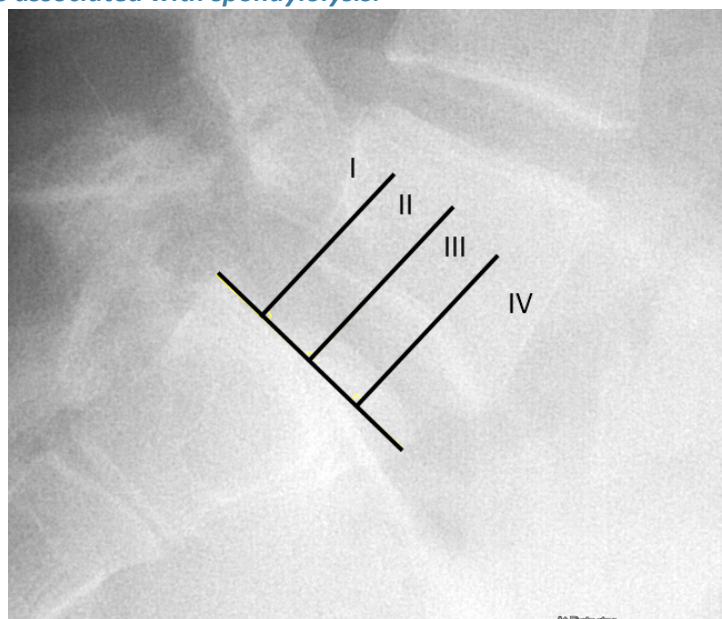
A study with a 45-year follow-up showed that spondylolisthesis appears in two-thirds of patients with spondylolysis, but none of these patients ended up with a slip of >39% (grade II) (Beutler et al, 2003). Severe

slips are uncommon, but do exist. These cases (grades III and IV) show more frequent symptoms, including neurological findings. Some predictors of high-grade slip have been identified: female sex; dysplastic slip; presence of a grade II spondylolisthesis during growth years; a high slip angle (kyphosis at the spondylolisthesis level); a familial history of higher grade spondylolisthesis and presence of hyperlaxity or connective tissue disorder. Many individuals are asymptomatic. Clinical signs may include altered gait, limited forward flexion, a palpable step-off of spinous processes and hamstring tightness (figures 5 and 6).

Picture 5. L5-S1 bilateral spondylolysis with grade I spondylolisthesis in a 16-year-old girl



Picture 6. The four grades of spondylolisthesis. The grading from I to IV is obtained by dividing the sacral plateau of S1 into four equal parts. A fifth stage, spondyloptosis is an uncommon finding. The image shows a grade I spondylolisthesis associated with spondylolysis.



Modern imaging studies can identify pre-lytic stages of spondylolysis. Different studies have shown that hyperflexion and hyperextension radiographs are not helpful as many patients have hypomobile segments. For safety and economic reasons, routine dynamic radiographs should not be obtained for adolescents. Conservative management includes bracing, which leads to excellent lesion healing when diagnosed at a pre-lytic stage (bone oedema) or at the beginning of the fracture, but clearly before the two bony extremities exhibit cortical bone. Surgery is recommended for patients with progressive high grades.

6.1.2 Scheuermann's disease

Scheuermann's disease is usually defined as a focal developmental kyphosis, but the causes are still not understood, although it was recognised more than 100 years ago. The main characteristics include an irregularity of the endplates of the vertebrae, sometimes with Schmorl's nodes and/or other vertical (ie, intracorporeal) disc herniations, disc narrowing and wedging of the vertebral bodies. For diagnosis, involvement of one vertebral body is sufficient for some authors, whereas others require at least three consecutive vertebrae. Wedging $\geq 5^\circ$ in three consecutive vertebral bodies is one of the usual criteria. Some consider that the thoracic kyphosis should be greater than 35° or 45° .

The diagnosis is frequently made around the time of puberty. Pain is often reported, but not always, and the functional capacity is usually good. Pulmonary function is not reduced unless the kyphosis exceeds 100° . A neurological examination is usually normal and hamstring tightness is often seen. The differential diagnosis includes compression fractures, spondyloepiphyseal dysplasia tarda, osteogenesis imperfecta (type I), neurofibromatosis and connective tissue disorders (eg, Marfan, Ehlers–Danlos). Conservative management relies on physical therapy and bracing. Physical therapy may alleviate pain, but has no effect on deformity. Bracing can improve the angle of kyphosis in patients with significant growth remaining. Severe deformities may require surgery.

6.1.3 Adolescent idiopathic scoliosis

By definition, this section excludes scoliosis that appears earlier in life (ie, congenital, infantile and juvenile scoliosis), and those types with a clearly identified aetiology. These are dealt with by specialised paediatric orthopaedic surgeons and rarely managed by rheumatologists (Sponseller et al, 2012).

The usually accepted definition of adolescent idiopathic scoliosis is that of a scoliosis of unknown cause with a Cobb angle $>10^\circ$ beginning after the age of 10 years (box 2) (Weinstein et al, 2008b; Makurthou et al, 2013). The aetiology remains unclear, although it is generally accepted that this is a multifactorial disease with genetic predisposing factors (table 5) (Altaf et al, 2013). Adolescent idiopathic scoliosis is neither associated with a decreased life expectancy nor should it be the origin of major pain. The major problems are cosmetic

and psychosocial, related to the progression of the curve, respiratory (not comparable with the dramatic consequences of scoliosis due to poliomyelitis) and, to some extent, pain.

Box 2 Classification of scoliosis

1. Congenital (associated with segmentation or formation defects)
2. Syndromic
2.1 Neuromuscular
2.2 Associated with neurofibromatosis or connective tissue diseases (Marfan's disease, Ehlers-Danlos)
3. Idiopathic (subdivided by age of diagnosis into the following categories)
3.1 infantile (from birth up to 3 years of age)
3.2 juvenile (from 3 to 10 years of age)
3.3 adolescent (from 10 years to skeletal maturity) that can be classified topographically according to Lenke into the following six main categories:
1. Main thoracic
2. Double thoracic
3. Double major
4. Triple major
5. Thoracolumbar/lumbar
6. Thoracolumbar/lumbar/main thoracic
3.4 adult

Table 5 Main pathogenic hypotheses underlying idiopathic scoliosis (Reproduced with permission from Altaf et al, BMJ 2013;346:f2508)

Intrinsic factors	Extrinsic factors
1. Genetics (well described; different inheritance modes; numerous candidate regions/genes have been suggested)	1. Left-right asymmetry (<u>not</u> handedness)
2. Growth and development of the spine (altered growth of the vertebral bodies and posterior elements; no evidence of a causative role)	2. Nervous system (decreased sensory input, dysfunctions at different sites, uncoupled neuro-osseous growth, etc.; role unclear in idiopathic scoliosis)
3. Intervertebral disc development asymmetry	3. Paravertebral muscle weakness
4. Spinal ligaments: no evidence in humans	4. Ribs (role unclear in idiopathic scoliosis)
5. Mechanics of the upright spine (type of rotatory instability of the immature spine).	5. Osteoporosis/low bone mineral density
	6. Increased platelet calmodulin levels (role unclear in idiopathic scoliosis)
	7. Melatonin (role unclear in idiopathic scoliosis)

**Some of the factors are based on animal models of scoliosis, consequences of surgical procedures, diseases, etc.*

The most relevant aspects for a clinician who does not specialise in deformity are the ability to identify the main prognostic factors and atypical elements requiring referral and/or MRI studies. A full history and clinical

examination, including three-planar spinal posture from the back and the side, is important and should encompass at least the elements listed in table 6 (Hresko, 2013).

Table 6 Key points from history and physical examination in idiopathic scoliosis (Reproduced with permission from Hresko, *N Engl J Med* 2013;368:834–41)

History	Full physical examination (from the back, side, and front)
Birth history	Gait
Developmental milestones	Skin inspection (signs of neurofibromatosis, dysgraphia signs, etc.)
Familial history of spinal deformity	Spinal balance with plumb line
Physiological maturity (growth spurt and menarchal status)	Shoulder and iliac crest elevation
Past medical and surgical history (elements that correlate to a syndrome or congenital condition)	Flank asymmetry
Pain history (nocturnal? constant? associated symptoms or signs?)	Adams forward bent test (at different levels)
Evolution of the deformity (rapid progression suggest a non-idiopathic aetiology)	Sagittal plane balance
Neurologic symptoms (weakness, sensory changes, gait problems, bowel or bladder control changes, etc.)	Anterior thoracic wall
	Full neurologic examination
	Joints range of motion, laxity, deformity, etc.
	Hyper laxity criteria
	Pubertal stages (auto-evaluation forms have been used with different accuracy rates)

The main prognostic factors are the maturity (menarchal status and Tanner stages), the magnitude of the scoliosis (Cobb's angle) and the remaining growth (Risser stage). As a general rule, a Cobb angle $>30^\circ$ represents a significantly increased risk of aggravation throughout adult life, whereas curves below that threshold have a very limited risk of progression. Double curves and scoliosis in girls have an increased risk of progression. Some characteristics are reassuring in adolescent scoliosis, thus allowing a rheumatologist with some experience of spinal disorders to take care of these patients. Other characteristics should be considered atypical and require prompt referral to a specialised spine orthopaedic surgeon (table 7).

Table 7 Key elements in the evaluation of adolescent scoliosis

Reassuring elements	Suspicious elements
Right thoracic, right thoracic and/or left lumbar, or left thoracolumbar curve.	Left main thoracic curve
Absence of sagittal imbalance, thoracic hypokyphosis	Hyperkyphosis combined with a thoracic scoliosis (increased risk of associated Arnold-Chiari malformation and syringomyelia).
Curves <20° without sharp angulation	Sharply angulated curves, curves with congenital bony anomalies, and very large curves
Growth spurt finished Sufficient maturity (Tanner stages, menarche, Risser stages)	
Absence of pain	Substantial pain
Normal neurologic examination	Neurologic complaints, bladder problems, neurologic signs e.g., muscle weakness and/or long tract signs
	<i>Pes cavus</i> Severe joint laxity

The evaluation requires full-length standing posteroanterior and lateral radiographs of the spine. For protection from radiation, an EOS system should be used when available. In addition to the list of suspicious elements cited previously, a full MRI study of the spine (from the craniocervical junction to the sacrum) and/or referral to a deformity specialist should be carried out for cases of neurofibromatosis, midline cutaneous abnormalities (associated with neural tube defect) and kyphotic apex of the curve.

The efficacy of bracing has been demonstrated by reviews and randomised clinical trials (Weinstein et al, 2013). It depends on compliance, and wearing a brace for ≥ 13 hours a day has a success rate >90%. For highly compliant patients, the number needed to treat to prevent one operation has been estimated as 4 (95% CI 2 to 7). Evidence also supports specific physiotherapy exercises aiming at autocorrection. In contrast, electrical stimulation has not been shown to be effective, and manipulations or massage have not been evaluated in high quality studies; thus no definite conclusion can be drawn. Surgery can be considered when progressive scoliosis exceeding 45° in an immature skeleton or progressive and/or associated pain occurs after skeletal maturity.

6.2 Inflammatory LBP

Inflammatory back pain is still not perfectly defined (Burgos-Vargas and Braun, 2012; Weisman, 2012). Diagnostic classification of axial spondyloarthritis prior to the emergence of radiographic features is important both in predicting prognosis and offering early and appropriate treatment (Corbett et al., 2016). Different sets

of criteria (mainly classification criteria) with some differences in sensitivity and specificity have been developed in order to identify an increased risk of axial spondyloarthritis (table 8).

Table 8 Comparison of published sets of criteria for inflammatory back pain (Backland et al, 2013; Solmaz et al, 2014)

Criteria	Calin et al	ESSG	Berlin 1	Berlin 2	ASAS
Pain location	Back	Neck/dorsal/back	Low back	Low back	
Age (now)	Any	Any	<50 years	<50 years	
Duration 3 months	✓	✓	✓	✓	
Insidious onset	✓	✓			✓
Age at onset of pain	<40	<45		<30	<40
Morning stiffness >30 min	✓ (duration not specified)	✓ (duration not specified)	✓	✓	
Pain improves with exercise	✓	✓			
Pain improves with activity/not with rest			✓	✓	✓
Pain awakens during 2 nd half of night			✓		✓ (no precise timing + improvement upon getting up)
Alternating buttock pain			✓		

ASAS, Assessment of the Spondyloarthritis International Society; ESSG, European Spondylarthropathy Study Group.

Although the odds for axial spondyloarthritis are tripled when inflammatory LBP is present, an important minority of patients classified as non-specific LBP (up to 25% according to some studies) will present with inflammatory back pain (Hamilton et al, 2014). MRI might reveal pre-radiographic axial spondyloarthropathy, and treatment of severe pre-radiographic disease with TNF-alpha blocking agents has been associated with good results (Corbett et al., 2016).

From the description of the Modic changes in the endplate, clinicians have been most interested in the so-called 'inflammatory changes' or Modic 1 changes, that might occur in people without spondylarthropathy (Kääpä et al, 2012). Although still controversial, there is some evidence that Modic 1 changes are infrequently found in asymptomatic individuals and are indeed associated with an inflammatory pattern of pain, which is

not the case for Modic changes 0, 2 and 3. The size of these lesions shows no direct correlation with clinical symptoms, although the clinical symptoms tend to be fewer when the inflammatory images are of a mixed type (Modic 1 and 2). Patients with Modic 1 changes may also have a worse outcome at 1 year, having greater pain and being less likely to return to work (Keller et al, 2012).

Two Danish articles highlighted the possible involvement of *Propionibacterium acnes* in patients developing Modic 1 in the months after an episode of sciatica due to disc herniation (Albert et al, 2013a; Albert et al, 2013b). The role of infectious agents and the value of antibiotic treatment in this cohort of highly selected patients were widely discussed, with different hypotheses proposed. However, these results remain controversial.

Several studies have suggested that patients with Modic type 1 changes have a better response to NSAIDs and corticotherapy than those with other Modic patterns (0, 2 or 3). Initial reports have described a better outcome after spinal fusion (spondylodesis), but this has not been confirmed.

6.3 Diffuse idiopathic skeletal hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic non-inflammatory condition characterised by ossification of the enthesis. Although all entheses can be affected, calcification of the anterior longitudinal ligament of the spine is most characteristic (Utsinger et al, 1976). The prevalence and incidence are undetermined, but DISH seems to affect mainly men aged >40 years. Obesity, hypertension, diabetes mellitus, hyperinsulinaemia, dyslipidaemia and hyperuricaemia are metabolic conditions that have all been associated with DISH.

DISH is often asymptomatic. Spinal stiffness is the most common complaint, whereas spinal pain is not usually a major problem, although it is reported by 30–50% of patients (Mata et al, 1997). Extraspinal lesions have been described for most joints but the most problematic is hip involvement, which can sometimes be associated with extensive joint destruction requiring arthroplasty.

The radiological changes are mainly located in the right side of the thoracic spine where the bony appositions tend to form a more or less complete flow of ossification (Resnick and Niwayama, 1976) (figure 7).

Ossification mainly affects the anterior part of the cervical spine and, on a lateral view, these images have been compared with a candle flame. These ossifications can rarely compress the oesophagus, causing dysphagia and disorders of the larynx or pharynx or of the lung. Myelopathy can result from ossification of the posterior ligaments. At the lumbar spine level ossifications are more horizontal, facing each other and forming a 'lobster claw', and are often asymptomatic.

Figure 7 Diffuse idiopathic skeletal hyperostosis. (Source: Cofer, <http://www.lecofer.org>)



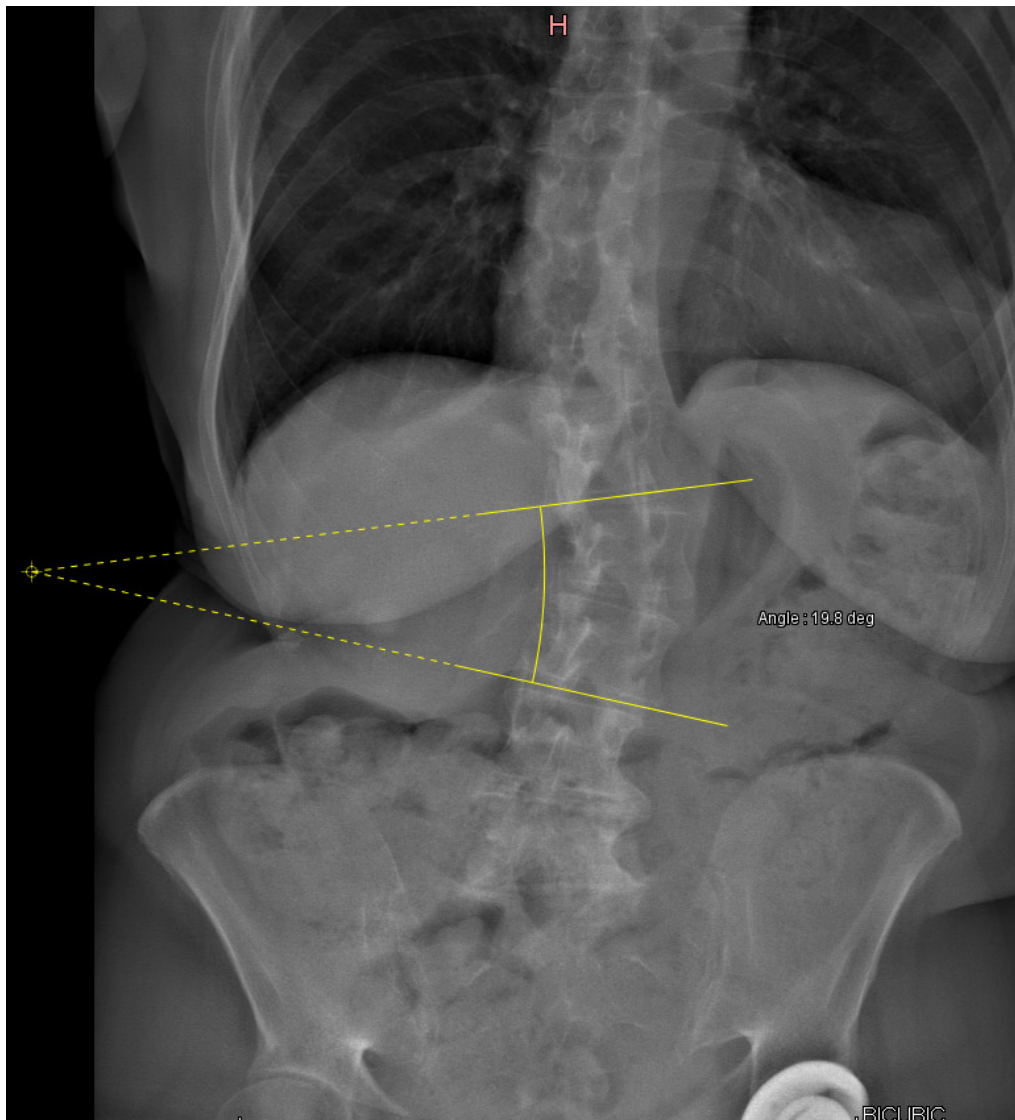
The main differential diagnosis is axial spondyloarthritis. The main features for distinguishing DISH from axial spondyloarthritis are the presence of ossification around the sacroiliac joint, the absence of sacroiliitis or extra-articular manifestations and normal acute phase.

Treatment parallels that for non-specific chronic LBP and a better control of associated metabolic disorders is advocated. Surgical procedures are sometimes required in cases of digestive (dyspepsia) or neurological manifestations (radiculopathy or myelopathy).

6.4 Degenerative scoliosis

Degenerative scoliosis is defined as a spinal deformity of $>10^\circ$ (Cobb angle) within the frontal plane in the skeletally mature spine (figure 8).

Figure 8 Degenerative scoliosis in a 71-year-old woman.



Aebi has highlighted three types: (1) primary degenerative de novo scoliosis; (2) progressive idiopathic scoliosis and (3) secondary degenerative scoliosis. The last of these has been further stratified as follows: (a) following idiopathic or other forms of scoliosis as a result of pelvic obliquity, leg length discrepancy, hip pathology or a lumbosacral transitional anomaly; and (b) related to metabolic bone diseases (mostly osteoporosis), leading to asymmetrical osteoarthritic disease and/or vertebral fractures (Aebi, 2005).

The aetiology of primary scoliosis (type 1) remains unclear. However, asymmetrical disc degeneration (discopathy) seems to trigger frontal plane deviation and asymmetrical facet joint loading, leading to rotatory movements of the vertebrae. The latter may result in spinal and foraminal stenosis (more often than in secondary forms). The apex is usually found at L3–L4 or L2–L3 levels with thoracolumbar or lumbar localisation. Instability can lead to ligamentum flavum hypertrophy, facet joint hypertrophy and, therefore, central spinal stenosis. Type 2 is often seen after instrumentation at a young adult age or after conservative treatment of idiopathic scoliosis. Sagittal plane deformity known as ‘flat back syndrome’ or loss of the

physiological lumbar lordosis is found when there are symptoms of pain. The underlying cause of type 3a may be either 'inside' (eg, hemi sacralisation) or 'beyond' the spine itself (pelvis, leg length discrepancy).

Malalignment is mainly seen in the frontal—but not in the sagittal—plane, which thus tends to have no rotatory component. Type 3a is found in the lumbosacral, lumbar or thoracolumbar segments, whereas type 3b can be found along all spinal segments. In the latter case, destruction of discs, facet joints (and capsules) can lead to deformity in the sagittal and frontal planes.

Degenerative scoliosis is rarely seen in people aged <40 years and has a balanced male:female ratio (Grubb et al, 1988*). Curve progression was found to be a Cobb angle increase of 1–3° a year but may be more rapid in the perimenopausal period. The dominating symptom is usually mechanical back pain with muscular overload if unbalanced and neurogenic symptoms, such as central spinal claudication or radicular claudication when standing or sitting, either on the concave side owing to foraminal (true) stenosis, or on the convex side owing to dynamic overstretching of the spinal nerve (Aebi, 2005; Kotwal et al, 2011).

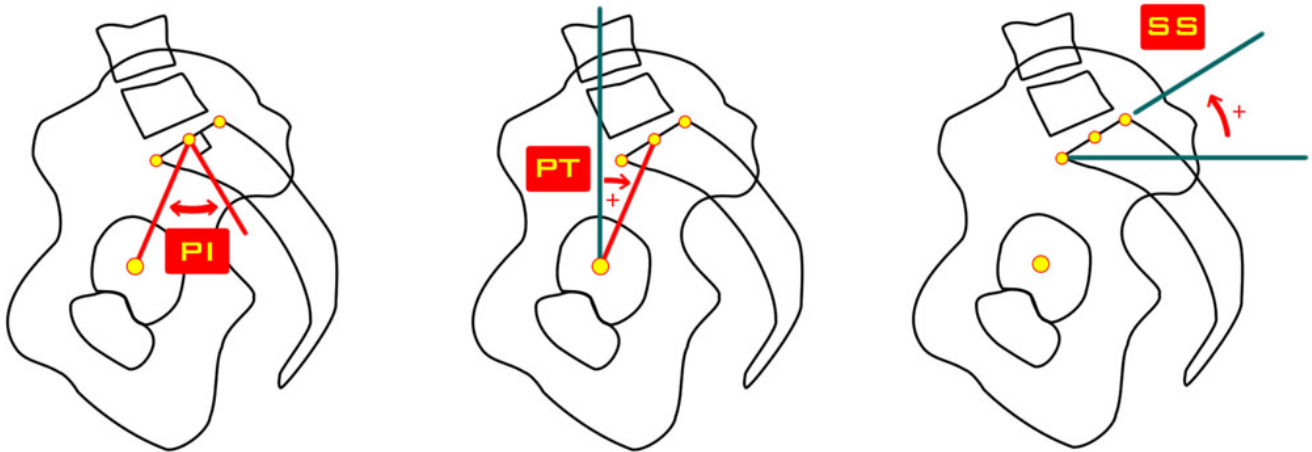
Treatment depends on the patient's current quality of life and functional disability. The clinician should start with a conservative approach (Everett and Patel, 2007); clinical and radiological monitoring should be organized, some individual may progress rapidly. Surgery can be considered depending on curve progression. Treatment for cosmetic reasons is rarely justified. Pain is treated as for non-specific LBP in the absence of specific evidence of differential effects in degenerative scoliosis. Asymptomatic patients require no treatment.

6.5 Sagittal imbalance

In contrast to frontal plane deviations, sagittal spine curvatures and their balance is a more recent concept (Roussouly et al, 2005). Spinal balance is maintained by keeping the centre of gravity positioned over the femoral heads, ensuring minimal energy expenditure when upright. The extent of spinal curvature (lordotic and kyphotic segments) and inclination of the pelvis vary in the normal population (Boulay et al, 2006). Facet joint osteoarthritis, disc or vertebral body height loss or spondylolisthesis (Labelle et al, 2011) can result in decreased lumbar lordosis and an increase in thoracic kyphosis. Sagittal imbalance has been defined as a C7 plumb line deviation of >5 cm (line joining the centre of the C7 and the S1 superior plateau) anteriorly (or posteriorly), but this classification requires whole spine radiographs in the upright position. A variety of spinopelvic parameters can be derived (figure 9).

Figure 9 Spinopelvic parameters. PI, pelvic incidence; PT, pelvic tilt; SS, sacral slope. (Courtesy of Professor J-C Le Huec.)

$$PI = PT + SS$$



To prevent falling over, spinal sagittal balance must be maintained, and several compensatory mechanisms have been described: pelvic retroversion; hip hyperextension; knee flexion; ankle extension; lumbar retrolisthesis and reduction of the thoracic kyphosis (Barrey et al, 2011*). It has been suggested that lumbar pain radiating into the leg, which may mimic neurogenic claudication, can arise from muscle tension secondary to sagittal imbalance. Incomplete restoration of sagittal balance has been suggested as a cause of persistent back pain and of disease in adjacent segments after spinal fusion. Conservative treatments have been designed aiming to decrease tension of back extensors by favouring pelvic retroversion (eg, through stretching of psoas muscles) and restoring hamstring and quadriceps muscle length. They include mobilisation exercises for flexible segments and core stability strengthening (figure 10).

Figure 10 Sagittal imbalance compensated by maximum hip extension and knee flexion. (Courtesy of Professor J-C Le Huec.)



6.6 Facet syndrome

Pairs of facet joints (zygapophysial or z-joints) are found at each level with hyaline cartilage articular surfaces, a fibrous joint capsule with a synovial layer, anteriorly limited by the ligamentum flavum and often meniscoid structures. Facet joints are innervated by the medial branch (or dorsal branch at the L5 level) of the primary dorsal ramus (L1–L4) of the spinal nerve; each joint is innervated by its own level and the level above (sometimes also one level below).

The facet syndrome is a clinical entity describing facet joint pain and, in some cases, ‘referred pain’ (in the lower extremity) that can be misinterpreted as radicular pain. This is most common at the L4–L5 and L5–S1 levels in the lumbar spine. The syndrome has been known since 1911, but the term ‘facet syndrome’ was coined by Ghormley in 1933 (Manchikanti and Singh, 2002). It is thought to account for 5–15% of non-specific LBP, with increasing prevalence in the elderly population (van Kleef et al, 2010).

There is no pathognomonic clinical test for facet joint pain. Pain on extension from the flexed position, particularly during lateral rotation, or pain on extension that is more severe than on flexion, might suggest pain originating from facet joints. However, the validity of these tests has not been definitively proven, and there remains divergence of professional opinions on which tests should most influence clinical decisions (Mars et al., 2015). Radiographic evidence of facet joint osteoarthritis does not usefully predict facet joint pain. Pain might originate from facet joints in people without osteoarthritis, and, as is also the case with other joints such as the knee, radiographic osteoarthritis is often pain-free. Possible contributions to facet syndrome from repetitive minor trauma, inflammation, hypo- or hypermobility remain unproven. Analgesic response to a local anaesthetic nerve block might be considered as the primary diagnostic criterion, and might be anticipated to

predict benefit from radiofrequency denervation. Clinical assessment including physical examination however is required to select patients and spinal levels for interventional diagnostic testing. Diagnostic blocks require imaging (fluoroscopy, CT scan or ultrasound) to ensure accurate placement. Positive has been defined as a pain reduction of 50% to >80% during the half-life of the local anaesthetic used (Cohen and Raja, 2007; Pampati et al, 2009). Placebo effects of injections can be high, so pain relief following diagnostic block procedures need not necessarily indicate a specific origin of pain. Double diagnostic blocks (for example, using two anaesthetic drugs with different half-lives) have been proposed to improve specificity. Diagnostic blocks might only be cost-effective in clinical practice where the outcome will determine whether invasive treatments such as radiofrequency denervation will be pursued.

Conservative treatment is multimodal and might include manual therapy (mobilisation/manipulation) and physiotherapy (range of motion gain) in addition to other treatments recommended for non-specific LBP. Patients with pain which is of at least moderate severity, persistent (ie not likely to improve spontaneously), and which is localised rather than originating from multiple spinal structures might be considered for radiofrequency denervation (*Ward et al., 2016). Radiofrequency denervation would usually be reserved for those in whom more conservative treatments have been ineffective, and who display positive responses to diagnostic blocks. Intra-articular and periarticular glucocorticoid injections into facet joints have often been performed in the past, although numerous systematic reviews and previous guidelines have failed to demonstrate cost-effectiveness (*Ward et al., 2016). Benefits even from radiofrequency denervation might not be sustained, possibly due to regrowth of nerves into denervated structures, or to complex and changing origins of pain over time. The benefits of multiple or repeat procedures remains unproven. More research is required to define the optimal assessment and holistic management of facet syndrome.

7 Neurological syndromes associated with back pain

7.1 Lumbar radiculopathy

7.1.1 Definition

Many synonyms for lumbar radicular pain have been used—for example, ischias pain, nerve root pain, nerve root entrapment, sciatic neuralgia or, most commonly, sciatica. Radicular pain is the most accurate term and is defined as ‘pain perceived as arising in a limb or the trunk caused by ectopic activation of nociceptive afferent fibres in a spinal nerve or its roots or other neuropathic mechanisms’. A common cause of lumbar radicular pain is a herniated disc and thus ‘lumbar radicular pain due to herniated disc’ seems to be the most appropriate terminology (van Tulder et al, 2010*). The term ‘sciatica’ refers to a symptom rather than an underlying pathogenic mechanism, and is used to describe pain referred from the lower back to the leg below the knee, in the distribution of the sciatic nerve innervation. Sciatica might or might not be associated with herniated lumbar disc.

7.1.2 Epidemiology

The lifetime incidence of sciatica varies from 13% to 40%, with an annual prevalence of 1–5% (Konstantinou et al, 2008). The incidence peaks in the 45–64-year age group and the odds ratio of an episode of sciatica increases by 1.4 for every additional 10 years of age, up to the age of 64. An estimated 5–10% of patients with LBP also have sciatica, but most patients with back and leg pain do not have lumbar radicular pain due to herniated disc, even when the pain is radiating to the foot. From twin studies, heritability has been estimated as about 20%. Few high-quality studies have been published on environmental and personal factors. In a prospective study of adolescents followed up for 30 years, none of the studied factors, including participation in sport, was associated with the development of sciatica (Rivinoja et al, 2011). However, being overweight and current tobacco use among men and obesity in women were associated with an increased risk of a second-time hospitalisation for surgical treatment of sciatica in adulthood. In cross-sectional studies, an association with certain occupational factors has been reported, including an awkward working position, such as in a flexed or twisted trunk position, and driving or working with the hands above the shoulders. A possible role of tobacco use has been inconsistently reported.

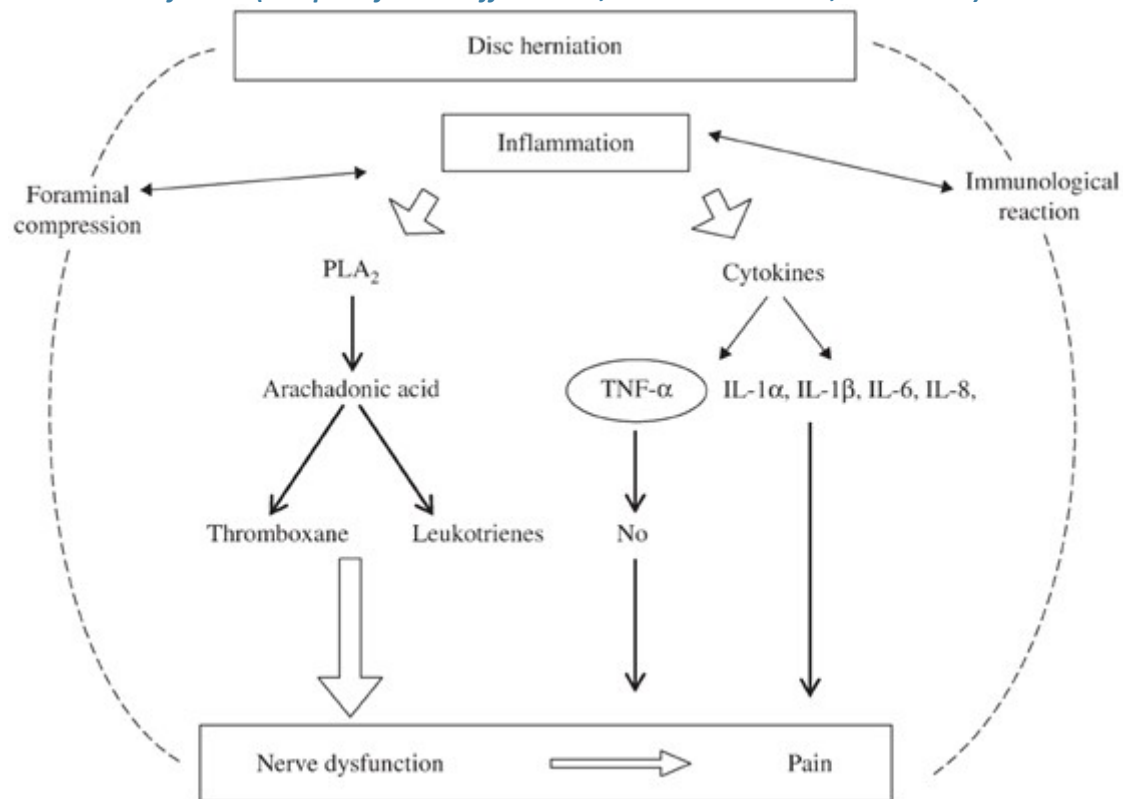
7.1.3 Pathophysiology

The intervertebral disc has been implicated in the pathophysiology of sciatica through different mechanisms (Figure 11). At first, the assumption that the protruded disc exerted pressure on the sciatic nerve root was commonly accepted. Therefore, treatment was surgical decompression. However, as early as the mid-20th century, it was suggested that pressure on a nerve results in loss of function and is rarely associated with pain. Several lines of evidence support this hypothesis: disc herniation with apparent neural compromise are common findings in asymptomatic patients, and also, symptomatic patients with disc herniation may improve without any alteration of the original pathology.

Although benefit from surgical decompression in carefully selected patients suggests that mechanical factors do play a role, additional inflammatory and/or immunological mechanisms are also involved (figure 5). Cytokines have been implicated in this inflammatory process (Valat et al, 2010). Tumour necrosis factor α (TNF α) may be the cytokine most strongly associated with the proinflammatory properties of the nucleus pulposus, as shown in many different animal models. The presence of interleukin 1 α (IL-1 α), IL-1 β , IL-6, IL-8 and TNF α in homogenates of discs removed from patients with sciatica has been documented. TNF α was significantly increased in the epidural fat surrounding the inflamed nerve root in patients with sciatica compared with controls (Genevay et al, 2008). There is preliminary evidence that TNF α blocking antibodies might reduce the pain of sciatica and hasten recovery in people with acute disc prolapse (Williams et al., 2013), although more detailed cost-effectiveness studies would be required to justify introduction of this treatment into routine clinical practice.

Immune mechanisms within the central nervous system also contribute to the development of neuropathic pain. Extensive preclinical data have linked the development of glial cell activation within the spinal cord to the development and maintenance of neuropathic pain, and novel pharmacological approaches that reduce neuroimmune activation have potential as analgesic agents. .

Figure 11 An overview of the pathogenesis of lumbar radiculopathy. IL, interleukin; PLA₂, phospholipase A₂; TNF, tumour necrosis factor. (Adapted from Stafford et al, Br J Anaesth 2007;99:461–72.)



7.1.3.1 Other causes of sciatica

Sciatica, as a symptom, need not always indicate radicular pain and non-discogenic causes should be considered even in people with imaging evidence of herniated intervertebral disc. MRI findings are not uncommon in asymptomatic individuals, and an important contribution from other mechanisms to sciatic symptoms might compromise response to specific interventions such as surgery, and might rarely indicate a need for other specific treatments. Red flags for sciatica do not differ from those for LBP.

Pain referred below the knee might originate from neuronal activation distal to the spine. Nerve irritation through the piriformis muscle has been proposed (piriformis syndrome), although definitive diagnostic classification is controversial. Claudicant features might indicate spinal or foraminal stenosis, but might also results from peripheral vascular disease (see below). Hip pain can sometimes be experienced radiating below the knee, and hip examination is an essential component of assessment of a person with sciatica. Where sciatica reflects lumbar radicular pain, non-discogenic causes should be considered. The main causes of non-discogenic sciatica are listed in table 9.

Table 9 Non-discogenic causes of sciatica (Adapted from Stafford et al, Br J Anaesth 2007;99:461–72)

Causes	Description
Malignancy	Metastatic, sarcoma, neuroma, hemangioblastoma
Infection	Abscess, discitis, epiduritis, herpes zoster radiculitis, Lyme radiculitis
Vascular compression	Epidural thrombosis, abnormal pelvic venous plexi, gluteal artery pseudoaneurysm
Muscular compression	Piriformis syndrome
Bony compression	Degenerative spinal stenosis, foraminal stenosis Osteophytes of the sacroiliac joint
Epidural	Epidural lipomatosis, epidural adhesions (after surgery)
Gynaecological	Pelvic endometriosis, uterine fibroid
Metabolic	Diabetic painful amyotrophy, alcoholic neuropathy

7.1.4 Diagnosis

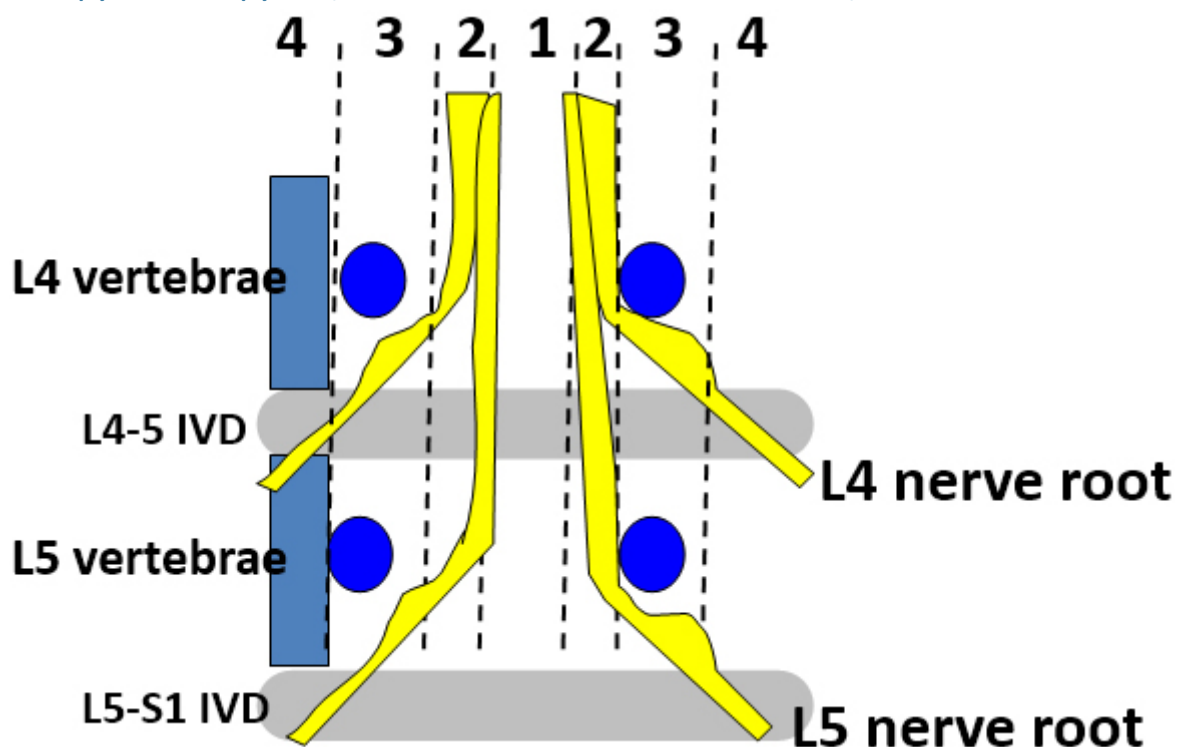
Sciatica is mainly diagnosed by history taking and physical examination (van Tulder et al, 2010*). By definition, sciatica is characterised by radiating pain that follows a dermatomal pattern. A patient should be asked about the distribution of pain and whether the pain radiates below the knee. Sensory symptoms additional to pain, for example paraesthesiae or reduced sensation, increase specificity for radiculopathy. Associated LBP is common, but is not always present and is often not the dominant symptom. In addition to ruling out red flags (identical to LBP), the history should determine the localisation and severity of pain, loss of strength, sensitivity disorders, duration, influence of cough and effect on daily activity. Progressive neurological deficit, particularly motor weakness, is an indication for early intervention, whereas gradual improvement might favour more conservative approaches.

Physical examination largely focuses on neurological symptoms. The diagnostic value of history and physical examination has not been well studied. No single history item or physical examination test has both high sensitivity and specificity to predict a disc origin of sciatica. The most common examination tools are the SLR test and the crossed SLR. SLR has a sensitivity of 0.92 and a specificity of 0.28 in surgical cohorts (van der Windt et al, 2010). As expected, results from studies using imaging are less homogeneous. Crossed SLR showed a high specificity (pooled estimate 0.92), but low sensitivity (0.28). The bell test (reproduction of the radicular pain by pressure applied with the thumb between the spinal processes of L4 and L5 or between L5 and S1) has a specificity of 63% and a sensitivity of 50%. The hyperextension test (reproduction of the radicular pain in standing position by passive mobilisation of the trunk in extension with the knees in extension) has a specificity of 70% with a sensitivity of 45%. Overall, if a patient reports a typical pain radiating to one leg combined with a positive result on one or several clinical tests indicating nerve root tension or neurological deficit, the diagnosis of sciatica by herniated disc is justified.

7.1.5 Imaging

Imaging is useful if the results influence further management. In acute sciatica, the diagnosis is based upon history taking and physical examination. At this stage, the treatment is mostly non-surgical and imaging is indicated only if there are red flags or indications that the sciatica may be caused by underlying diseases, such as malignancies or infections rather than disc herniation. Otherwise imaging should be performed when needed to direct specific treatments, for example transforaminal epidural injection or surgical intervention. A good correlation between pain distribution and the level and side of disc herniation is important to validate the diagnosis before introducing more invasive treatment. Clinicians should keep in mind that disc herniations detected by MRI or CT scan are highly prevalent in the general population (up to 40%) without sciatica. It must be recalled also when considering whether imaging findings are likely to explain symptoms that at each lumbar level, foraminal and extraforaminal disc herniation are in contact with the cranial nerve root, whereas paramedian disc herniation is in contact with the caudal nerve root (figures 6 and 12).

Figure 12 Topography of the nerve root at the lumbar level (example L4–L5 disc). A disc herniation located in the extraforaminal (4) or foraminal (3) area is in contact with the L4 nerve root, whereas when located in the paramedian (2) or medial (1) area, it is in contact with the L5 nerve root. IVD, intervertebral disc.



Furthermore, no lumbar disc herniation can be identified on MRI or CT scan in some patients with sciatica. MRI may be slightly more accurate than CT scan at diagnosing lumbar disc herniation because soft tissue in the spinal canal is better characterised. Some authors also favour MRI because CT scan has a higher radiation dose. On the other hand, bone tissue is better analysed by CT scan. Finally, radiography is not recommended for the diagnosis of lumbar disc herniation.

7.1.6 Natural history

Most patients with acute sciatica respond to conservative symptomatic management and the sciatica resolves over a period of weeks to months (Valat et al, 2010). Data from an old randomised trial of non-surgical interventions indicated that 50% of patients with very acute sciatica included in the placebo group reported improvement within 10 days, about 75% reported improvement within 4 weeks and 60% returned to work. However, up to 30% of patients continued to have pain for 1 year or longer. When patients with an average of 4 months of leg pain were randomised into two groups, immediate surgery or conservative treatment for 6 additional months, those assigned to early surgery recovered more quickly (Peul et al, 2007). At 1 year, the percentage of recovery reached 95% for both groups, but one-third of patients in the group receiving prolonged conservative treatment underwent surgery between 6 and 12 months after randomisation because of intractable leg pain. The long-term rate of persistent pain (back and/or leg pain) is between 10% and 20%.

No early-stage predictors of poor outcome have been clearly identified. In particular, baseline imaging is not a good predictor of symptomatic outcome in sciatica. Abnormalities on MRI resolve more completely with large disc herniations than with bulging discs, and disc sequestrations are more likely to resolve partially or completely than herniations without signs of migration (disc protrusions). For disc herniation or sequestration, 76% might completely or partial resolve on MRI at 1 year compared with 18% for generalised or focal disc bulge. In summary, large disc protrusions, far from indicating a need for early invasive treatment, might indicate a likely good prognosis with conservative management.

7.1.7 Non-surgical treatments

Conservative treatment for sciatica is primarily aimed at reducing pain and nerve irritation, either by medications or glucocorticoid epidural injections. Systematic reviews have found no support for opioid analgesia, bed rest, exercise therapy, traction and percutaneous discectomy (Lewis et al, 2013, *Ward et al., 2016). Patient education/advice is an expected component providing context to any treatment, but is not effective for sciatica when used alone. Indeed one systematic review found that conservative treatments do not clearly improve the natural course or reduce symptoms of sciatica in most patients (van Tulder et al, 2010*). However, there is reasonable evidence that non-opioid drugs, epidural injections and disc surgery can be effective (Lewis et al, 2013, *Ward et al., 2016).

Many patients with sciatica also have back pain, and back pain can often persist after resolution of sciatic symptoms. Therefore, where specific evidence of benefit in sciatica is absent, treatment as for LBP might seem appropriate. Many of the clinical trials in LBP did not exclude patients with sciatica, and guidelines often refer to management of LBP with or without sciatica (*Ward et al., 2016). Concerns have been raised that exercise might lead to extension of disc prolapse, but, on the other hand, fear of exercise predicts poor prognosis in people with LBP with or without sciatica (*Hill et al., 2011). Little difference in pain or functional outcome has

been shown between bed rest and advice to stay active. The addition of physical therapy to general practitioner care for sciatica had benefits on 'patient-perceived global effect', with a rate of improvement of 79% vs 56% in the control group at 1 year (Luijsterburg et al, 2008). Symptom-guided exercises in addition to information and advice to stay active was followed by a global improvement in 80% of participants at 8 weeks (compared to 60% those receiving sham exercises), although no difference in pain or function was found (Albert et al, 2012). Specific benefit from guided exercises for sciatica therefore remains inconclusive, but the limited evidence from controlled trials does not support the fear that exercise is harmful. Onset of pain during activity does not indicate that continuing activity will exacerbate damage. Indeed, the loss of strength and proprioceptive reflexes that can follow inactivity might increase the risk of further injury in the future. Therefore, bed rest is no longer widely recommended (Valat et al, 2010), and patients are encouraged to maintain normal activities where possible.

Only a few studies have examined medication specifically for sciatica. Mechanistic classification of sciatica as neuropathic (rather than nociceptive) pain encourages generalisation of findings from randomised controlled trials in other painful neuropathic conditions. Taking this approach, tricyclic antidepressants such as amitriptyline in doses up to 75 mg at night, gabapentinoids or selective serotonin and noradrenaline reuptake inhibitors (SSNRIs, e.g. duloxetine, milnacipran) might be considered for sciatic pain. However, it is unclear that neuropathic pain represents a single entity, and therefore treatments for one form of neuropathic pain might not work for others. Topical capsaicin can be helpful for neuropathic pain originating in cutaneous afferents, but would not be expected to help pain from deep structures such as in sciatica. An old study on gabapentin (3 × 300 mg/day) found a positive effect on pain, whereas an early trial on pregabalin did not show any effect despite a complex design (Baron et al, 2010). A further randomised controlled trial suggested similar efficacy of oral gabapentin to glucocorticoid epidural injection for sciatica (Cohen et al., 2015). Some studies focusing on sciatica reported a positive, short-term benefit from NSAIDs, consistent with inflammatory mechanisms in acute sciatica. Diazepam had no additional effect on hospitalised patients with sciatica compared with those receiving a placebo and the median duration of hospital stay in hospital was shorter (8 vs 10 days; $p = 0.008$) in the placebo arm. Despite benefit from epidural glucocorticoid injection (see below), systemic glucocorticoids are no better than placebo for sciatica, possibly because adequate drug levels cannot be achieved local to the involved nerve root.

The most extensively evaluated conservative treatment for sciatica is the epidural injection of glucocorticoids. Epidural injections are recommended as part of the treatment for acute and severe sciatica (Kreiner et al, 2014*, *Ward et al., 2016), although controversies remain. There is fair evidence that epidural injections are effective in the short term (<3 months), but poor evidence of any long-term effectiveness (Pinto et al, 2012). Epidural glucocorticosteroids is thought to reduce pain by reducing perineural inflammation, and if uncontrolled inflammation is a cause of long term nerve damage (neuropathy), then it might be expected that

they might reduce long term pain. Furthermore, short term analgesia might permit an early return to normal activity. However, the contribution of inflammation or physical activity to persistence of sciatica remains unproven. Glucocorticosteroids injections in other contexts (e.g. intra-articular) typically produce only temporary benefit. Without further evidence, it might be most appropriate to consider epidural injection as a form of analgesia, alongside oral medications, that might hasten recovery rather than a disease modifying intervention that would remove a need for surgery or risk of long term symptoms. Epidural injections do not significantly improve LBP and therefore their indication is severe sciatica, and they should not be offered for severe disability mainly due to LBP.

Different procedures are all referred to as 'epidural', whether injection is directed through the sacral hiatus (caudal epidural), interlaminar or transforamina (periradicular). There is evidence that injections performed without imaging guidance are less effective. Ultrasound may be used to guide caudal epidural injection, whereas fluoroscopy (or CT imaging) is required for the transforaminal approach. It has been suggested that transforaminal injection might be more effective than caudal epidural, particularly for higher lumbar root involvement (e.g. L4). Tracking of injectate to more rostral levels of pathology might be incomplete via the caudal route. Randomised controlled trials provide some, but inconclusive evidence for this assertion. Transforaminal injection requires access to specialist facilities for imaging, whereas caudal epidural might be offered within primary care. Cases of spinal cord infarction after lumbar foraminal injections have been reported, mainly in patients with previous back surgery at the injected level. Definitive guidance cannot therefore be provided on which type of epidural should be offered, but delays to more definitive treatment by sequentially administering multiple epidural injections through differing routes is clearly undesirable.

7.1.8 Minimally invasive interventions

Minimally invasive interventions for sciatica are mainly procedures of disc decompression performed through a needle. The goal is to remove or destroy tissue from the centre of the disc in order to decrease pressure exerted by the disc herniation on the nearby nerve root. To achieve this, these techniques are limited to contained disc herniation (also called subligamentous disc herniation as they have not crossed the posterior longitudinal ligament that lies between the disc and the epidural space). Chemonucleolysis (intradiscal chymopapain injection) has been used. According to a Cochrane review, it is better than conservative treatments, including steroid injections, but inferior to surgery. However, it has now been abandoned in most parts of the world because of its potential side effects (anaphylaxis). Several different techniques have been developed based on the same concept, including laser discectomy, which might have similar efficacy to open surgery (Brouwer et al., 2105), although further evidence is desirable.

7.1.9 Surgical treatment

Removal of disc herniation, part of the disc or correction of foraminal stenosis are the main objectives of surgical procedures for sciatica. The purpose is to eliminate the suspected mechanical cause of nerve root compression. Treatment is aimed at decreasing the leg pain and corresponding symptoms, but not at reducing back pain. Indications for immediate surgery include cauda equina syndrome or progressive motor loss (with muscle strength <3 on a 6-point scale). Randomised controlled trials have compared surgery with usual conservative care, epidural injection or early surgery with prolonged conservative care (Jacobs et al, 2011). Unfortunately, however, study quality has often been limited. Early surgery appears to provide better short-term relief of leg pain than prolonged conservative care, but no difference was seen at 1 or 2 years. From a societal perspective, early surgery might be more cost-effective because of reduced loss of productivity.

7.1.10 Prognosis

In studies performed in secondary or tertiary centres, the rate of total clinical recovery (pain and function) following surgery varies between 40% and 50% at 1 and 2 years. Identified factors of poor prognosis are the presence of back pain at baseline; intensity of back and leg pain; general health (comorbidities); fear-avoidance beliefs and the SLR test result. Results from a randomised controlled trial showed that recovery from motor deficit occurs in 70–80% of patients at 1 year (Overdevest et al, 2013). Although recovery was faster in surgically treated patients, there was no difference between groups at 1 year.

7.1.11 Summary of care and shared decision-making process

In clinical practice, information about the condition, pain treatment using NSAIDs, opioids and neuropathic pain treatment and epidural injection when severe pain persists after a few weeks, set the scene for conservative treatments. Physical therapy is important to encourage maintenance of activity, particularly when back pain becomes the main source of pain and disability. Three months after onset, if severe sciatica persists despite conservative treatment, the possibility of a surgical intervention should be considered. Physicians and patients should consider fully the benefits and harms of all treatments, and the patient's treatment preference may have a direct positive influence on the magnitude of the treatment effect. This process is known as shared decision-making. To ensure the quality of information necessary for an informed choice, a list of items that should be discussed during the consultation is provided in box 3 (Sepucha et al, 2012). This must be part of a dynamic process that should be revisited at each consultation.

Box 3 Items forming the basis of informed decision-making for surgery in patients with continuing sciatica

1	Herniated disc does not become worse during normal activities
2	Over time, with or without surgery, the leg pain caused by a herniated disc usually improves
3	Lots of bed rest does not help to relieve pain caused by a herniated disc
4	Over-the-counter pain medicine helps some individuals to relieve the pain caused by a herniated disc
5	Surgery is most likely to provide faster relief from pain caused by a herniated disc
6	Between 10-30% of individuals who undergo surgery for a herniated disc will have the same or more pain after surgery
7	Failure to relieve pain, dural puncture, infection, and hematoma are the most common complications of surgery for a herniated disc
8	Without surgery, almost no patient will develop permanent weakness that results in not being able to walk at all
9	The rate of serious complications in individuals who undergo surgery for a herniated disc is between 1–5 %
10	The rate of recovery from leg pain at five years is the same, with or without surgery
11	Stomach ulcer, excessive bleeding, and kidney problems are possible side-effects when using over-the-counter pain medicine for a long time

Reproduced with permission from Sepucha et al, Spine 2012;37:834–41. To this might be added that prescribed medications might also relieve pain caused by a herniated disc, and clarification that the listed adverse events of over the counter analgesics refers to non-steroidal anti-inflammatory drugs.

7.2 Neurogenic Claudication

Lumbar spinal stenosis with neurogenic claudication is one of the most commonly diagnosed and treated pathological spinal conditions of the elderly population and is expected to rise even further with the increased ageing of the population (Watters et al, 2008). This neurogenic syndrome is hypothesised to result from the compression of the vasa nervorum of the nerve roots in the spinal canal. A diagnosis of the clinical syndrome of lumbar spinal stenosis requires both the presence of characteristic symptoms and signs and radiographic or anatomical confirmation of narrowing or stenosis of the lumbar spinal canal (Genevay and Atlas, 2010*). As many people with radiographic or anatomical lumbar spinal canal stenosis may not have any symptoms, the clinical diagnosis is extremely important and an alternative diagnosis (table 10) must be ruled out before establishing the final diagnosis.

Patients with neurogenic claudication have a variable amount of pain or discomfort in the buttock, thighs, lower legs or feet, brought on by walking or prolonged standing. Typical features include improvement (or complete relief) with sitting or lumbar flexion (ie, leaning forward on a shopping cart) and worsening with lumbar extension (eg, walking downhill). Some individuals may have more subtle leg symptoms, including fatigue, heaviness, abnormal sensations, weakness or gait changes. Back pain is not always present and its relationship with anatomical canal stenosis remains controversial. The classic radiological picture on MRI or CT (less accurate) associated with neurogenic claudication is a narrowing of the spinal canal second to

degenerative changes (bulging disc, facet osteoarthritis and yellow ligament (ligamentum flavum) hypertrophy). It has been suggested that the surface area of the dural sac is more predictive of symptom severity than that of the spinal canal.

The clinical course of neurogenic claudication is often stable or only slowly progressive and most patients with mild or moderate pain have a favourable outcome with conservative treatment (Watters et al, 2008). Evidence for treatment benefit are mainly based on cohort study and expert opinion. Treatment of pain may be pharmacological, including medications recommended for neuropathic pain such as tricyclic antidepressants, gabapentinoids or SSNRIs. The risk: benefit ratio for analgesics can, however, be relatively high, given that people with spinal claudication might have little if any pain at rest despite severe symptoms on walking, and patients are often elderly and with comorbidities. Definitive evidence is still required that medical treatments can either reduce pain or increase walking distance. Physical therapy is a core treatment. Muscle reinforcement with attention to body posture aims to decrease lordosis, and so increase the spinal canal area in order to relieve pain (Ammendolia et al, 2012). Graded exercise can be helpful once the patient understands that the pain does not mean ongoing damage. It has been proposed that spinal claudicant pain might in part result from intermittent neuronal ischaemia rather than frank compression, and that stenosis reduces the capacity of spinal blood vessels to dilate during exercise. Certainly, patients should be discouraged from smoking. Glucocorticoid epidural injections have been found to not be of benefit for chronic spinal claudicant pain, and therefore are not recommended (Radcliff et al, 2013, *Ward et al, 2016). Decompressive surgery may be considered for severe cases and there is good evidence that it is better than 'standard care', although risks of major spinal surgery should be weighed carefully against likely benefits for each individual patient (Weinstein et al, 2008a). Less invasive interspinous devices that increase kyphosis locally are sometimes proposed in stenosis that affects only one disc level in people with serious comorbidities. Overall, evidence for surgical and non-surgical treatment to improve walking ability is of low or very low quality (Ammendolia et al, 2014).

Table 10 Main differential diagnoses for buttock and leg pain with or without radiating leg pain in an elderly patient

Diagnosis	Clinical characteristics
Spinal disorders	
Lumbosacral radicular pain secondary to nerve root impingement	Lumbosacral radicular pain (with or without low back pain) in the setting of lumbar disk herniation may be accompanied by a positive straight leg raise test or femoral stretch test
Referred pain from lumbar spine structures	Low back pain and proximal lower extremity referred pain in non-radicular pattern
Lumbar vertebral compression fracture	Low back pain or thoracic pain in an older patient, often of acute onset, with or without specific history of recent injury
Extraspinal disorders: musculoskeletal diagnoses	
Sacral fracture	Buttock pain uni- or bilateral, with or without low back pain, with or without specific history of recent injury
Sacro-iliac joint disease	Buttock pain with or without posterior thigh radiating pain. Inflammatory pain or mechanical pain depending on the disease (spondyloarthritis, infection, or mechanical problem).
Hip joint referred pain	Groin pain, buttock pain, with or without low back pain, referred symptoms are mainly proximal to the knee, often with weight bearing; may limp and have limited internal rotation of the hip
Trochanteric bursitis	Lateral hip and thigh pain, with tenderness over the greater trochanter; low back pain may or may not be present
Piriformis syndrome	Pain localized over the piriformis muscle in the buttocks, with or without radiating posterior buttock and lower extremity pain; tight hip external rotators may be appreciated
Myofascial referred pain	Pain can be reproduced by pressing on tender points or trigger points (e.g., <i>gluteus medius</i> and <i>minimus</i>)
Extraspinal disorders: other diagnoses	
Intermittent claudication due to peripheral arterial disease	Leg muscle discomfort, cramping, tightness, or tiredness in the buttock or lower extremity that is induced by exercise, often consistently reproduced after walking a certain distance, relieved rapidly with rest, eased with standing, and not affected by trunk posture; decreased pulses or impaired ankle brachial index may be present
Peripheral neuropathy	Pain, numbness, and tingling in the distal lower extremities, particularly the feet and ankles, not substantially affected by posture or exertion
Visceral referred pain	Low back pain, lower extremity pain, or both may be referred from structures in the abdomen and pelvis, including the gastrointestinal tract and genitourinary system

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SUMMARY POINTS

- Low back pain (LBP) is an extremely common symptom. Most people will not require any treatment.
- Excluding the causes for specific LBP (fracture, tumour, spondylodiscitis, spondyloarthropathy) is the first and most important step. Investigations (primarily radiological examinations) are only performed when 'red flags' have been identified (through medical history and physical examination), or where needed to guide specific interventions.
- Patients with associated neurological symptoms (lumbar radicular pain or neurogenic claudication) should be managed specifically.
- Once these conditions are excluded, patients are classified as having non-specific LBP. CT or MRI descriptions (eg, discopathy, osteoarthritis, ...) have no influence on the diagnosis. The presence or absence of non-radicular leg pain (radiating pain) does not affect the diagnosis or the treatment.
- Non-specific LBP is usually divided into acute (up to 4 weeks), subacute and chronic LBP (>3 months); however, many patients will develop an intermittent pain syndrome.
- A subgroup of patients with intermittent or chronic non-specific LBP will develop chronic disabling pain. Hence detecting factors predicting chronicity is the second most important step in managing patients with non-specific LBP.
- These factors are categorised in three main domains: psychological, social and professional. They must be taken into account when designing the treatment plan.
- Information, reassurance, advice to stay active, analgesia are the main points for the treatment of acute non-specific LBP.
- Exercise therapy, spinal manipulation and a specific multidisciplinary programme (ie, that includes a psychological component) are recommended for the treatment of subacute and chronic LBP. For the latter, additional recommended therapeutic interventions include yoga, behavioural therapy and active rehabilitation as well as a self-management programme.
- Spinal injections (epidural injection for sciatica) or radiofrequency denervation of facet joint structures may be considered in carefully selected cases, and referral for a surgical opinion may be considered if severe lumbar radicular pain persists beyond 3 months despite optimal care.
- Lumbar radicular pain and neurogenic claudication require specific attention as they are associated with a different epidemiology, physiopathology, prognosis and treatment plan.
- Additional entities should be recognised as they may, at times, influence the treatment plan: spondylolysis/listhesis, Scheuermann's disease, idiopathic and degenerative scoliosis, diffuse idiopathic skeletal hyperostosis, sagittal imbalance, Modic I endplate modification, facet syndrome.

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module

EULAR on-line course on Rheumatic Diseases

Low back pain and associated syndromes

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A previous version was coauthored by Francois Rannou, Serge Poiraudau, Yves Henrotin, Christelle Nguyen, Stéphane Genevay

IN-DEPTH DISCUSSION I

**Multi/inter-disciplinary approaches to chronic
lumbar back pain**

Non-specific chronic low back pain (NSLBP) has become a worldwide health problem. Encouraging physical activity is a cornerstone of musculoskeletal rehabilitation, and supervised exercise therapy is recommended as a first-line treatment in the management of chronic LBP. These mono-disciplinary approaches are of limited efficacy to achieve significant pain reduction, improving disability and return to work. Following the recognition of the importance of the bio-psycho-social perspective to tackle chronic pain patients in general, and NSLBP in particular multi- or interdisciplinary rehabilitation treatment programs have been implemented. Whereas the biomechanical approach relies on classic physiotherapy, multi- or interdisciplinary rehabilitation programs are built on approaching the patient psychologically and functionally (1).

Interdisciplinary programs should offer an integrated rehabilitation intervention plus a psychological and/or social/occupational component (2) seeking a common goal. Often this will include physiotherapists, occupational therapists, psychologists and/or psychiatrists, pain clinicians, rheumatologists and/or physiatrists. By definition multidisciplinary interventions include multiple actors. However, an interdisciplinary treatment additionally comprises proficient knowledge of each other team members' expertise (3). This diverse group of clinicians, each contributing to the patients' care, should meet at least weekly to discuss the patients' progresses (4). Cognitive behavioural therapy (CBT) may also be included (5). Inviting spouses to participate in the rehabilitation (spouse assisted strategies) have also been proposed (6). The intensity of the programs varies between 12 and 50 hours per week, most of the time conducted over 2 to 4 weeks (7,8).

Not all patients with non-specific low back pain (NSLBP) need a multidisciplinary approach and not all of the patients recruited will adhere to such a program. Compliance is difficult to predict (9). Early detection of the ideal participant (i.e. responder) would be useful; some tools and criteria have been put forward: Guidelines from the USA recommend including patients suffering from « persistent and disabling back pain » whereas European guidelines largely opt for any chronic NSLBP patients. It has also been recommended to implement such a program to help decision making before undertaking surgery; mid-term results seem promising when comparing surgery versus multidisciplinary approach for NSLBP favouring the latter (10). The inclusion of subacute NSLBP in multidisciplinary rehabilitation program (MDRP) is controversial as these programs may not be as effective (11). Focusing on patients having a high level of modifiable risk factors has been suggested (12). Modifiable risk factors may include anxiety, fear avoidance behaviour, catastrophism, bothersomeness and biomechanical issues.

The goal of a rehabilitation program explicitly addressing bio-psycho-social factors is mainly focused on decreasing functional limitations and promoting return to work. Improved self-management and self-efficacy has been revealed as key elements (13). The most recent Cochrane review on systematic reviews of RCT's comparing MDRP and "usual (i.e. individual) care "reveals a significant effect on pain and disability reduction (14). For most studied outcomes, the treatment effect size seems to be moderate (13).

Concerning return to work (RTW) a meta-analysis found only a small effect with possible publication bias (15). When analyse was limited to the 5 studies from Scandinavian countries (countries with similar social setting) the homogeneity was good and the effect on RTW was found clinically significant. A more recent meta-analysis concluded that the effect on work equates to a person having roughly double the odds of being at work after 12 months if they received a MDRP rather than a physical treatment (14).

Limited effectiveness has been shown on the long-term. Whereas M. Van Middelkoop et al. (16) found no significant improvement after five years compared to an active treatment regimen Van Hooff et al. (8) underlined reduced use of medication two years after the program. Others found moderate effect on ICF levels of impairment (17), less subjective disturbance in activities of daily life (8), but no impact on return to work. Interestingly no difference was shown at 9 years follow-up comparing surgical fusion versus interdisciplinary rehabilitation, clearly questioning the place of surgical interventions in these patients (18). The risk of experiencing adverse events was obviously higher in the surgical group.

In a systematic review on guideline-endorsed treatments for low back pain, MDRP were found to be cost-effective (19). This was confirmed in a recent large German study (20). Compared to a brief intervention (6 hours, mainly directed to reassuring patients) performed in a population of patients (partly or fully) on sick leaves for 4 to 12 weeks, Jensen et al. found that MDRP was cost-effective only in a subpopulation of patients at risk of losing their job or having little impact on their work situation (21). In a large (over 1600 patients) cohort of sick-listed (50% of them fully sick-listed) chronic NSLBP patients still having work contract at baseline, the only modifiable factor that predicts full return to work at 1-year was “more work-participation” at baseline (22).

In conclusion, multidisciplinary rehabilitation programs for chronic low back pain are effective in reducing functional limitations and improving return to work. Overall the clinical effectiveness is at best moderate and no significant change is to be expected beyond one year. The exact composition of the interdisciplinary group, the best time to perform the intervention, as well as the intensity and the duration of the treatment are yet to be defined on solid evidence.

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module

EULAR on-line course on Rheumatic Diseases

Low back pain and associated syndromes

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IN-DEPTH DISCUSSION II

Symptomatic lumbar spinal stenosis

Neurogenic claudication and radicular leg pain are the clinical syndromes associated with lumbar spinal stenosis (LSS). On the one hand, lumbar spinal stenosis is frequently found in asymptomatic patients and on the other, up to 20% of older adults complain of lower extremity pain in the setting of low back pain. However, there are many other causes of lower leg pain, even in the presence of low back pain, that are not related to LSS. Because neurogenic claudication and radicular leg pain may require specific treatments (including surgery), reaching the correct diagnosis is paramount.

There are several classifications of spinal stenosis. The most widely used differentiates primary stenosis, caused by congenital abnormalities, from secondary, acquired, stenosis caused by degenerative changes, trauma, surgery or infection. The most common form of secondary stenosis results from slowly progressive degenerative changes affecting the facet joints (hypertrophy), the ligamentum flavum (hypertrophy secondary to fibrosis) and disc (decreasing height, bulging). These degenerative changes may result in stenosis of the central canal or/and of the foramen. Central stenosis mainly affects the three lower levels of the lumbar spine; its clinical expression will mainly be neurogenic claudication and, sometimes, cauda equina syndrome. Foraminal stenosis most commonly affects L5 nerve roots because the L5-S1 foramen has the smaller foramen/root area ratio; pain arising from foraminal stenosis will be of the radicular type relatively similar to radicular pain related to disc herniation. In addition to these anatomical changes, LSS has a dynamic component. The area of the central canal and of the foramen increases with axial distraction and flexion and decreases with extension, resulting respectively in decrease and increase in local pressure.

Neurogenic claudication is thought to result from vascular compromise to the vessels supplying the cauda equina (central stenosis) or from pressure on the nerve root complex (lateral stenosis) by the degenerative changes. Experimentally, it has been shown that moderate constriction-induced pressure involving the cauda nerve roots will disturb their nutrition. There is almost no data on the potential role of inflammatory mediators in the pathophysiology of neurogenic claudication despite rapidly increasing rate of corticosteroid spinal injection in these patients.

Clinical symptoms and physical examination

As the frequency of LSS on imaging is high in the asymptomatic population, the diagnosis of neurogenic claudication has to rely first on clinical findings. A recent review of the literature found that in a population with a prevalence of the clinical syndrome of LSS of 45%, in addition to age (>70 years, likelihood ratio (LR) = 2.0 and < 60 years LR = 0.4), the most useful symptoms for increasing the likelihood of the clinical syndrome of LSS were: having no pain when seated (LR = 7.4), having unexplained urinary disturbance (LR 6.9), improvement of symptoms when bending forward (LR 6.4), the presence of bilateral buttock or leg pain (LR = 6.3) and neurogenic claudication (LR 3.7). Physical examination tests were less useful. However, a wide base gait (LR = 13), an abnormal Romberg test (LR 4.2) and induced pain by bending forward (LR 0.48) are additional

useful clues to reach the correct diagnosis. Although less studied, the loading extension test (reproduction of leg symptoms while maintaining moderate extension up to 30 seconds) may have some interesting specificity.

In a very recent case control study involving 1448 patients with a primary complaint of back pain, the authors found that the most diagnostic combination for the clinical syndrome of LSS included a cluster of 1) bilateral symptoms 2) leg pain more than back pain 3) pain during walking/standing 4) pain relief upon sitting and 5) age >48 years. Failure to meet the condition of any one of five positive examination findings demonstrated a high sensitivity of 96% and a low negative likelihood ratio (LR) of 0.19. Meeting the condition of four of five examination findings yielded a positive LR of 4.6 and a post-test probability of 76%.

Additional investigations

Once clinical symptoms and signs suggest neurogenic claudication, radiological investigations may be useful to confirm LSS. There are no definite radiological definitions of lumbar stenosis. It has been determined both from in vitro and in situ studies that the cross-sectional area of the dural sac above 70 to 80 mm² would be unlikely to cause symptoms. There are however conflicting results about the correlation between the cross-sectional area of the dural sac and the severity of clinical symptoms of neurogenic claudication. Electro-diagnostic studies are sometimes used in clinical practice, however these studies have low sensitivity and specificity for neurogenic claudication.

Conservative Treatments

The clinical course of mild to moderate symptomatic LSS patients is favourable in up to 50% of cases. There are few studies of conservative treatments. Patients are commonly treated according to recommendations published for chronic low back pain patients. Gabapentin might be the only exception. In a small randomized controlled study, the addition of gabapentin to standard therapy was shown to be superior to the addition of placebo in terms of pain and walking distance.

Rehabilitation programs are often used in addition to pain medication with the assumption that exercises might delay the consequences of deconditioning. Postural therapy (body posture) is also prescribed to enhance lumbar spinal canal diameters and relieve pain. There are no solid studies to sustain these approaches. There is only one randomized trial testing a complex combination of manual physical therapy interventions, exercise, and a progressive body-weight supported treadmill walking regimen. A positive effect was found on perceived recovery but not on pain or function.

There is good evidence that inter-laminar epidural corticosteroid injection without fluoroscopic guidance is ineffective. A recent systematic review suggests that epidural steroid injections provide limited improvement in short-term and long-term benefits in LSS patients. The addition of corticosteroids to bupivacaine does not

have an additional effect. Foraminal injection appears to be less effective in LSS than in patients with radicular pain due to disc herniation.

Surgical treatments

There is some evidence that inter-spinous devices and good evidence that decompressive laminectomy are better than “usual care”. Results of randomized trials comparing surgery and non-surgical care are often confounded by high rate of cross-over. A recent study showed no difference between the two groups but the non-surgical group followed a well-structured physical and education program. According to a systematic review the long-term success rate of surgery varies between 45% and 72%. In one randomized controlled study bilateral laminotomy was found to be superior to bilateral laminectomy in terms of pain relief but it had no additional beneficial effect on walking distance.

Predictors of poor surgical results are depression, cardio-vascular co-morbidities, scoliosis and associated disorder influencing walking abilities. Serious complications appear to be very rare in randomized controlled studies.

In a recently published RCT, a comprehensive post-surgical rehabilitation program failed to improve surgical results.

Shared decision making

As symptomatic LSS is a fluctuating chronic disease, the need for surgery and the best time to perform surgery is often difficult to determine. In addition, these patients often have unrealistic expectations about the risk/benefit ratio of surgery. Thus, it is recommended that for patients with persistent severe pain and disabling functional impairment, decisions regarding surgery for LSS should be based on a shared decision-making approach. Shared decision making involves providing patients with the knowledge needed to make an informed decision and ensuring that the decision reflects the patient’s preferences and values in terms of what matters most to the patient (e.g. pain, function, risk, etc...). For patients with LSS, key knowledge would include the moderate benefit associated with surgery that may diminish over time, the likelihood of improvement with or without surgery and the potential risk and costs. Shared decision-making video program have been shown to improve the patient’s knowledge and influence treatment decisions regarding spine surgery.

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Regional musculoskeletal pain syndromes

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LEARNING OBJECTIVES

- ➔ To list and describe the spectrum of conditions that can present as regional musculoskeletal pain
- ➔ To outline the classification of regional musculoskeletal pain syndromes
- ➔ To describe and explain the anatomical basis of regional musculoskeletal conditions
- ➔ To evaluate the individual with regional musculoskeletal pain by obtaining an appropriate history, examination and investigation approaches
- ➔ To make adequate decisions about additional diagnostic procedures (mainly diagnostic imaging)
- ➔ To describe and explain the diagnostic capabilities and advantages of musculoskeletal ultrasound, over physical examination, in regional musculoskeletal conditions
- ➔ To educate patients about the expected course of their symptoms, and factors that might influence prognosis
- ➔ To manage these disorders

1 Introduction

Pain at regional sites, such as the shoulder, knee, lateral elbow, heel or trochanter, is the most common form of musculoskeletal complaint encountered by clinicians in musculoskeletal practice. Most of these complaints are due to soft tissue disorders, and these will form the focus of this chapter. Complex regional pain syndromes (CRPS) are also described here.

This chapter starts with a general overview of the classification of regional musculoskeletal complaints and their epidemiology. The importance of a thorough knowledge of functional anatomy in understanding many of these conditions and their clinical assessment (history, examination and investigation) and management is emphasised. The role of musculoskeletal ultrasound in the diagnosis and local management of the above disorders is also described.

Finally, common specific regional pain syndromes are discussed and interactive cases will help to provide a more in-depth view of two selected conditions.

2 Definition, classification, aetiology and pathogenesis

Regional musculoskeletal pain syndromes (MPS) are disorders of tendons, ligaments, bursae, joint capsules, fasciae, muscles and peripheral nerve entrapments in one or more regions of the body. The presenting symptom is typically pain, arising from soft tissue owing to underlying structural pathology, pain in soft tissues without underlying structural pathology or more diffuse pain syndromes such as CRPS.

Clear, concise and universally accepted terminology in the description and classification of regional MPS is important. Much of the confusion in terminology relates to the many complexities in disorders of the soft tissues, the lack of a true anatomical basis, the lack of evidence for validity and reliability of most classification systems, and the difficulty in establishing a clear diagnosis by clinical assessment. However, with advances in understanding of pain pathways and imaging techniques, our insight into the diagnosis and treatment of these conditions is improving. The implementation of musculoskeletal ultrasound in rheumatological practice leads towards the objective classification of specific disorders, and should be considered as the 'rheumatologist's stethoscope'.

2.1 Classification systems for regional MPS

Classification of regional MPS can be as follows;

2.1.1 Underlying pathology

1. Pain with underlying structural lesions; tendon, ligament, muscle disorders, bursal pathology, enthesopathy, neurovascular entrapment (carpal, tarsal, cubital tunnel syndrome, thoracic outlet syndrome).
2. Pain without underlying structural pathology: referred pain, myofascial syndrome.
3. Complex regional pain syndromes (CRPS type I, type II).

2.1.2 Pain: regional site, and duration

1. Regional site of pain: shoulder, elbow, wrist, hand, hip, knee, ankle, etc.
2. Duration: <2 weeks (acute), 2–12 weeks (subacute) and >12 weeks (chronic)

2.2 Aetiology and pathogenesis of soft tissue lesions

Information on the aetiology of the symptoms helps to classify the complaint and also to manage it.

Local and systemic risk factors predisposing to soft tissue lesions are presented in boxes 1 and 2. In some patients, however, no explicit cause can be identified.

Box 1 Aetiological or risk factors in soft tissue lesions

Intrinsic

- Strength and proprioception decline with age
- Biomechanical malalignments
- Muscle imbalance
- Hypermobility/hypomobility (localised or general)
- Impaired vascularity/innervation
- Fatigued muscles (altered movement patterns)

Extrinsic

- Poor equipment
- High musculoskeletal demand—musculoskeletal overuse
- Inadequate training patterns (volume, content, intensity, timing)
- Trauma
- Environment (e.g., extremes of temperature)
- Drugs (see box 2)

Others

- Immobilisation (tissue atrophy, weakness)
- Local steroid injection
- NSAIDs (can mask injury)

NSAIDs, non-steroidal anti-inflammatory drugs.

Box 2 Systemic disorders and drugs associated with soft tissue disorders

- Inflammatory and crystal arthropathies
- Any joint pathology which may alter biomechanics
- Diabetes mellitus
- Oestrogen deficiency (including menopause)
- Drugs: glucocorticoids, fluoroquinolone antibiotics, anabolic steroids.
- Possibly, stress and overtraining: increased circulating glucocorticoids and catecholamine

2.3 Myofascial syndrome

Regional myofascial pain syndrome presents with muscle pain in a specific region of the body. Exertion of pressure on sensitive points in the muscles trigger points (TPs) causes pain in seemingly unrelated parts of the body (referred pain). It can be associated with a number of other sensory, motor or autonomic phenomena (Cummings and Baldry, 2007).

2.4 Complex regional pain syndromes

Reflex sympathetic dystrophy and causalgia were changed and renamed (1994) as CRPS according to the type of inciting event (CRPS type I and II), rather than by any differences in the clinical presentation or pathophysiology. The modified diagnostic criteria, mentioned above, produced better discrimination between CRPS and non-CRPS neuropathic pain (Harden et al, 1999; Harden et al, 2007).

CRPS type I is characterised by the presence of an initiating noxious event or a cause of immobilisation. CRPS type II is characterised by the presence of a defined nerve injury. Both, types I and II have the following characteristics:

1. Continuing pain, allodynia or hyperalgesia disproportionate to the inciting event.
2. Evidence of oedema, changes in skin blood flow or abnormal sudomotor activity in the painful region at some point during the evolution (figure 1).
3. The diagnosis excludes conditions that would otherwise account for the degree of pain and dysfunction.

Figure 1 Complex regional pain syndrome. (Source: Cofer, <http://www.lecofer.org>)



Note: Criteria 1, 2 and 3 are necessary for a diagnosis of complex regional pain syndrome.

3 Clinical principles and paraclinical examinations

3.1 History

Assessment starts with taking a careful history, usually a pain history (site, radiation, character- mechanic/ inflammatory, time and mode of onset, aggravating factors, associated symptoms, functional limitation). A further history is obtained, noting past medical history, previous episodes of pain, management to date, presence of other pain problems, hand dominance, occupation, sports and hobbies. This information may help to establish a diagnosis, and to estimate the prognosis of the pain problem. A systemic enquiry is also important, as regional pain may be due to an underlying medical condition (e.g., neoplasm or inflammatory arthritis).

3.2 Examination

Clinical examination of a regional musculoskeletal complaint involves specific steps: inspection, palpation (areas of tenderness), movement assessment by specific testing). Remember that examination is not restricted to the site of pain—for example, upper limb pain syndromes may be referred from the neck. The examination is completed by performing a general medical examination including neurovascular status.

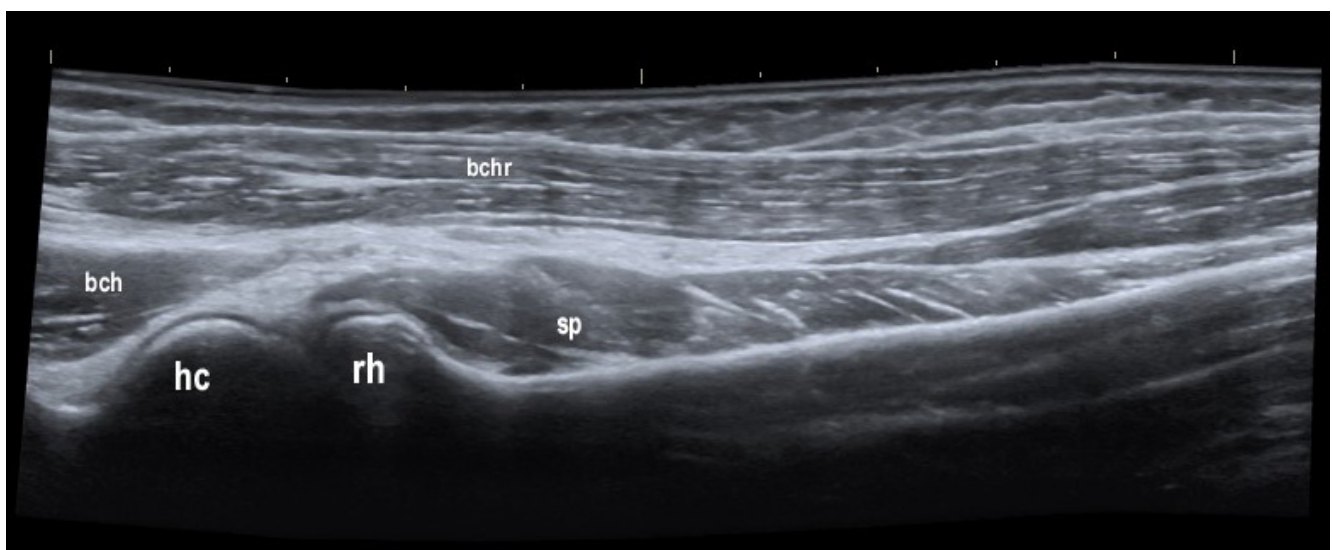
3.3 Investigation

In some patients, further investigation, guided by the clinical picture is necessary to clarify the diagnosis and/or take the appropriate therapeutic decision. This may involve blood tests if an underlying systemic disease is suspected. However, in most cases investigation will involve imaging—in particular, diagnostic ultrasound. Plain radiography, magnetic resonance imaging (MRI), computed tomography (CT) and nuclear medicine techniques may be alternative imaging modalities in a few patients when a thorough history and examination do not provide sufficient diagnostic information.

3.3.1 Diagnostic musculoskeletal ultrasound

Over the past decade, high-resolution, high-frequency musculoskeletal ultrasonography has been progressively incorporated into rheumatology practice. This imaging modality provides valuable real-time morphological and functional information about musculoskeletal structures (figure 2).

Figure 2 Panoramic ultrasound image of the elbow and forearm in longitudinal plane. The humeroradial joint and different muscles are visualised. bch, brachialis muscle; bchr, brachioradialis muscle; hc, humeral condyle; rh, radial head; sp, supinator muscle.



Musculoskeletal ultrasound performed at the time of the consultation allows for an immediate correlation between imaging findings and clinical data, which can greatly enhance diagnosis capability and improve management of patients with soft tissue disorders (Micu et al, 2013). The principal applications of ultrasonography in soft tissue disorders are summarised in box 3. Power and colour Doppler enables assessment of blood flow in soft tissue lesions. However, its value is extremely user-dependent and the user must have a solid knowledge of functional anatomy, scanning technique, normal sonoanatomy and pathological findings.

Box 3 Applications of musculoskeletal ultrasonography in soft tissue disorders**1. Tendon lesions**

- 1.1 Differential diagnosis between tendinosis, tenosynovitis/paratenonitis, enthesopathy, tear and subluxation
- 1.2 Evaluation of extension and size of tendon tears
- 1.3 Detection of tendon calcification and microcrystal deposits
- 1.4 Assessment of tendon function

2. Bursitis

- 2.1 Detection of bursitis, including some that are neither visible nor palpable by clinical examination
- 2.2 Differential diagnosis between bursitis, cellulitis and arthritis

3. Ligament lesions

- 3.1 Diagnosis of acute and chronic ligament rupture (medial collateral ligament at the knee, lateral ligaments at the elbow and ankle)

4. Muscle lesions

- 4.1 Detection of muscle ruptures
- 4.2 Evaluation of extension and size of muscle ruptures
- 4.3 Assessment of muscle function
- 4.4 Monitoring of healing process of muscle ruptures
- 4.5 Detection of ossificant myositis

5. Peripheral nerve entrapments

- 5.1 Diagnosis of nerve compression at osteofibrous tunnels
- 5.2 Detection of local causes of peripheral nerve entrapment
- 5.3 Diagnosis of some superficial neurogenic tumours (Morton's neuroma, schwannomas)

6. Ganglia and cysts

- 6.1 Diagnosis of ganglia and assessment of their size and relation with neighbouring structures

7. Subcutaneous masses

- 7.1 Differentiation between solid or liquid nature

8. Guidance of perilesional and intralesional musculoskeletal injections**3.3.2 MRI**

MRI has the advantage over ultrasound of allowing imaging of any anatomical structure or location (particularly bone marrow, which is not visible on ultrasound). It provides excellent multiplanar imaging of all anatomical structures and T1- and T2-weighted images, and fat-suppressed and proton-dense views provide information about bone oedema, blood or water content and muscle atrophy. MRI is helpful in the differential diagnosis of some disorders such as meniscal lesions or malignant lesions in soft tissues or bones as well as in the management of recalcitrant soft tissue complaints that can lead to clinical misdiagnoses. The disadvantages of MRI are its cost and limitations of accessibility.

3.3.3 CT

CT involves exposure to radiation and is reserved for defining details of bony anatomy that may contribute to soft tissue pain—for example, subtle osteophyte formation, when MRI has been insensitive or when contraindicated. Otherwise it has few advantages over MRI.

3.3.4 MRI or CT arthrography

MRI or CT arthrography are useful for the identification of labral and capsular pathologies in the shoulder.

3.3.5 Plain radiography

Radiography need not be performed routinely but allows confirmation or can help to exclude bony pathology (e.g., ruling out glenohumeral osteoarthritis in painful shoulder).

Radiographs also allow identification of any anatomical features that may be contributing to the injury or condition (e.g., an acromial spur in rotator cuff tendinopathy contributing to subacromial impingement, tendon calcifications, or a Haglund's deformity in retrocalcaneal bursitis and Achilles tendinitis).

3.3.6 Radionuclide imaging

Radionuclide imaging (bone scans) can be useful to exclude osseous or joint pathology. Triple phase bone scans are used in the assessment of CRPS.

3.3.7 Electrophysiological studies

Electrophysiological studies (i.e., nerve conduction and electromyography) can be useful for confirming the diagnosis of clinically suspected peripheral nerve entrapments and evaluating their severity.

3.3.8 Positron emission tomography (PET)

PET is a nuclear medicine functional imaging technique feasible for studying skeletal muscles (superficial and deep) during exercises. No studies have examined applications of PET or single-photon emission CT for regional pain syndromes.

4 Principles of management

Although there is limited high-quality evidence for the efficacy or effectiveness of many interventions, several general principles can be followed in the management of patients with regional MPS. The underlying principle of management of most regional musculoskeletal complaints is to control pain so that rehabilitation can proceed. Rehabilitation is a customised process, which aims to achieve an optimal functional outcome. In addition, providing information to the patient about the nature of the condition, beneficial and negative habits

and activities, self-help exercises, expected response to treatment and outcome should all be part of the approach to these patients.

4.1 Exercise

Relative rest, active rehabilitation and a gradual return to tendon-loading activities are key points in successful treatment of soft tissue disorders. Progressive exercise is a fundamental part of the treatment of most regional musculoskeletal complaints (Cummings and Baldry, 2007). An exercise programme can be designed and supervised by well-trained physiotherapists and can be started early, initially with postures and active isometric muscle contractions (against resistance, without joint movement) in the acute injury, in order to achieve a functional recovery and prevent further injury. The goal should be to work towards full, specific, pain-free functional activity. All activity should be followed by further flexibility exercises. Aquatic treatment, when possible, should be part of the rehabilitation strategy as it promotes non-weight bearing movements of the affected anatomical region.

In myofascial pain syndromes, a review of postural problems and ergonomics should be carried out. The aim in these conditions is to reduce the neural sensitisation that is considered to drive much of the pain.

Proprioceptive training is important in some conditions, such as ankle sprains and rotator cuff complaints. Muscle imbalances, which are common and yet overlooked, must be assessed and considered when designing an exercise programme.

4.2 Pain management

Non-pharmacological and/or pharmacological approaches to pain management can be used.

4.2.1 Non-pharmacological approaches

The most frequently used modality in acute soft tissue injuries is ice, which has anti-inflammatory and analgesic actions.

Therapeutic ultrasound is used in soft tissue injuries, although there is no good evidence to support its use (Speed, 2001). It increases soft tissue extensibility, decrease tissue stiffness and muscle spasm, increase blood flow and modulate pain. Some experimental evidence suggests that ultrasound may speed resolution of inflammation, accelerate fibroblast function, accelerate angiogenesis and increase matrix synthesis and the strength of healing tissues.

Laser therapy has effects similar to those of ultrasound. It decreases inflammation and may be useful in superficial injuries.

Extracorporeal shock wave therapy (ESWT) is used in the treatment of insertional tendon lesions (enthesopathies). Animal model studies have indicated that its effects include tissue repair, reduction of nociceptors and reduction of calcification. Evidence supports the use of focused ESWT in calcific tendinopathies (Speed, 2014).

Acupuncture and transcutaneous electrical nerve stimulation (TENS) may also be helpful in the management of pain, particularly that resulting from chronic soft tissue injuries (Johnson and Martinson, 2007).

Resting splints, used intermittently, are often useful for the prevention of soft tissue shortening while healing is taking place (e.g., in plantar fasciitis and Achilles tendinosis). They can also stop excessive movement.

4.2.2 Pharmacotherapy

When intervention with medication is considered necessary in the management of regional pain, analgesic therapy or non-steroidal anti-inflammatory drugs (NSAIDs) may be an alternative as first choice. Those patients with night pain who do not respond to these treatment alternatives may benefit from short-term supplementation with an opioid compound (synergistic effect). (e.g., Green et al, 2002; Speed, 2005).

The potentially significant side effects of NSAIDs are many and varied, including gastrointestinal effects (less marked with cyclo-oxygenase 2 selective drugs) and thrombotic cardiovascular effects. The results of some small randomised trials support the use of topical NSAID gel or iontophoresis for short-term pain control, without systemic side effects (Mazières et al, 2005).

Other more potent drugs that may be useful in the management of regional pain include regular basic analgesics, tricyclic agents, gabapentin and pregabalin, which are used mostly where there is significant neuropathic pain. Although considered standard approaches in this situation, evidence for efficacy is lacking and side effects are a concern. Antibiotics are indicated when a soft tissue infection is confirmed.

4.3 Injection therapies

4.3.1 General approach

Local injection therapies are commonly used for soft tissue disorders and include a spectrum of injectates. Again, strong evidence is lacking for their use in most musculoskeletal complaints.

Classic routes and injectates for local injection therapies in soft tissue complaints are listed in box 4. The choice of injectate depends upon the specific characteristics of the condition. Those most commonly used include glucocorticoid for its anti-inflammatory properties and pain control, local anaesthetic (LA), particularly for diagnostic purposes, sclerosants for pain management, dry needling and platelet-rich plasma to promote healing, botulinum for muscle pain, and nerve blockades for general pain relief regionally.

Musculoskeletal injections are often performed using external anatomical landmarks ('blind' injections). Some studies have reported a variable accuracy of palpation-guided needle placement in extra-articular and intra-articular injections and higher incidental damage of adjacent non-target structures in comparison with ultrasound-guided interventional manoeuvres (Slawsky et al, 2011).

Ultrasound is a valuable tool for guiding accurate and safe musculoskeletal perilesional or intralesional injections. At the same time, this technique provides confirmation of the clinical diagnosis and the indication for injection. Real-time ultrasound enables accurate needle placement. Drug delivery can be visualised during and after the procedure (figures 3 and 4, video 1 and 2). Injections into anatomical structures adjacent to the intended target (e.g., vessels, nerves, subcutaneous fat) can be avoided because they are easily identified by ultrasound.

Video 1. Real time video for corticosteroid injection inside the subacromial subdeltoid bursa Transverse scanning of the supraspinatus tendon. The needle is penetrating (free hand injection, 'in plane' technique) the skin, subcutaneous tissue, deltoid muscle and superficial SASDb wall. CS deposition is made strictly inside the bursa. (You must be connected to internet and use Acrobat reader to see the video. Another version is available in the "images" section of the course)



Video 2. Postprocedural hyperechoic (white) corticosteroid deposition strictly inside the subacromial subdeltoid. Longitudinal scanning of the supraspinatus tendon. (You must be connected to internet and use Acrobat reader to see the video. Another version is available in the "images" section of the course)



Box 4 Routes and materials for regional musculoskeletal pain

Routes

- Intra-articular (capsulitis)
- Intrasheath (tenosynovitis)
- Intrabursal (bursitis)
- Intratendinous (sclerosant treatment for pathological neovascularisation, autologous blood, platelet-rich plasma, dry needling)
- Local infiltration (carpal tunnel, trigger point, ligament, muscle)
- Peripheral nerve blockade (perineural injection)

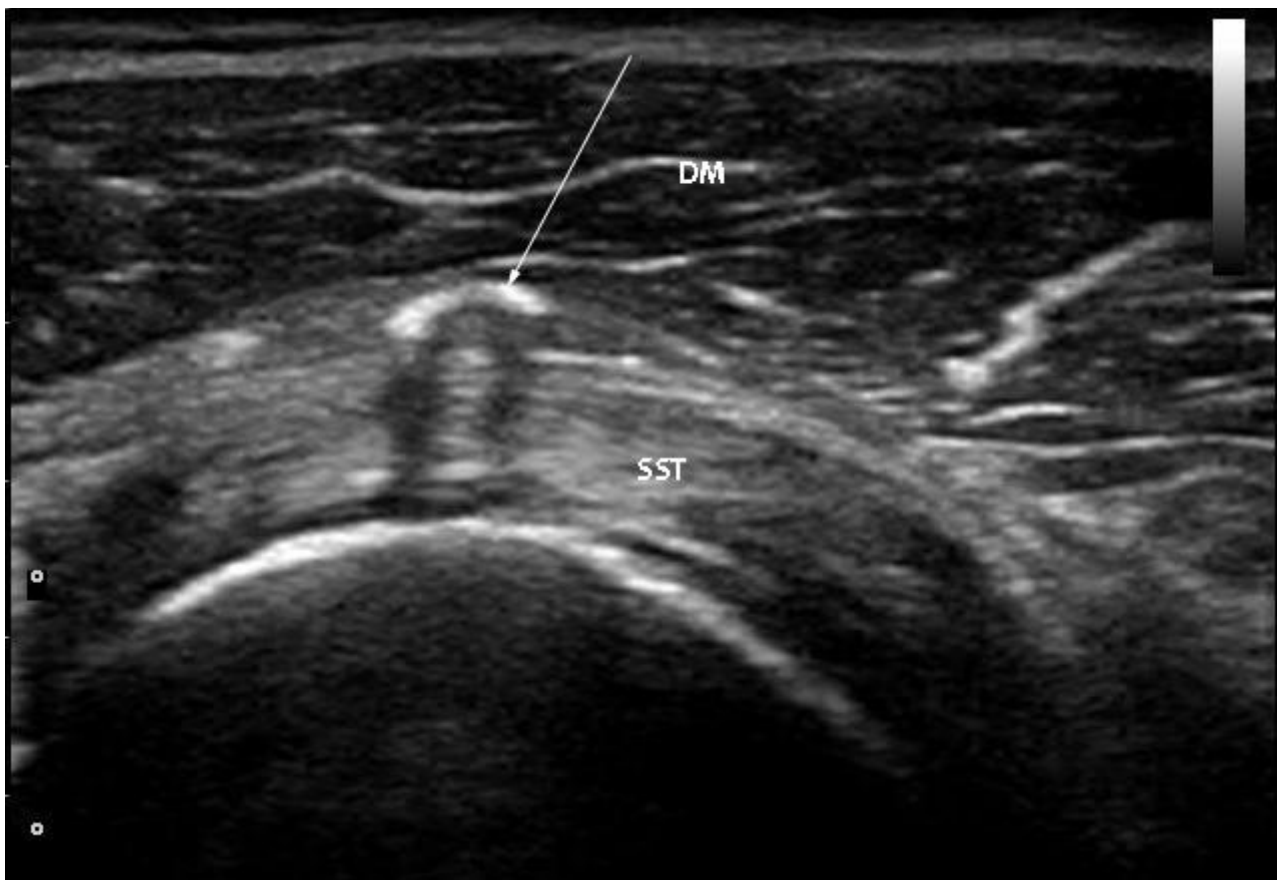
Materials

- None (dry needling)
- Local anaesthetic
- Glucocorticoids (with/without local anaesthetic)
- Viscosupplementation agents (joint pain)
- Sclerosants
- Platelet-rich plasma
- Botulinum toxins
- Heparin
- Prolotherapy (dextrose and lidocain)

Figure 3 Glucocorticoid deposition (hyperechoic spots, long arrow) inside the subacromial-subdeltoid bursa during injection. The needle (short arrow) is visualised as hyperechoic. DM, deltoid muscle; SST, supraspinatus muscle tendon.



Figure 4 Glucocorticoid deposition (hyperechoic spots, long arrow) inside the subacromial-subdeltoid bursa after injection. DM, deltoid muscle; SST, supraspinatus muscle tendon.



Although the impact of accurate needle placement in the therapeutic response to local glucocorticoid injection reported in the literature needs further elucidation (Naredo et al, 2004), injection accuracy is significantly higher when imaging is used to guide musculoskeletal injections than with landmark-guided traditional injections (Daley et al, 2011).

4.3.2 LA injections

Injections of LA alone are used for both diagnostic and therapeutic purposes in soft tissue conditions. In the patient with myofascial pain, local injection of a TP with anaesthetic aims to mechanically disrupt it and, where LA is used, desensitise the area. Reduction of pain then allows a stretching and exercise programme, to increase the range of motion, and to improve exercise tolerance.

4.3.3 Glucocorticoid injections

Most local glucocorticoid injections for soft tissue disorders are extra-articular, and are either delivered around the lesion (e.g., peritendinous or tendon sheath infiltration), or into the lesion itself, (e.g., intrabursal injection). Steroid injections are also used for diagnostic and therapeutic nerve blockades. Contraindications and unwanted effects of local glucocorticoid injections are listed in box 5.

Box 5 Contraindications and unwanted effects of local glucocorticoid injections in soft tissue lesions

Contraindications

- Local or systemic infection
- Coagulopathy
- Tendon tear

Potentially unwanted effects of local glucocorticoid injections

- Hypersensitivity—local or systemic
- Tissue atrophy
- Tendon rupture
- Infection—local or systemic
- Post injection ‘flare’ of symptoms
- Osteonecrosis/steroid arthropathy (intra-articular injections, weight bearing joints)
- Facial flushes
- Abnormal menstrual bleeding

Some suggestions for the practical application of local glucocorticoid injections are given in box 6. Intra-articular injections for soft tissue conditions include those used for capsulitis, with or without hydro distension of the joint.

Box 6 Suggestions for practice when using local glucocorticoid injections

- Informed consent should be obtained from the patient, who must be willing to follow post injection guidelines
- The practitioner should have full knowledge of the local anatomy
- Select the finest needle that will reach the lesion according to the injected drug
- The practitioner's hands and the patient's skin should be cleansed and a no-touch technique used
- Use short-/medium-acting glucocorticoid preparations in most cases, with local anaesthetic
- Injection should be peritendinous; avoid injection into tendon substance
- A minimum interval should be respected between injections (e.g., 3–6 weeks)
- Use a maximum of three injections at one site. However, it depends on the anatomical area, interval between injections and previous response
- Soluble preparations may be useful in those patients who have had hypersensitivity/local reaction to previous injection
- Details of the injection should be carefully recorded
- Do not repeat if two injections do not provide at least 4 weeks' relief
- Warn the patient of early post injection local anaesthesia, to avoid initial overuse
- The patient should inform the doctor if there is any suggestion of infection or other significant adverse event
- Use ultrasound guidance if available, especially for complex anatomical areas

4.3.4 Botulinum toxins

Botulinum toxins block the presynaptic release of the neurotransmitter acetylcholine in a number of painful conditions, including myofascial pain, muscular low back pain, spasticity, headache and other neurological disorders.

4.3.5 Others

Low-dose heparin has been used in the management of acute Achilles paratenonitis on the basis of limiting the formation of adhesions. However, there is some evidence showing no beneficial effect and it has been suggested that heparin may, itself, cause a degenerative tendinopathy.

Hyaluronic acid injection has also been proposed as an approach in the management of soft tissue mediated pain. Some promising results have been seen in the treatment of tendinopathies. The positive effect relies on its anti-inflammatory activity, enhanced cell proliferation and collagen deposition and lubricating action (Abate et al, 2014).

Subacromial injection of anakinra, has been proposed for the management of rotator cuff tendinopathy and subacromial bursitis. However, no randomised controlled trials (RCTs) have been performed.

Other injection techniques that are sometimes used in chronic conditions include autologous blood injections and sclerosant treatments, but the evidence for these is limited (Hoksrud and Bahr, 2011; Burke CJ et al, 2016).

Platelet-rich plasma (PRP) injections may help in tendon healing by modifying their intrinsic reparative capacity (Dragoo et al, 2014; Lhee SH and Park JY, 2013; Gosens T et al, 2012; Zhang JY et al, 2016)..

4.4 Surgery

Surgery is usually avoidable for soft tissue disorders, but can be considered under some circumstances (box 7).

Box 7 Indications for surgery in soft tissue conditions

Assessment

- Arthroscopic assessment of soft tissue disorders related to joint pathology

Repair of structures

- To repair total rupture of a structure, such as the Achilles tendon or the rotator cuff
- To repair tears within the tendon substance that have failed to heal and continue to prevent a positive response to conservative management

Excision of degenerate lesions or partial tears

- To resect mucoid degeneration in patellar or elbow common extensor tendon tendinopathy

Release of structures (if strongly impairing function)

- To release tight or scarred structures (e.g., adhesive capsulitis)
- To release an area of stenosis surrounding a tendon (e.g., stenosing tenosynovitis) or a peripheral nerve (e.g., carpal tunnel syndrome)

Alteration of contributing anatomical structures

- On failure of conservative management in a tendinopathy where there is a precipitating mechanical cause, such as Haglund's deformity in retrocalcaneal bursitis (see below)

Instability

- Continuing mechanical and functional instability of a joint such as shoulder dislocation, especially in young people

Inadequate response to conservative treatment—persistent pain and functional impairment

5 Common regional MPS

This section describes the diagnosis and management of several regional musculoskeletal pain problems in more detail. It is certainly not exhaustive, but covers several important regional pain syndromes found in rheumatology practice. At the end of this chapter suggestions are given for further reading on MPS.

In clinical practice we rely on proposed guidelines or protocols and stratify our therapeutic options according to a certain identified pathology. Ultrasound evaluation performed immediately after clinical examination may deliver new information about the underlying pathology, may change the clinical diagnosis and lead to a change in the therapeutic strategy (Micu et al, 2013).

5.1 The shoulder

5.1.1 Epidemiology and risk factors

Shoulder complaints cause significant pain and disability in the general population and place a major burden on the economy owing to the cost of healthcare, lost earnings and social security payments. Shoulder pain has a point prevalence of 7–21% of adults in the community and is the second most common musculoskeletal complaint presenting to primary care, with only back pain presenting more often (Killian et al, 2012).

Most shoulder complaints are due to soft tissue lesions, with chronic degenerative rotator cuff disorders being the most common group. The origin of many shoulder complaints is multifactorial and articular and extra-articular disorders can coexist. Repetitive work or sport overhead activity are considered the major risk factors for rotator cuff lesions. Other risk factors include old age, shoulder anatomical variants and glenohumeral instability or hypermobility in young people (Killian et al, 2012).

5.1.2 Clinical anatomy

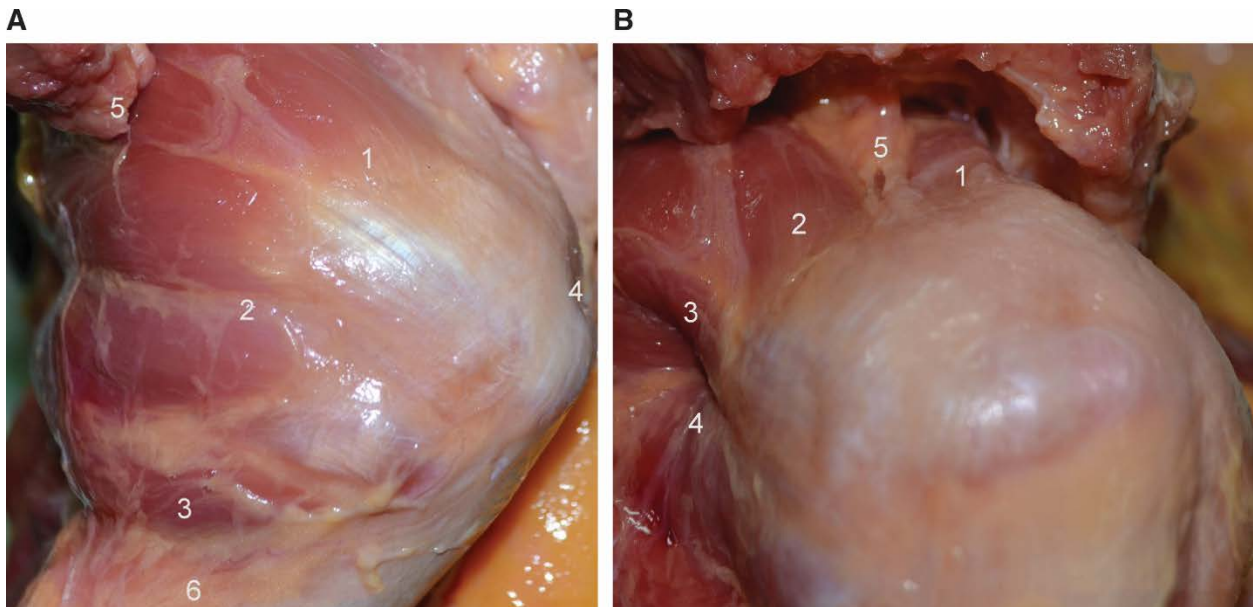
The functional anatomy of the shoulder is complex, probably because it has the greatest mobility among all joints in the body. The shoulder girdle is composed of four articular surfaces (i.e., sternoclavicular, acromioclavicular, glenohumeral, and scapulothoracic). Surrounding muscles and ligaments provide stability to the glenohumeral joint. Among them, the rotator cuff (RC) is the primary dynamic stabiliser by compressing the humeral head in the glenoid fossa during shoulder abduction. The RC is composed of four muscles (i.e., supraspinatus, infraspinatus, subscapularis and teres minor) that form a cuff around the head of the humerus, to which these muscles attach (figures 5A, B).

The biceps muscle is made up of a long and a short head, each of which has different proximal tendon origin, and shares a distal attachment at the radial tuberosity and the ulna. The coracohumeral and the transverse humeral ligament (an extension of the subscapularis tendon) maintain the biceps tendon into the bicipital groove.

The large subacromial–subdeltoid bursa covers the rotator cuff and lubricates and protects these tendons from the pressure and friction of the under surface of the acromion.

The principal actions attributed to the rotator cuff muscles are humerus abduction by the supraspinatus (along with the deltoid muscle), external rotation by the infraspinatus primarily and teres minor, and internal rotation by the subscapularis. The pectoralis major, latissimus dorsi and teres major also assist in internal rotation. The action of the biceps brachii muscle is supination and flexion of the forearm.

Figure 5 (A) Rotator cuff. 1, supraspinatus muscle; 2, infraspinatus muscle; 3, teres minor muscle; 4, greater tuberosity; 5, spine of the scapula; 6, humeral shaft. **(B) Rotator cuff and subacromial space.** 1, subscapularis muscle; 2, supraspinatus muscle; 3, infraspinatus muscle; 4, teres minor muscle; 5, coracohumeral ligament. (Image provided as a courtesy of I Moller, M Miguel, D Bong, University of Barcelona, Spain.)



5.1.3 Main causes of shoulder pain

The main causes of shoulder pain are outlined in table 1. Most patients with shoulder pain have lesions involving the RC tendons, particularly the supraspinatus tendon. RC impingement is considered the initial stage of tendinosis and tear in most patients with painful shoulder syndrome. In clinical practice and on imaging (i.e., ultrasound, MRI), these disorders are often found to overlap in the same patient.

5.1.4 Pathogenesis of shoulder tendinopathy

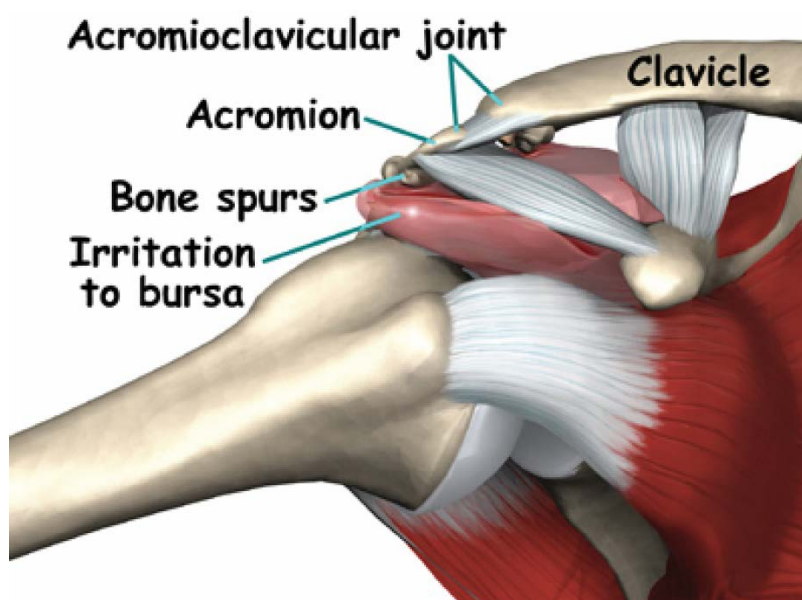
The pathogenesis of tendon disorders in painful shoulder syndrome remains unclear. Histopathological studies have described a degenerative process of the tendon with little evidence of inflammation, which may play a role only in the early stages of the pathogenic process (Rees et al, 2006; Dean et al, 2013). Because inflammatory changes are seldom present, the terms ‘tendinosis’ or ‘tendinopathy’ may be more appropriate than ‘tendinitis’.

Intrinsic (i.e., tendon degeneration due to overuse and ageing, microvascular insult) and extrinsic factors (i.e., compression of the rotator cuff by surrounding structures such as the acromion, the coracoacromial ligament and/or the coracoid process) (figure 6) have been involved in the pathophysiology of rotator cuff disorders.

Table 1 Main causes of shoulder pain

Site	Lesions
Rotator cuff (associated lesions commonly found)	Impingement Tendinosis Tear (partial-thickness, full-thickness, complete) Calcifying tendinopathy
Tendon of long head of biceps	Tendinopathy and tenosynovitis Tear (partial, complete) Subluxation/dislocation
Bursae	Subacromial–subdeltoid bursitis Other bursitis
Capsule	Adhesive capsulitis
Joint complex	Capsulolabral lesions
Joints	Glenohumeral osteoarthritis Acromioclavicular osteoarthritis, dislocation
Nerves	Lesions of cervical roots, brachial plexus or peripheral nerves, thoracic outlet syndrome
Muscle	Myofascial pain syndromes
Others	Local bone or muscle destructive lesions
Referred pain	Cervical spine, intrathoracic tumours, ischaemic heart disease, hepatic and gallbladder diseases

Figure 6 Subacromial impingement. (eOrthopod Images provided as a courtesy of Medical Multimedia Group (MMG). Copyright MMG 2001.)



5.1.5 Diagnosis of shoulder pain

The first step in the diagnosis process of non-traumatic shoulder pain should be differentiation between intrinsic causes and referred symptoms caused by disorders extrinsic to the shoulder. Unlike intrinsic shoulder pain, referred pain usually is neither caused nor affected by shoulder movements.

Intrinsic shoulder pain may arise from the intra-articular or the periarticular structures. A careful clinical history and physical examination are useful to distinguish both groups of disorders. However, they can coexist in the same patient. In addition, degenerative periarticular lesions, which frequently overlap, are difficult to distinguish by clinical assessment. In contrast, imaging modalities like ultrasound and MRI are very accurate in the differential diagnosis of most shoulder disorders.

5.1.5.1 History

The primary symptom is pain. A careful history of the shoulder pain should be obtained.

The *onset* of most shoulder symptoms is insidious and may be associated with repetitive microtrauma (overuse).

The *site* of the pain is a relatively useful indication of its source. Pain secondary to RC disease, glenohumeral joint and capsular disorders have similar distributions (mainly shoulder and lateral aspect of the arm). Acromioclavicular and sternoclavicular pain are usually well localised in the joint.

Exacerbating and relieving features are also noted. Pain with activities involving overhead work is suggestive of subacromial impingement or acromioclavicular joint problems. Pain which is unaffected by movement is often due to referred pain from extrinsic pathologies.

Clicking and clunking are symptoms of labral lesions and of instabilities which, in the case of the acromioclavicular and sternoclavicular joints, are well localised compared with the more diffuse symptoms when the glenohumeral joint is involved.

Weakness may be reported, which may be true weakness, pain inhibition or mechanical restriction. True weakness can result from a complete disruption of the rotator cuff tear. Neurological lesions may also cause weakness.

Nerve entrapments typically present with pain, paraesthesia and weakness distal to the site of entrapment.

Swelling of the shoulder region can occur in relation to subacromial–subdeltoid bursitis (most common) or arthritis (acromioclavicular, glenohumeral).

Enquiry about the presence of *systemic symptoms* is mandatory. Symptoms such as fever, weight loss and anorexia may suggest infection, malignancy, inflammatory arthritis or polymyalgia rheumatica.

The degree of *functional disability* may be assessed informally by determining the types and degree of activities affected and the number of days lost from work/play, or by a formal evaluation.

5.1.5.2 Physical examination

Examination of the patient starts with inspection and palpation of the region (site of tenderness, crepitus, temperature). Evaluation of movement starts with inspection of the range, comfort and rhythm of movement while the patient performs active movements in all planes. A painful arc of abduction in mid-range is typical of subacromial pathology, and the pain is often eased with supination of the arm, which decreases impingement. A superior painful arc is found with acromioclavicular pathologies—in particular, osteoarthritis. RC tendinosis and partial-thickness tears are often difficult to distinguish as both may cause pain with little or no loss of motion. Active range of movement can be compared with that of passive movement. Restriction of both is indicative of glenohumeral joint or capsular pathology, whereas good passive range of motion in the presence of active restriction indicates either a musculotendinous or neurological injury.

There are some simple active manoeuvres that provide quick information about the main shoulder movements.

Specific active movements are tested against resistance provided by the examiner, who notes the presence of pain and weakness and whether the latter is out of proportion to the pain. Some of the manoeuvres most used to detect RC and biceps tendon involvement are listed in table 2. These tests are positive when they elicit the pain usually experienced by the patient. In addition, the patient's inability to resist the examiner's pressure may indicate tendon rupture.

Overall, physical examination techniques for RC pathology show moderate sensitivity for the presence of some lesions and low specificity for the distinction of specific tendon involvement and lesions (Naredo et al, 2002*; Lasbleiz et al, 2014), (figures 7 and 8).

The *cervical spine* should also be assessed since it is a common source of shoulder pain. This includes evaluation of range of movement and the surrounding musculature. A full general examination and neurovascular assessment of the upper limbs should also be performed.

Table 2 Principal clinical manoeuvres used to detect rotator cuff and biceps tendon involvement in shoulder pain syndrome

Clinical tests and description	Tested tendon
Impingement manoeuvres of Neer: the examiner stands behind the seated patient and uses one hand to prevent rotation of the scapula while passively raising the patient's arm with the other hand to produce both forward elevation and abduction in order to reduce the space between the greater tuberosity and the anteroinferior aspect of the acromion	Coracoacromial rotator cuff impingement
Hawkins's test: the examiner stands facing the patient, and, after raising the patient's arm to 90° of strict forward elevation with the elbow in 90° flexion, rotates the arm medially by lowering the forearm	Coracoacromial rotator cuff impingement
Yocum's test: the patient is asked to place the hand on his or her other shoulder and to raise the elbow without raising the shoulder	Coracoacromial rotator cuff impingement
Jobe's manoeuvre: the examiner stands facing the patient, who places both arms in 90° abduction and 30° horizontal adduction, in the plane of the scapula, with his thumbs pointing downward in order to produce medial rotation of the shoulder; the examiner then pushes the patient's arms downward while asking the patient to resist the pressure	Supraspinatus tendon
Patte's manoeuvre: the examiner supports the patient's elbow in 90° of forward elevation in the plane of the scapula with the elbow in 90° flexion while the patient is asked to rotate the arm laterally in order to compare the strength of lateral rotation	Infraspinatus tendon
Gerber's lift off test: the patient is asked to place the hand against the back at the level of the waist with the elbow in 90° flexion. The examiner pulls the hand to about 5–10 cm from the back while maintaining the 90° bend in the elbow. The patient is then asked to hold the position without the examiner's help	Subscapularis tendon
Yergason's test: resisted supination of the forearm; the patient is asked to perform a combined movement of flexion at the elbow along with medial rotation of the arm while the examiner resists	Long head of the biceps tendon
Speed's test (palm up test): the patient is asked to raise the arm anteriorly against resistance, with the elbow extended and the palm facing upward	Long head of the biceps tendon
Popeye's sign: visible prominence in the distal arm (i.e., distal displacement of the rupture biceps muscle belly)	Long head of the biceps tendon

Figure 7 Resisted abduction of the shoulder. The rotator cuff (supraspinatus and infraspinatus) is put under tension and the subacromial bursa is compressed. (Courtesy of Professor J A P Da Silva. Reproduced with permission from da Silva and Woolf. Rheumatology In Practice, Springer, 2010.)*



Figure 8 Subacromial impingement test. (Courtesy of Professor J A P Da Silva. Reproduced with permission from da Silva and Woolf. Rheumatology In Practice, Springer, 2010.)*



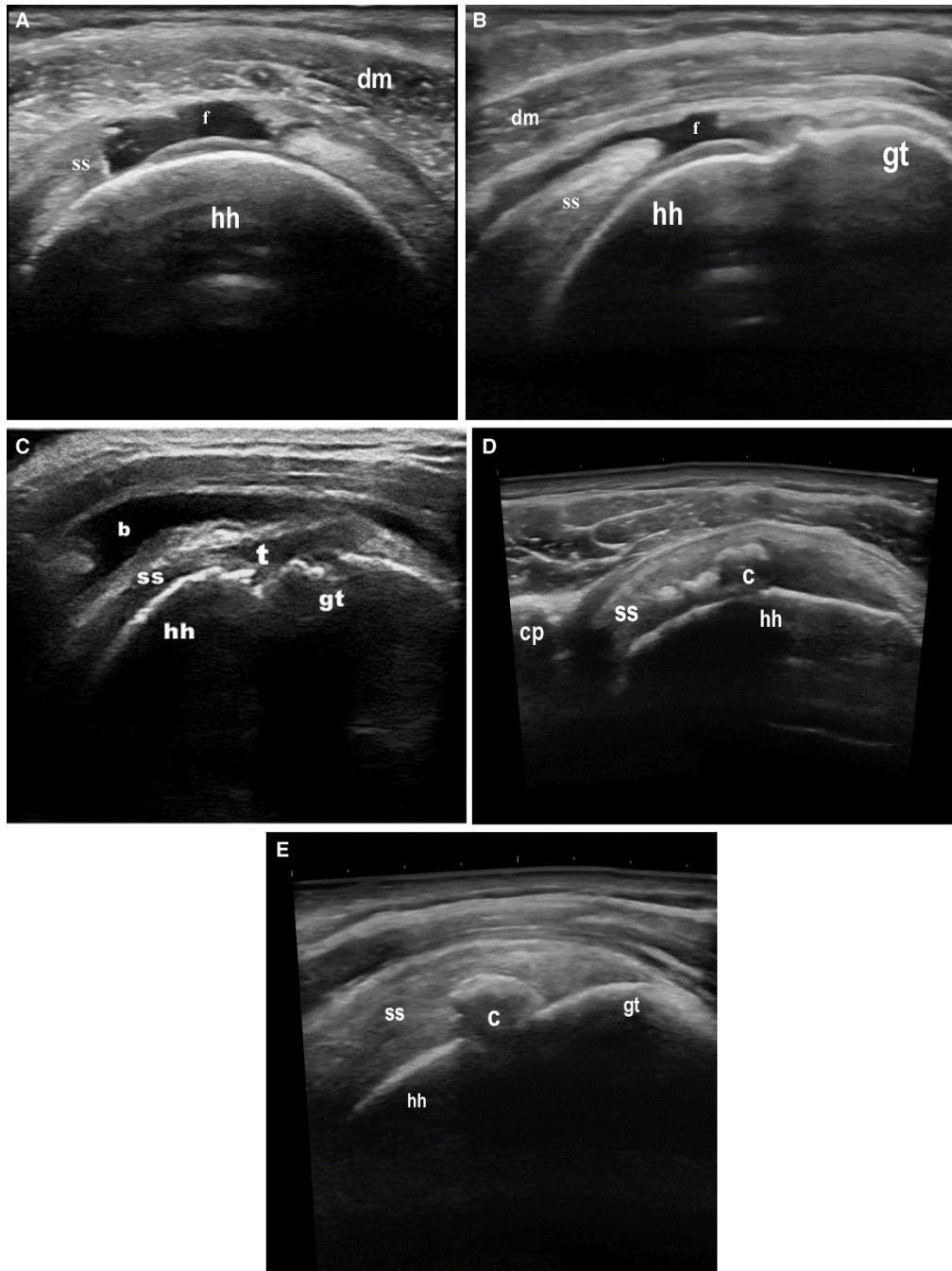
5.1.5.3 Imaging investigation

Diagnostic imaging of the shoulder can be very useful when directed by initial clinical assessment.

Musculoskeletal ultrasound allows both morphology and functional assessment, dynamic investigations of tendon, muscles and joints, comparison with the contralateral shoulder to differentiate anatomical variants from real lesions, immediate correlation between clinical and other imaging findings at the time of consultation, and accurate and safe guidance for injections with better outcome (Tagliafico et al, 2014*). The diagnostic accuracy of ultrasound for detecting subacromial disorders has been dealt with in a systematic literature review and meta-analysis. The results showed a high accuracy of ultrasound for detecting rotator

cuff tears, tendinosis and calcifications, and subacromial–subdeltoid bursitis (Ottenheijm et al, 2010; Ottenheijm et al, 2014). Some illustrative examples are shown in figures 9A–E.

Figure 9 (A) Transverse ultrasound image of the supraspinatus tendon (ss) showing a full-thickness tear filled with anechoic fluid (f). (B) Longitudinal ultrasound image of the supraspinatus tendon (ss) showing a full-thickness tear filled with anechoic fluid (f). (C) Longitudinal ultrasound image of the supraspinatus tendon (ss) showing a partial-thickness tear (t) and subdeltoid bursitis (b). (D) Transverse ultrasound image of the supraspinatus tendon (ss) showing calcifications as hyperechoic foci with acoustic shadowing (c). (E) Longitudinal ultrasound image of the supraspinatus tendon (ss) showing calcifications as hyperechoic foci with acoustic shadowing (c). cp, coracoid process; dm, deltoid muscle; gt, greater tuberosity; hh, humeral head.



Plain radiography of the shoulder generally provides little useful information in non-traumatic shoulder pain. However, this classic imaging technique has considerable value in the diagnosis of fractures, glenohumeral or acromioclavicular osteoarthritis, glenohumeral dislocation and large rotator cuff calcifications.

MRI is highly accurate in the diagnosis of RC tear and bone abnormalities (avascular necrosis, tumours). It is especially valuable in the overall assessment of the rotator cuff muscles and tendons when conservative treatment fails and surgery is planned or when shoulder pathology is complex or unclear. One important limitation is that it does not allow dynamic real-time shoulder examination.

5.1.6 Management

Many treatments for soft tissue disorders of the shoulder exist, but few are supported by strong scientific evidence.

Initial conservative treatment for RC tendinopathy consists of cryotherapy (e.g., ice), relative rest (i.e., avoiding activities that aggravate symptoms, including overhead activities), and NSAIDs (Rees et al, 2006). A short course of scheduled NSAIDs (i.e., 7–10 days) may be recommended by some during the acute symptomatic phase. Thereafter, patients may use NSAIDs occasionally for analgesia if they find the medication effective (Rees et al, 2006; Van der Sande et al, 2013).

Adjunct therapies may include electrical stimulation, phonophoresis and iontophoresis, therapeutic ultrasound, laser and suprascapular nerve blockade.

Physical therapy is used to rehabilitate patients with RC tendinopathy even though there are few well-performed clinical trials of this treatment (active and passive range-of-motion exercises, stretching and strengthening of the muscles of the rotator cuff). Once rehabilitation is complete, the need for home exercises to prevent recurrence and maintain fitness should be emphasised (Burbank et al, 2008).

Subacromial bursal glucocorticoid injection is a commonly used treatment for symptomatic rotator cuff disorders that do not improve after several weeks of conservative management, including physical therapy, or with severe pain that limits rehabilitation therapy. However, evidence of its benefit over NSAIDs, xylocaine or placebo is controversial (Gaujoux-Viala et al, 2009). Although there is still a paucity of clinical trials on image-guided versus landmark-guided shoulder steroid injections, ultrasound-guided injections potentially offer a significantly greater clinical improvement over blind injections in patients with shoulder pain (Naredo et al, 2004; Sage et al, 2013; Tao Wu et al 2015). In addition, ultrasound guidance has proved useful for calcification lavage (barbotage) in calcific tendinitis of the rotator cuff.

Viscosupplementation drugs periarticular injections (hyaluronic acid). Few studies have provided data about the clinical benefits and safety profile of these drugs in shoulder osteoarthritis/supraspinatus tendinosis (open-label studies) and RC lesions without complete tear (RCT) (Tagliafico et al, 2014*; Saito S et al 2010).

There are some studies providing preliminary data on the efficacy of **platelet-rich plasma** in RC lesions.

ESWT is an established treatment (level 1 evidence) for RC calcific tendinitis. However, there is insufficient evidence to support its use in non-calcific tendinopathy (Rees et al, 2006).

For adhesive capsulitis no consensus about the first choice for conservative treatment has been established. When treatment with ice, NSAIDs and glucocorticoid oral treatments fail, glucocorticoid or hyaluronic acid intra-articular injections, capsule distension with sodium chlorate, air, TENS, ultrasound and exercise programmes are used.

Surgical treatment for RC disorders (i.e., debridement, acromioplasty or rotator cuff repair) is considered if after 6–9 months of conservative treatment, patient function and symptoms fail to improve significantly or earlier in young patients with high shoulder occupational or sport demands.

5.2 The elbow

Non-articular causes of elbow pain include muscle strains, ligamentous injuries, epicondylitis, olecranon bursitis and compressive neuropathies. This section will focus on two of the elbow pathologies—lateral/medial epicondylitis and cubital tunnel syndrome.

5.2.1 Lateral and medial epicondylitis

These soft tissue disorders consist of a tendinopathy at the origin of the wrist extensor and flexor tendons, respectively, characterised by peri-epicondylar pain. Lateral epicondylitis is also known as tennis elbow and medial epicondylitis, golfer's elbow. Both conditions represent a tendinosis and/or an enthesopathy of the respective tendon groups. Hence tennis elbow is best termed 'common extensor tendinopathy' and golfer's elbow 'common flexor origin tendinopathy'.

5.2.1.1 Epidemiology and risk factors

Overuse and trauma commonly cause these conditions. Although called 'tennis elbow' or 'golfer's elbow', most cases occur in workers who do repetitive flexion–extension or pronation–supination activities. Lateral epicondylitis, more common than medial epicondylitis, has an incidence of between 1% and 3% a year in the adult general population.

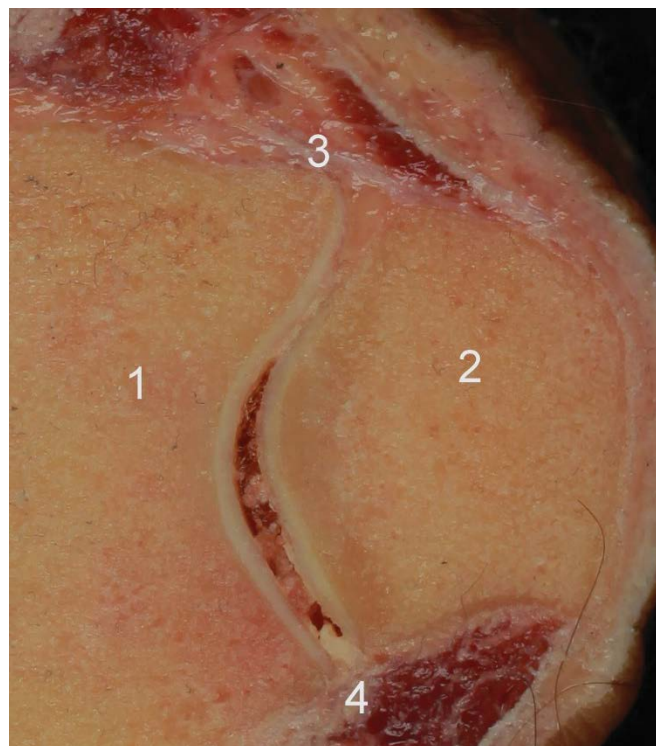
5.2.1.2 Clinical anatomy

The lateral and medial epicondyles are extra-articular structures located at the distal part of the humerus.

Lesions of the extensor carpi radialis brevis tendon, which is attached to the tip of the lateral epicondyle, and (less often) of the common extensor tendon, which attaches just posterior and distal to the tip of the lateral epicondyle, causes lateral epicondylitis. Lesions of the pronator teres and flexor carpi radialis tendons, which are attached at the medial epicondyle, cause medial epicondylitis.

The ulnar and radial collateral ligaments provide stability to the elbow. The ulnar nerve passes through the cubital tunnel into the ulnar groove, which is located between the medial epicondyle and the olecranon in the posterior aspect of the elbow and bridged by the Osborne fascia (figure 10).

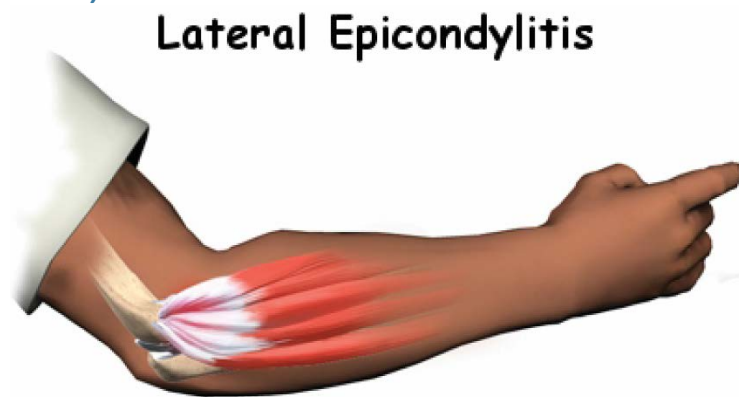
Figure 10 Elbow joint. Posterior view: 1, humerus; 2, olecranon; 3, medial epicondyle; 4, lateral epicondyle. (Image provided as a courtesy of Professor Maribel Miguel, Human Anatomy and Embryology Unit, Department of Pathology and Experimental Therapy, Faculty of Medicine (Bellvitge), University of Barcelona, Spain.)



5.2.1.3 Pathogenesis

Lateral and medial epicondylitis are work- and sport-related overuse lesions. The pathogenesis consists of tendinosis, usually with involvement of the enthesis, and degenerative microtears as a result of repetitive mechanical overload (figure 11).

Figure 11 Lateral epicondylitis. (eOrthopod Images provided as a courtesy of Medical Multimedia Group (MMG). Copyright MMG 2001.)



5.2.1.4 Diagnosis

5.2.1.4.1 History

The history is that of lateral or medial epicondylar pain and tenderness which may extend to proximal wrist extensor or flexor muscle masses, respectively, worse with grip and resulting in functional difficulties. Such symptoms may be acute or insidious in onset. The severity of pain can range from mild, with minimal effect on sports or work activities, to severe, with marked impairment in basic daily tasks and sleep.

5.2.1.4.2 Physical examination

In lateral epicondylitis, localised tenderness over the lateral epicondyle and proximal wrist extensor muscle mass, pain with resisted wrist extension and resisted extension of the middle finger with the elbow in full extension, and pain with passive maximal wrist flexion with the elbow in full extension are the most useful diagnostic findings.

In medial epicondylitis, physical examination shows localised tenderness over the medial epicondyle and proximal wrist flexor muscle mass, pain with resisted wrist flexion with the elbow in full extension and pain with passive maximal wrist extension with the elbow in full extension (figure 12).

Figure 12 Palpating the insertion of the extensors of the wrist and hand, just below the lateral epicondyle. (Courtesy of Professor J A P Da Silva. Reproduced with permission from da Silva and Woolf. *Rheumatology In Practice*, Springer, 2010*.)



5.2.1.4.3 Differential diagnosis

Box 8 presents conditions that must be considered in the differential diagnosis of lateral/medial elbow pain.

Box 8 Differential diagnosis of lateral/medial elbow pain

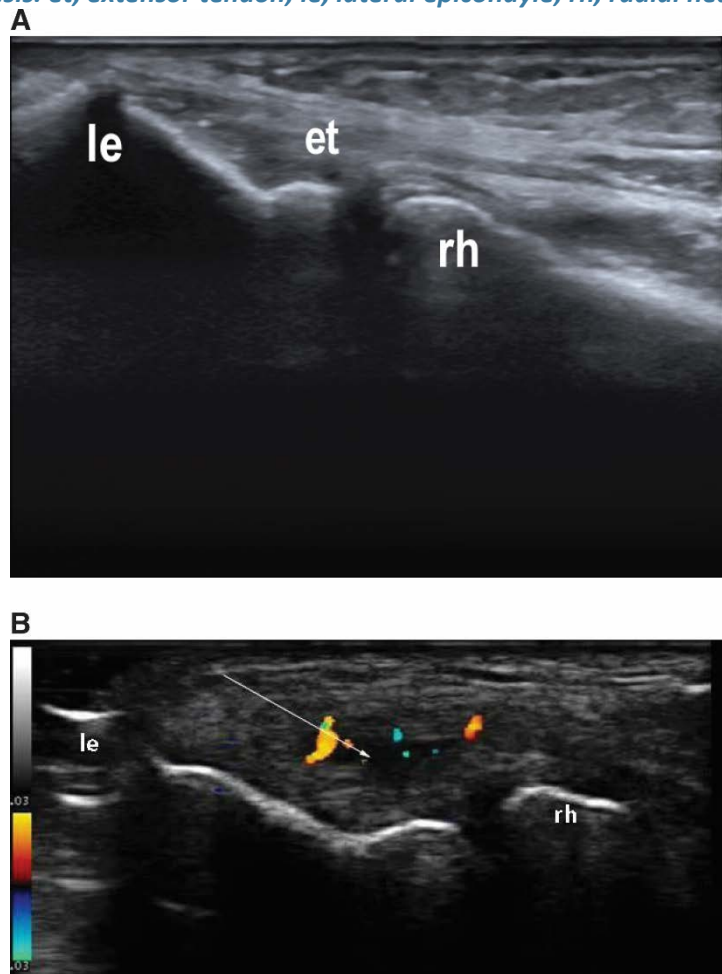
- Lateral/medial epicondylitis
- Radial/ulnar collateral ligament lesion
- Epicondylar apophysitis (adolescents)
- Radiocapitellar bursitis
- Olecranon bursitis
- Forearm compartment syndrome
- C6 root pathology
- Radial tunnel syndrome (compression of the posterior interosseous nerve)
- Cubital tunnel syndrome (compression of the ulnar nerve)
- Radiohumeral joint pathology:
 - Synovitis
 - Osteochondritis dissecans
 - Osteochondrosis
 - Instability
- Fracture/stress fracture

5.2.1.4.4 Imaging investigation

Radiography is often unnecessary for the diagnosis and treatment of epicondylitis. MRI may demonstrate increased signal intensity of the extensor or flexor tendons close to their insertion on the epicondyles, but evidence for diagnostic performance is limited.

Ultrasound is used to identify the different elementary lesions that may be present in epicondylitis (i.e., tendinosis and/or enthesopathy, partial tears, dystrophic calcification, neovascularisation, which is likely to represent more active severe disease, and bone surface abnormalities) (figures 13A, B). This technique can be very useful to distinguish tendon involvement from other conditions causing lateral or medial elbow pain such as intra-articular synovitis, periarticular bursitis, collateral ligaments lesions and radial or ulnar nerve compression. In addition, ultrasound is helpful in guiding accurate therapeutic injections to the selected local target (e.g., peritendinous area, pathological intratendinous vascularisation, calcifications) (Radunovic et al, 2012).

Figure 13 (A) Longitudinal ultrasound image of common extensor enthesopathy with loss of normal tendon pattern and small calcifications at the enthesis. (B) Longitudinal ultrasound image of common extensor enthesopathy with loss of normal tendon pattern; hypoechoic area exhibiting Doppler sign inside the common extensor enthesis. et, extensor tendon; le, lateral epicondyle; rh, radial head.



5.2.1.5 Management

A systematic review of prospective randomised clinical trials for management of lateral epicondylitis provided a wide range of treatment options, but little evidence supporting any particular approach (Cowan et al, 2007). The treatment of epicondylitis in the more acute stages includes relative rest (R), the use of ice (I), compression (C) due to intermittent strap or counterforce braces applied distal to the bulk of the extensor mass which may reduce activity in the affected muscles, and elevation (E) (RICE treatment strategy), analgesia including acupuncture and short-term use of (preferably topical) NSAIDs. The benefit of ultrasound has not been proved but low-level laser therapy may be helpful. Local glucocorticoid injection may help with pain relief (Gaujoux-Viala et al, 2009). Other injection techniques include dry needling, PRP injection, sclerosant therapies, botulinum toxin or other therapeutic modalities such as ultrasound-guided percutaneous needle tenotomy, but the evidence is limited (Petrella et al, 2010; Tosun HB et al 2015). Extracorporeal shock wave shows mixed results in chronic cases and therefore should be reserved for recalcitrant cases where surgery is being considered.

All these approaches are used to allow rehabilitation to start. Stretching of the forearm extensor or flexor muscles and range-of-motion exercises at the elbow and wrist should start early. Progressive eccentric and isometric strengthening rehabilitation starts as soon as pain allows. Surgery should be reserved for those patients with disabling symptoms who do not respond to any of the above measures. Options include open, arthroscopic or percutaneous surgical approaches with repair of the extensor/flexor origin after excision of the torn tendon, granulation tissue and local drilling of the subchondral bone of the epicondyle, with the aim of increasing blood supply.

5.2.2 Cubital tunnel syndrome

Ulnar neuropathy at the elbow is the second most common upper extremity compressive neuropathy after the entrapment of the median nerve at the wrist (i.e., carpal tunnel syndrome). The most frequent site of focal ulnar entrapment is at the elbow, followed by the wrist (i.e., Guyon's canal syndrome).

Ulnar lesions at the elbow typically present with numbness and paraesthesia in the fourth and fifth fingers which worsen with repeated elbow or wrist flexion. Medial elbow pain with or without nocturnal awakening is common and many patients report referred pain along the medial forearm. Motor symptoms involving the intrinsic hand muscles are less common than sensory symptoms.

Clinical diagnosis of cubital tunnel syndrome is obtained from a careful history and physical examination together with knowledge of the peripheral nerve anatomy. There are a number of provocative manoeuvres for ulnar neuropathy at the elbow, including Tinel's test (i.e., tapping over the ulnar nerve at the ulnar groove), elbow flexion, pressure and combined elbow flexion with pressure. These tests are considered positive when they elicit paraesthesia or pain in ulnar-innervated regions of the hand, particularly the fourth and fifth fingers. In addition to the clinical assessment, electrophysiological studies are usually performed in ulnar neuropathy.

Ultrasound is a promising complementary diagnostic tool for cubital tunnel syndrome. An abrupt thickening of the nerve with or without abnormal echogenicity proximal to or at the ulnar groove is the principal diagnostic sign. Ultrasound can also be useful for detecting local causes of ulnar nerve compression such as bone abnormalities (e.g., spurs, deformities), ganglia or cysts, intra-articular loose bodies, muscle abnormalities and ulnar nerve cubital tunnel subluxation while performing dynamic assessment (forearm flexion).

There is a lack of studies that have prospectively tested the different conservative treatments for cubital tunnel syndrome, such as pain relief (analgesic, NSAIDs) and splints. It is generally recommended that patients should avoid keeping the elbow in a flexed position and maintaining pressure to the elbow when seated or driving.

Surgical treatment with ulnar nerve decompression or nerve transposition can be considered for patients with evidence of moderate to severe ulnar neuropathy at the elbow who have persistent or progressive symptoms beyond 6 months that are refractory to conservative treatment.

5.3 The wrist and hand

Painful soft tissue disorders of the wrist and hand such as carpal tunnel syndrome, dorsal ganglia or de Quervain's tenosynovitis, usually due to overuse, are very common in clinical practice. Occasionally, it may be difficult to differentiate overuse lesions from wrist pain resulting from a subacute injury (e.g., scaphoid fracture, triangular fibrocartilage lesion, ligament sprains, Kienböck's disease (i.e., avascular necrosis of the lunate). Radiography, ultrasound or MRI are necessary in such circumstances.

5.3.1 Clinical anatomy

The carpal tunnel (figure 14) is elliptical shaped and enclosed by the inelastic flexor retinaculum ventrally and the carpal bones dorsally. The median nerve (the most superficial structure), eight deep and superficial flexor tendons covered by synovial sheath, and the flexor pollicis longus tendon and its sheath pass through the carpal tunnel.

The dorsal wrist is divided into six extensor compartments formed by the extensor retinaculum where the extensor tendons run lined by synovial sheath (figure 15). The flexor tendons for each finger, covered by synovial sheath, travel in a fibro-osseous tunnel between the metacarpal and the distal interphalangeal joint. The superficialis tendon attaches to the middle phalanges and the profundus tendon to the distal phalanges. The tunnel provides mechanical stability by a pulley system made up of specialised ligament system (i.e., five annular pulleys and three cruciform pulleys) that anchor the flexor tendon to the bone during finger flexion.

Figure 14 Anatomical image of the distal carpal tunnel. The median nerve and flexor tendons are seen. (Image provided as a courtesy of Professor Maribel Miguel, Human Anatomy and Embryology Unit, Department of Pathology and Experimental Therapy, Faculty of Medicine (Bellvitge), University of Barcelona, Spain.)

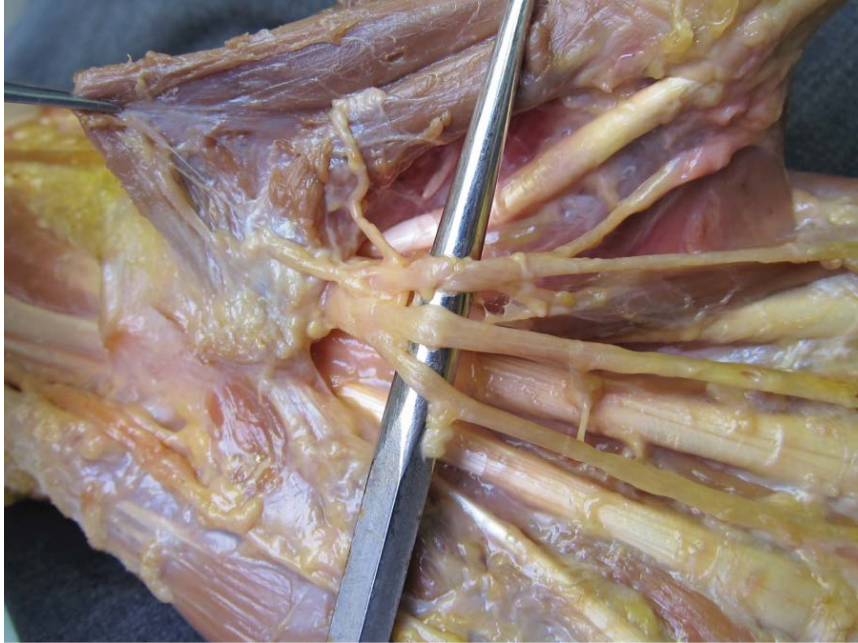
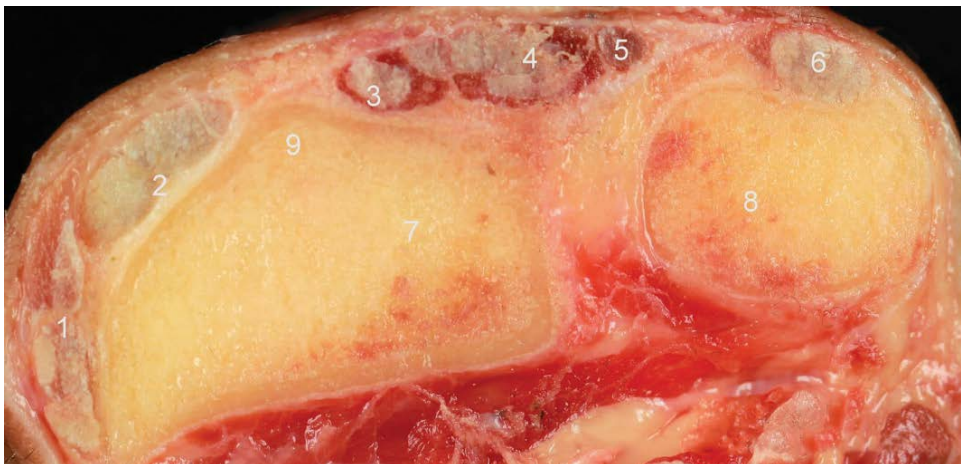


Figure 15 Extensor compartments of the wrist. 1, first compartment; 2, second compartment; 3, third compartment; 4, fourth compartment; 5, fifth compartment; 6, sixth compartment; 7, radius bone; 8, ulnar bone; 9, Lister's tubercle. (Image provided as a courtesy of I Moller, M Miguel, D Bong, University of Barcelona, Spain.)



5.3.2 Wrist tenosynovitis

5.3.2.1 De Quervain's tenosynovitis

De Quervain's tenosynovitis involves the abductor pollicis longus and extensor pollicis brevis tendons at the first wrist extensor compartment. These tendons are enclosed by a thick fibrous sheath at the level of the radial styloid process. Overuse of the thumb (e.g., repetitive gripping and grasping) leads to friction and irritation of the tendon and thickening of the fibrous tendon sheath that may progress to fibrosis and stenosing tenosynovitis.

Patients with de Quervain's tenosynovitis typically present with pain at the radial side of the wrist during grasping or thumb movements and local tenderness on the radial styloid (figure 16). Pain is aggravated by resisting thumb extension and abduction and by passively stretching the thumb tendons over the radial styloid in thumb flexion (i.e., Finkelstein's manoeuvre).

Figure 16 Palpation of the tendon sheath of the abductor pollicis longus and extensor pollicis brevis—De Quervain's tenosynovitis. (Courtesy of Professor J A P Da Silva. Reproduced with permission from da Silva and Woolf. *Rheumatology In Practice*, Springer, 2010*.)



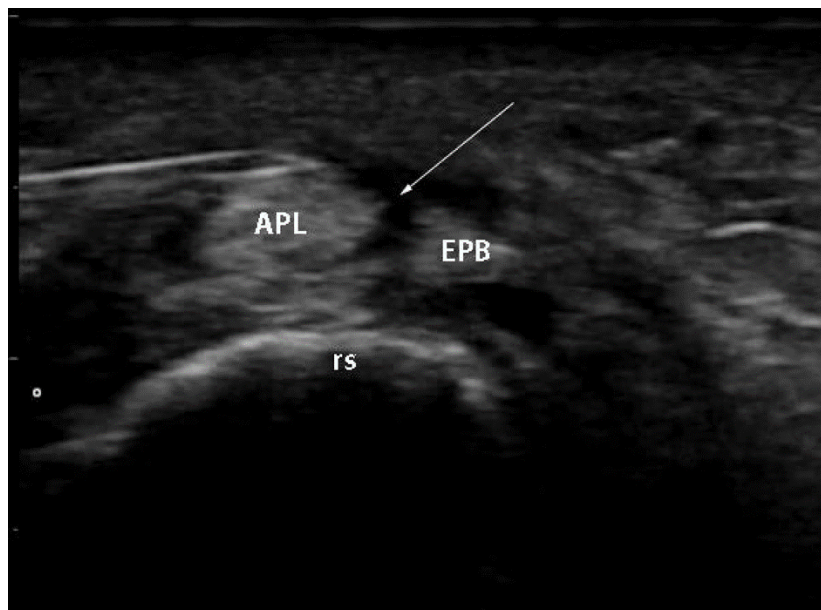
Clinical differential diagnosis of de Quervain's tenosynovitis includes osteoarthritis of the first carpometacarpal joint (Finkelstein's manoeuvre can also be positive (figure 17), intersection syndrome, ganglia, and radial sensory nerve entrapment in the forearm (i.e., Wartenberg syndrome). Ultrasound allows us to confirm the clinical diagnosis of the above conditions and to guide accurate therapeutic injections.

Figure 17 Finkelstein's manoeuvre. Positive in De Quervain tenosynovitis. (Courtesy of Professor J A P Da Silva. Reproduced with permission from da Silva and Woolf. *Rheumatology In Practice*, Springer, 2010*.)



The treatment of de Quervain's tenosynovitis aims at reducing inflammation in the tenosynovial sheath, preventing the formation of adhesions, and preventing recurrence owing to exercises and change in hand overload. For pain relief, ice applications to the radial styloid, an appropriate splint and NSAIDs are indicated. Glucocorticoid injections, preferably guided by ultrasound to avoid inaccurate drug delivery (i.e., into the tendon instead of within the synovial sheath), can be effective especially in the acute phase (Sawaizumi et al, 2007*; McDermott JD et al, 2012) (figure 18).

Figure 18 *Transverse scanning at the first extensors compartment. Glucocorticoid injection inside the tendon sheath. The needle is visible (hyperechoic line, left). Hypoechoic material distending the tendons sheath (arrow). APL, abductor pollicis longus tendon; EPB, extensor pollicis brevis tendon; rs, cortex of the radial styloid.*



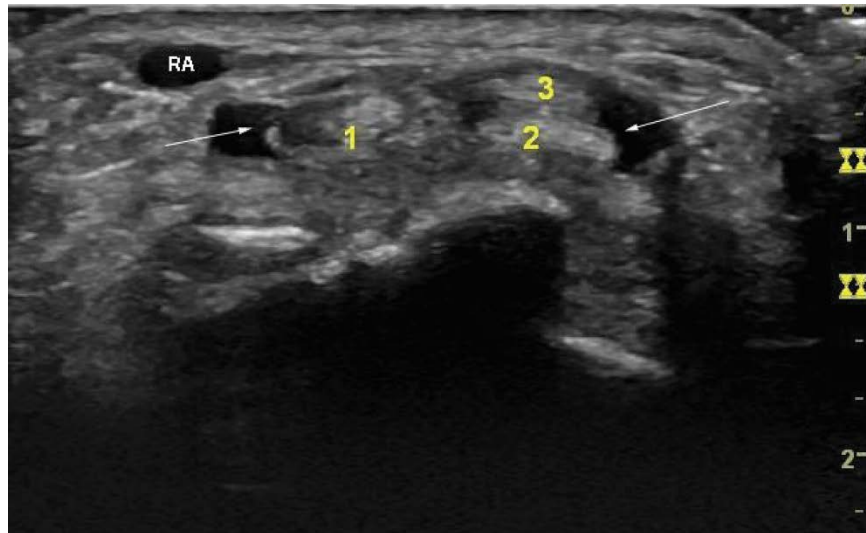
Once the symptoms of active tenosynovitis have resolved, gentle passive stretching exercises of the extensor and abductor tendons should begin. Surgery (i.e., decompression of the first extensor compartment with or without tenosynovectomy) can be indicated with persistent or recurrent symptoms despite conservative treatment.

5.3.2.2 Intersection syndrome

Intersection syndrome is caused by a conflict between the extensor carpi radialis longus and extensor carpi radialis brevis tendons (second compartment) at the intersection of the first extensor compartments, just proximal to the extensor retinaculum or between the second and third extensor compartments just distal to the extensor retinaculum. It is characterised by tenosynovitis, tendon thickening and tenosynovial adhesions. The main clinical complaint is radial wrist or forearm pain that is exacerbated by repetitive wrist flexion and extension. On physical examination, tenderness, swelling and crepitus on motion at the intersection level are the principal findings. Although much less common than de Quervain's tenosynovitis, both conditions can be

clinically confused. Ultrasound examination provides quick information about the morphology and function of these compartments (figure 19).

Figure 19 Transverse scanning of the second and third extensors compartments at the wrist level. The third compartment is just crossing the second compartment. Hypoechoic material distending the tendon sheath of the second compartment (arrows). RA, radial artery; 1, 2 extensor carpi radialis longus and brevis tendons; 3, extensor pollicis longus tendon.



5.3.3 Wrist ganglia

The wrist is one of the most common sites for ganglion cysts, which are well-delimited hard masses filled with gelatinous fluid that originate from joint capsules or tendon sheaths. Volar ganglia are less common and usually located on the lateral aspect of the wrist.

Ganglia can be painless or can cause wrist pain if they compress adjacent tendons or peripheral nerve branches. Some symptomatic ganglia are undetectable by palpation (i.e., occult ganglia). Ultrasound is an accurate imaging tool for detecting occult ganglia as well as for guiding aspiration of internal fluid and/or steroid injection into the cyst (figures 20A, B, video 3).

Video 3. Real time video for corticosteroid injection inside a radiocarpal ganglia. Longitudinal scanning of the radiocarpal joint. The needle is inserted 'out of plane' (hyperechoic dot) is penetrating inside the ganglia and drug deposition is made strictly inside the lesion. Corticosteroid deposition is presenting as a hyperechoic mass distending the ganglia. (You must be connected to internet and use Acrobat reader to see the video. Another version is available in the "images" section of the course)



5.3.4 Finger tenosynovitis

Stenosing flexor tenosynovitis, also known as trigger finger is a common condition that consists of irritation or inflammation of the fibrotenosynovial tunnel that surrounds the finger flexor tendons usually owing to overuse. The lesion leads to the formation of palpable nodules at the A1 pulley level (proximal to the metacarpophalangeal joint) which prevent the normal gliding of the tendon on motion and produce the involved finger to lock in flexion with consequent dysfunction and a variable grade of pain. In addition to overuse, diabetes mellitus is also associated with the development of trigger finger.

The diagnosis is mainly based on the clinical finding of finger locking in flexion and palpation of the typical nodule proximal to the metacarpophalangeal joint.

Treatment is based on pain relief, stretching exercises, glucocorticoid injections (video 4 and 5), (Peters-Veluthamaningal et al, 2008; Lee DH et al, 2011, Gutierrez M et al, 2016) and percutaneous or open surgical release of the A-1 pulley for persistent or recurrent cases.

Video 4. Real time video for corticosteroid injection inside the flexor pollicis longus tendon (FPLT) sheath. Transverse scanning of the FPLT shows hypoechoic halo around the tendon (tenosynovitis). The needle is penetrating 'in plane' and corticosteroid deposition (hyperechoic substance distending the tendon sheath and flowing around the tendon) is made exactly inside the tendon sheath. (You must be connected to internet and use Acrobat reader to see the video. Another version is available in the "images" section of the course)

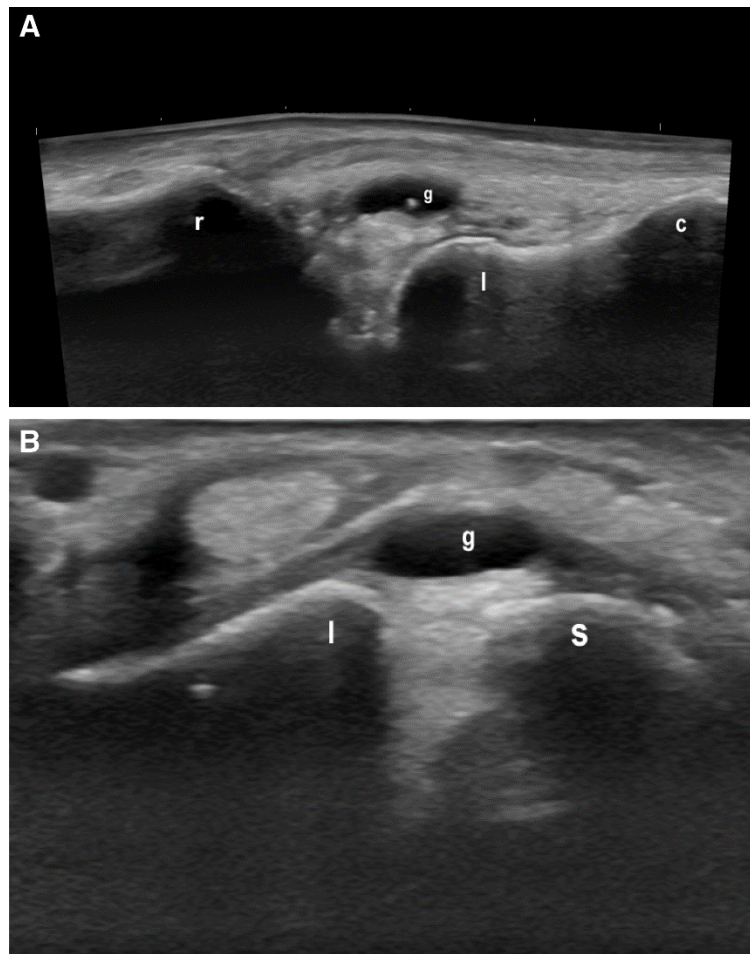


Video 5. Postprocedural hyperechoic (white) corticosteroid deposition strictly inside the tendon sheath, with dispersion along the tendon when performing multiplanar transverse scanning of the FPLT. (You must be connected to internet and use Acrobat reader to see the video. Another version is available in the "images" section of the course)



Trigger finger should be distinguished from Dupuytren's contracture, a progressive painless fibrosis of the palmar fascia and consequent flexion contractures of the fingers. This condition is associated with work-related hand overuse, diabetes mellitus, complex regional pain syndrome, smoking, alcohol consumption and malignancy.

Figure 20 (A) Longitudinal ultrasound image of a wrist ganglion (g). (B) Transverse ultrasound image of a wrist ganglion (g). c, capitate; l, lunate; r, radius; s, scaphoid.



5.3.5 Carpal tunnel syndrome

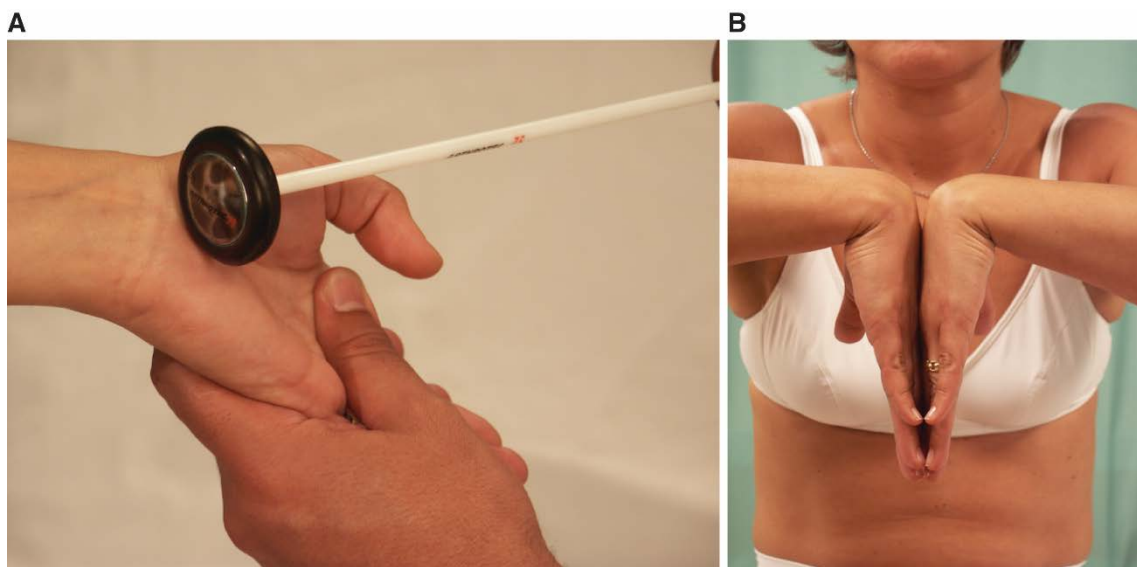
The most common peripheral nerve entrapment is carpal tunnel syndrome. This focal neuropathy is a condition of inflammation, swelling and/or mechanical compression of the median nerve, which provides motor and sensory innervation to the hand, in the carpal tunnel of the wrist. At this site the nerve is particularly susceptible to compression, particularly with repetitive flexion–extension of the wrist and repetitive occupational use. Other causes are local trauma, swelling of tendon sheaths within the tunnel, stenosis of the tunnel by bone enlargement or fracture, thickening of the volar carpal ligament or any condition occupying the carpal tunnel. Female gender, obesity, pregnancy, menopause and hypothyroidism are also predisposing factors.

Bilateral carpal tunnel syndrome is common, although in many patients, symptoms are unilateral with subclinical involvement of the contralateral side. Symptoms are pain and paraesthesia in the distribution of the median nerve (i.e., the thumb, index, middle and radial side of the ring finger), worse at night and often wakens patients from sleep, and relieved by shaking the hand or hanging it down to the side. In chronic more severe cases there may be evidence of palmar wasting in the thenar eminence, and weakness of grip and pinch

(involvement of first and second lumbrical muscles, abductor pollicis brevis, opponens pollicis, superficial head of flexor pollicis brevis).

On physical examination, there are two classic provocative manoeuvres, the Hoffman–Tinel test (i.e., tapping over the nerve in the middle of the volar aspect of the wrist) and the Phalen test (maintained flexion of the patient's hands for 30–60 s), which are considered positive if the typical symptoms are reproduced or enhanced (figures 21A, B). However, Phalen and Tinel tests are usually inaccurate.

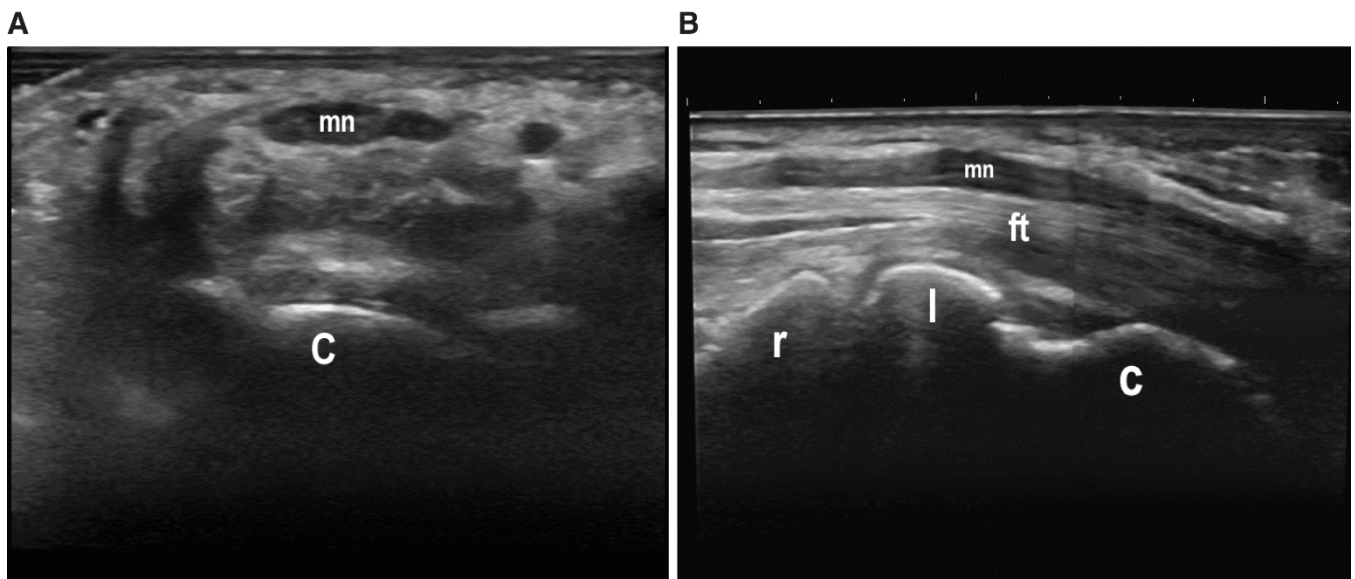
Figure 21 (A) Tinel's sign of the median nerve in the carpal tunnel. (B) Phalen's test. This position is kept for about 1 min: paraesthesia in the median nerve distribution suggests carpal tunnel syndrome. (Courtesy of Professor J A P Da Silva. Reproduced with permission from da Silva and Woolf, *Rheumatology In Practice*, Springer, 2010*.)



Neurophysiology studies are helpful in confirming the diagnosis and excluding other causes, such as polyneuropathy, plexopathy and radiculopathy, but may be normal in 20% of patients with carpal tunnel syndrome, especially in mild and/or early disease. The above studies are also useful for assessing the severity of nerve compression, which can help in making therapeutic decisions about surgical intervention.

Many ultrasound studies have shown a significantly increased cross-sectional area of the median nerve at the carpal tunnel in patients compared with controls (figures 22A, B). However, the optimal cross-sectional area cut-off point for the diagnosis of median nerve entrapment has varied widely in these reports. Nevertheless, ultrasound can be useful in detecting local causes of median nerve compression at the carpal tunnel, such as ganglia, flexor tenosynovitis, wrist synovitis and muscle or bone abnormalities, which may change the approach to treatment. It has several advantages over MRI assessment, showing a higher spatial resolution, an ability to explore quickly long nerve segments accompanied by dynamic examination during muscle activity (Bruyn et al, 2012*).

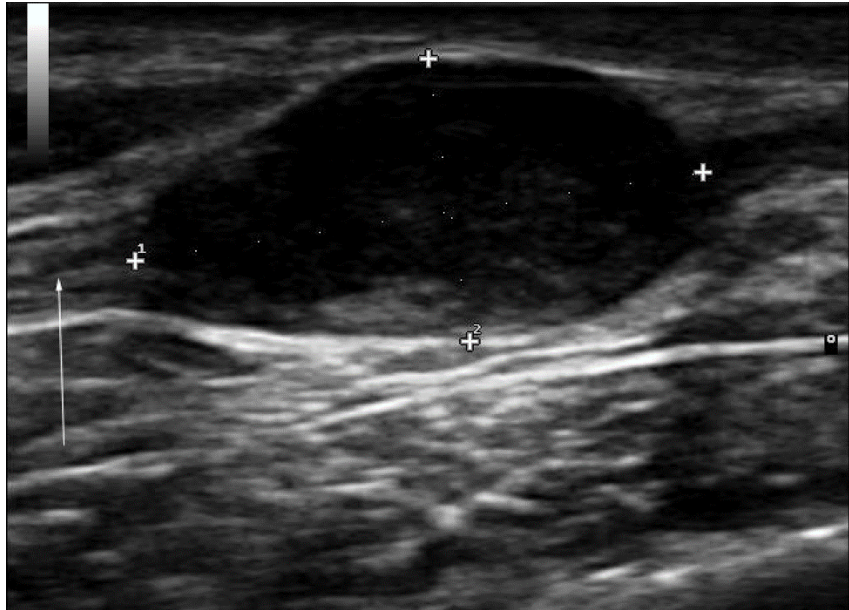
Figure 22 (A) Transverse ultrasound image of median nerve (mn) enlargement in carpal tunnel syndrome. (B) Longitudinal ultrasound image of median nerve (mn) enlargement in carpal tunnel syndrome. C, capitate; ft, flexor tendons; l, lunate; r, radius.



A change of life and work style is mandatory for these patients. NSAIDs and night splints can be helpful in many cases. Although evidence for many conservative treatment options is scarce, local injection (preferably under ultrasound guidance) of glucocorticoid into the carpal tunnel is an effective therapeutic strategy. The presence of underlying causes (e.g., inflammatory arthritis, hypothyroidism) should be looked for. Where treatment is ineffective, patients may be suitable for carpal tunnel surgical decompression.

Carpal tunnel syndrome should be differentiated from the much less common entrapment of the median nerve where it passes through the pronator teres muscle in the proximal forearm (i.e., pronator teres syndrome) or other intrinsic nerve pathological conditions (e.g., schwannoma, figure 23). Patients present with forearm pain and sensory loss typically affecting the thenar eminence, which is usually not involved in carpal tunnel syndrome.

Figure 23 Schwannoma of the median nerve immediately proximal to the flexors retinaculum (outside the median nerve tunnel) is seen as a hypoechoic mass (between crosses). Preserved median nerve fascicular structure on the left side (arrow).



5.4 The hip

Accurate diagnosis of painful soft tissue disorders of the hip may be difficult in clinical practice. This section helps to clarify the frequent and unrecognised problem of non-traumatic lateral hip pain, the so-called greater trochanteric pain syndrome (GTPS) and describes the external and internal snapping hip that may cause lateral and medial hip pain.

5.4.1 Greater trochanteric pain syndrome

GTPS is a multifactorial syndrome characterised by dull aching lateral hip pain with a tender point(s) over the region of the greater trochanter. Although the cause of GTPS is not completely known, evidence suggests that it is associated with tendinopathy, from tendinosis to tendon tear, involving the gluteus medius and minimus with or without associated bursitis. Historically, GTPS has been named as hip periarthrititis, trochanteric bursitis or trochanteric tendinobursitis but these terms create confusion because bursal distension is an inconsistent feature of lateral hip pain. GTPS is usually diagnosed by clinical signs, with imaging techniques, conventional radiography, ultrasound or MRI useful for further elucidation.

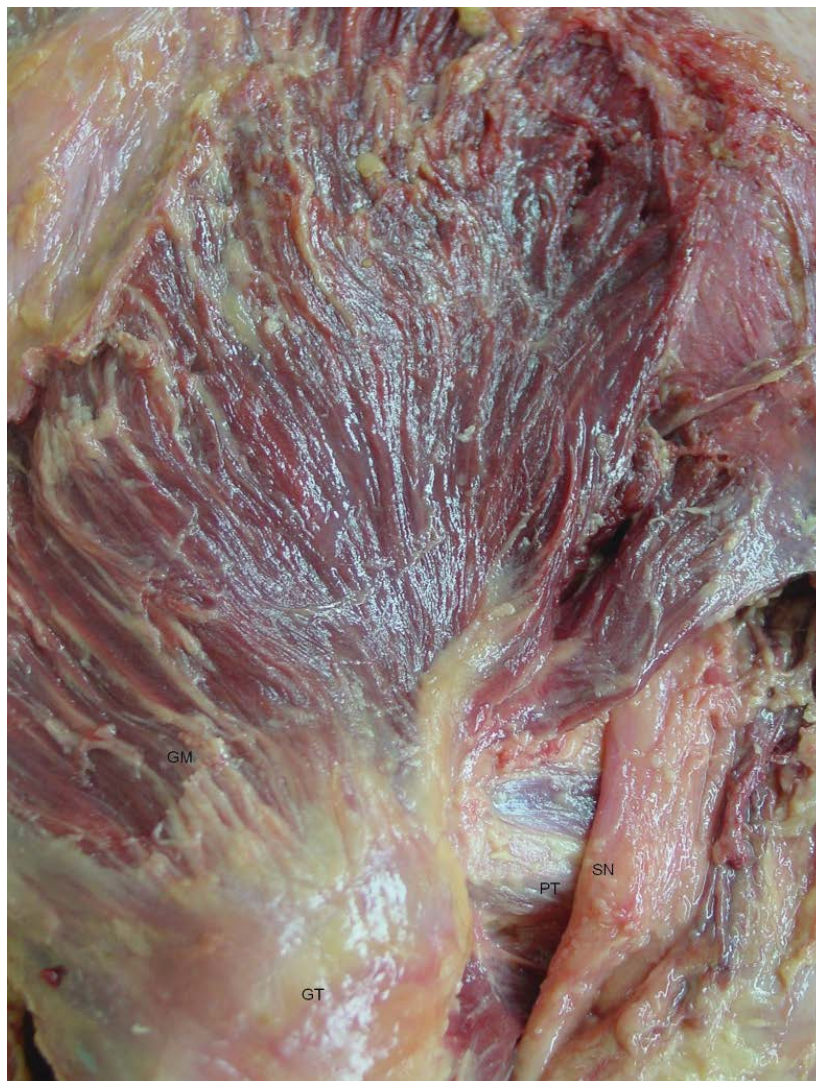
5.4.1.1 Epidemiology and risk factors

The real prevalence of GTPS is unknown. It has been reported that GTPS is more prevalent in women than in men, and that unilateral GTPS is more common than bilateral GTPS. GTPS can be a comorbid condition in patients with altered lower limb biomechanics, obesity, low back pain or hip osteoarthritis (Segal et al, 2007).

5.4.1.2 Clinical anatomy

The gluteus medius and minimus are abductors of the hip joint. These muscles stabilise the hip joint, control pelvic rotation and ensure that the trunk maintains an upright position during the initial, mid- and late phase of the gait cycle. The outer and most superficial aspect of the greater trochanter is the insertion point of the tendons of the gluteus medius and minimus (figure 24). Three bursae have been consistently described surrounding the greater trochanter: sub gluteus minimus, sub gluteus medius and sub gluteus maximus bursae. The sub gluteus minimus is located next to the gluteus minimus tendon at the anterior facet medially to the anterior hip capsule. The sub gluteus medius bursa is located superior to the lateral facet. The sub gluteus maximus bursa is also known as the greater trochanteric bursae. The sub gluteus maximus bursa lies lateral to the greater trochanter, deep to the fascia lata and the gluteus maximus muscle.

Figure 24 Anatomical image of the gluteus medius. GT, greater trochanter; PT, piriformis tendon; SN, sciatic nerve. (Image provided as a courtesy of Professor Maribel Miguel, Human Anatomy and Embryology Unit, Department of Pathology and Experimental Therapy, Faculty of Medicine (Bellvitge), University of Barcelona, Spain.)



5.4.1.3 Diagnosis

5.4.1.3.1 History

The patient is usually a middle-aged woman, with a history of frequent low back pain who has chronic, intermittent aching pain and tenderness in the lateral hip or buttock. The most common referral pattern extends from the lateral aspect of the thigh, rarely reaching the knee. Initially, the symptoms may be just a feeling of discomfort that insidiously increases or they can have a subacute onset. The patient's pain becomes worse when walking, climbing, running, sitting with the affected leg crossed, prolonged standing or switching to standing position. Occasionally, she/he refers to nocturnal pain that may be exacerbated by lying on the affected side. GTPS can be associated with variable degrees of disability.

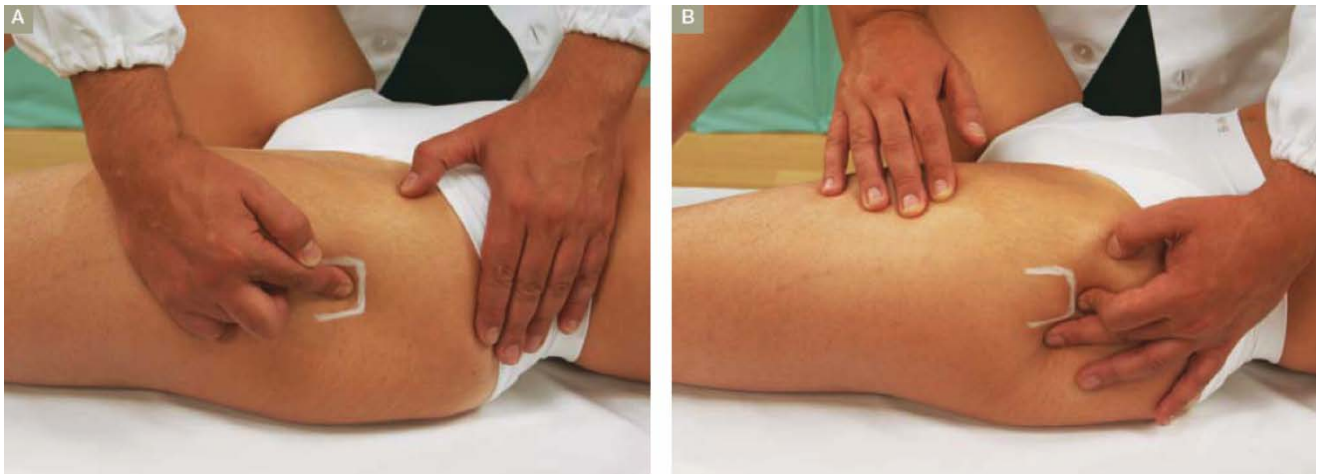
5.4.1.3.2 Physical examination

The physical examination includes palpation and a provocative test. In patients with GTPS a painful area over the greater trochanter can be found.

Passive, active and resisted movements can reproduce the symptoms. The diagnosis is based on the presence of a history consistent with the complaint, and exclusion of an underlying alternative cause, such as spinally referred pain. Patients will often have gluteal weakness and a positive Trendelenburg test simply because they have gluteal weakness manoeuvres (Lequesne et al, 2008).

Hence, an extensive physical examination is essential in the differential diagnosis of GTPS (figure 25). The spine and peripheral neurology, and neural stretch tests must all be performed. As a general rule, the loss of flexion and extension movements of the hip owing to either pain or structural problems is characteristic of intra-articular problems of the joint. Depending on when and/or where the pain is reproduced, the Patrick-FABER (flexion, abduction, external rotation) test helps to diagnose iliopsoas tendinopathy and adductor muscle and tendon pathology. Ober's test is used to identify tensor fasciae or iliotibial band (ILT) contracture (i.e., patient lying on a table with the side to be tested up and the hip extended and abducted; attempting to adduct the leg towards the table, a positive test is found if the leg remains in the abducted position).

Figure 25 Palpating the trochanteric bursa (A) and muscle insertions in the vicinity (B). (Courtesy of Professor J A P Da Silva. Reproduced with permission from da Silva and Woolf. *Rheumatology In Practice*, Springer, 2010*.)



5.4.1.3.3 Imaging investigation

Radiography. Reactive sclerosis and bone proliferation can be seen in patients with gluteus tears. However, trochanteric spurs do not have clinical relevance at the site of a ligamentous or tendinous attachment. Bursal calcifications are often seen in the conventional radiographic examination of the elderly population.

MRI may be recommended in patients with a positive Trendelenburg's sign depicting a gluteus medius tear. The presence of peritrochanteric oedema seems to be associated with GTPS. The presence of bursitis on MRI has been reported in a variable number of patients independently of the presence of GTPS.

Ultrasound serves to identify bursae, trochanteric facets and the corresponding tendinous and muscular attachments of the gluteus. Ultrasound allows us to depict the direct and indirect signs of tendinopathy, ranging from tendinosis to partial or full thickness tear, and enthesopathy and corresponds well to MRI and surgical pathological findings in GTPS. The signs of gluteus tendinopathy include thickening of the tendon, hypoechogenicity and loss of the homogeneity of the tendon fibres in comparison with the contralateral side. In the case of a partial thickness tear, partial discontinuity of the gluteus minimus or medius is seen (figures 26 and 27). When there is a full thickness tear of the gluteus medius at the lateral facet insertion, ultrasound shows a complete absence of the tendon, creating an image of the 'bald trochanter' with direct contact between the fascia lata and the lateral facet of the greater trochanter. Indirect signs of rupture are represented by irregularity of the cortical bony surface or the presence of bursitis (Klauser et al, 2013*).

Figure 26 Longitudinal ultrasound image of the gluteus minimus. AF, anterior facet of the greater trochanter; FL, fascia lata; Gm, gluteus minimus.

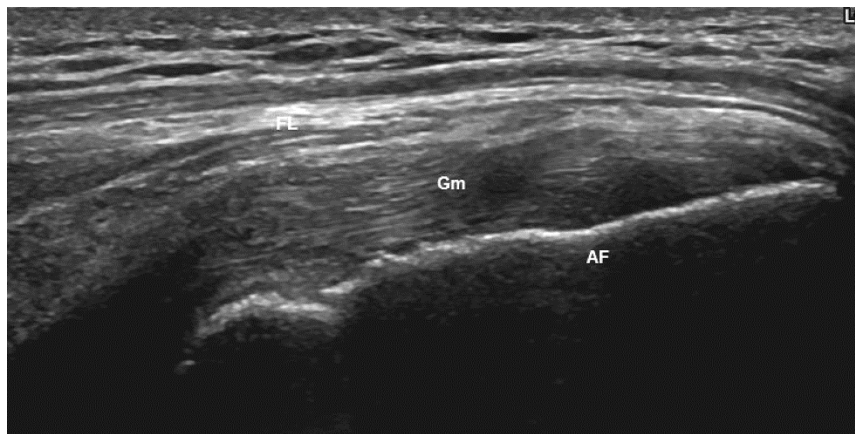
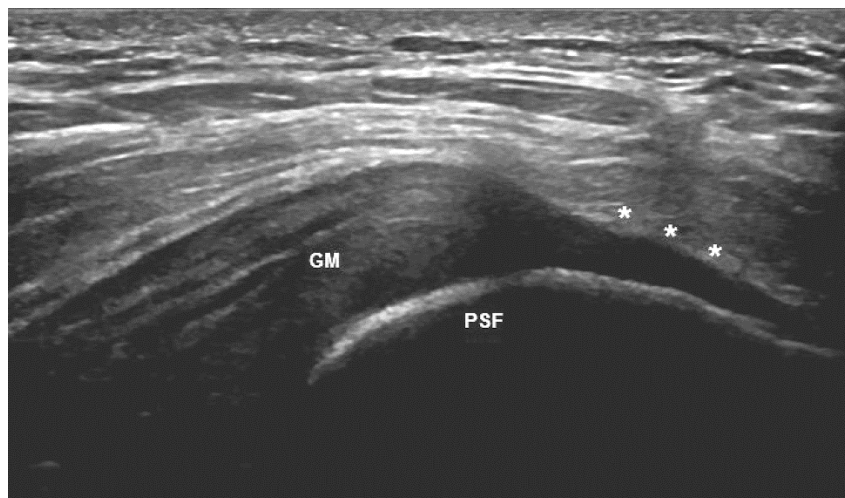


Figure 27 Longitudinal ultrasound image of partial tear of the gluteus medius. GM, gluteus medius; PSF, superoposterior facet of the greater trochanter; ***, loss of convexity of the gluteus medius tendon owing to partial tear.



5.4.1.4 Management

Few controlled studies have tested the efficacy of the different strategies for treatment of GTPS. Conservative treatment includes behaviour modification, weight loss in obese patients and the use of NSAIDs or analgesics according to need, physical therapy.

Guided injection of local glucocorticoid and anaesthetic at the point of maximal tenderness or slightly more posteriorly can provide a short to mid-term beneficial effect for pain relief. Variable rates of response have been described, (Labrosse JM et al, 2010), video 6. Hence injection is optimally reserved for those cases where bursitis is present rather than solely for tendinopathy. Some patients may have relapse within the next few months, especially those with severe degenerative disease. Most patients respond to non-surgical management but in patients refractory to treatment, arthroscopic bursectomy, ILT lengthening,

decompression of the peritrochanteric space and, if the gluteus tears, suture anchor tendon repair to the greater trochanter have been used. These interventions should be considered only rarely.

Video 6. Real time video for corticosteroid injection inside the trochanteric bursitis. Transverse scanning at the level of the greater trochanter. Hypoechoic material is distending the bursa. The needle is penetrating 'in plane' and drug deposition (hyperechoic substance distending the bursa) is made strictly inside the trochanteric bursa. (You must be connected to internet and use Acrobat reader to see the video. Another version is available in the "images" section of the course)



5.4.2 Coxa saltans (snapping hip)

Coxa saltans is a clinical condition with multiple causes. It is characterised by a painful, audible snap when the hip is flexed and extended. Snapping hip commonly occurs in young adults, who report mechanical symptoms such as clicking, popping or catching in activities involving hip flexion such as dancing, running, gymnastics or soccer. Depending on the location of the snapping it can be classified as external and internal.

The external coxa saltans is the most common snapping hip. An abnormally thickened area of the posterior border of the ILT, tensor fascia lata muscle, gluteus medius tendon or the leading anterior edge of the gluteus maximus snaps back and forth over the greater trochanter. The syndrome can be reproduced during flexion, extension, adduction or internal rotation of the hip. Clicking appears more often when hip moves from flexion to extension. The underlying bursa may become inflamed. This syndrome may be associated with leg length discrepancy, weakness in hip abductors and external rotators, tautness in the ILT, lumbopelvic instability and excessive pronation of the foot.

The internal coxa saltans can be produced by either extra-articular or intra-articular causes, which have similar mechanisms. The musculotendinous iliopsoas snaps over the femoral head, the anterior capsule of the hip, the lesser trochanter or the iliopectineal ridge with extension of the hip from a flexed position. Enlarged iliopsoas bursa can be seen. Intra-articular snapping is due to lesions in the joint itself.

Diagnosis of coxa saltans is usually based on medical history and clinical examination. Dynamic ultrasound studies help to clarify the different causes of extra-articular snapping hip. The main principle of management is conservative treatment. When needed, glucocorticoid injections and the use of ultrasound to guide the needle in barely accessible structures, such as the iliopsoas bursa, improve the patient's symptoms. Surgery is required only occasionally in recalcitrant cases.

5.5 The knee

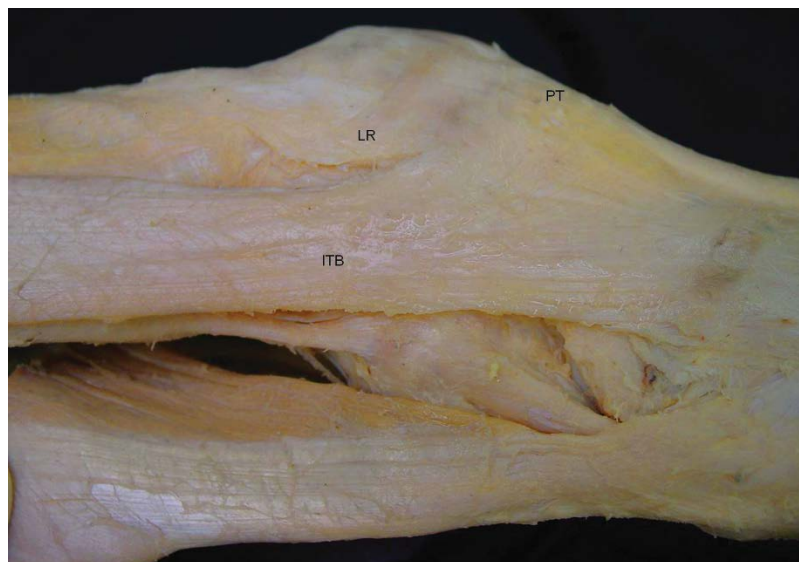
To determine the origin of pain in soft tissue around the knee is a challenge because of extensive differential diagnoses. The patient's age, medical history and physical examination specifying the anatomical site of the pain are fundamental to achieving an accurate diagnosis. Knee soft tissue pathologies are common in sports and often appear in those with little training. This section aims to review the most common soft tissue pathologies of the knee. Pathologies of the quadriceps and patellar tendon are grouped for a didactic purpose under the concept of extensor knee mechanism pathology.

5.5.1 The iliotibial band syndrome

The iliotibial band syndrome (ILTS) consists of pain and tenderness over the lateral femoral condyle during movements of flexion and extension of the knee.

The ILT has two distal insertions in the knee joint. Proximally, it is inserted, into the lateral epicondyle of the femur with a broad expansion between the lateral aspect of the patella, whereas distally it is inserted into Gerdy's tubercle. The ILT is an anterolateral knee stabiliser. (figure 28). An 'impingement zone' has been described when at 30° of knee flexion the ILT passes over, and posterior to, the lateral femoral epicondyle.

Figure 28 Anatomical image of the iliotibial band. ITB, iliotibial band; LR, lateral retinaculum; PT, patellar tendon. (Image provided as a courtesy of Professor Maribel Miguel, Human Anatomy and Embryology Unit, Department of Pathology and Experimental Therapy, Faculty of Medicine (Bellvitge), University of Barcelona, Spain.)



The cause of ILTS is multifactorial and diverse. Several anthropometric variables have been implicated, including excess internal tibial rotation, genu varum, over pronation of the foot or leg length inequality. Extrinsic factors such as improper footwear, running, bicycle fit or saddle position and training errors may overstress the ILT and cause ILTS. Comorbid conditions such as knee or hip osteoarthritis may also influence the appearance of ILTS. It is a common overuse running injury.

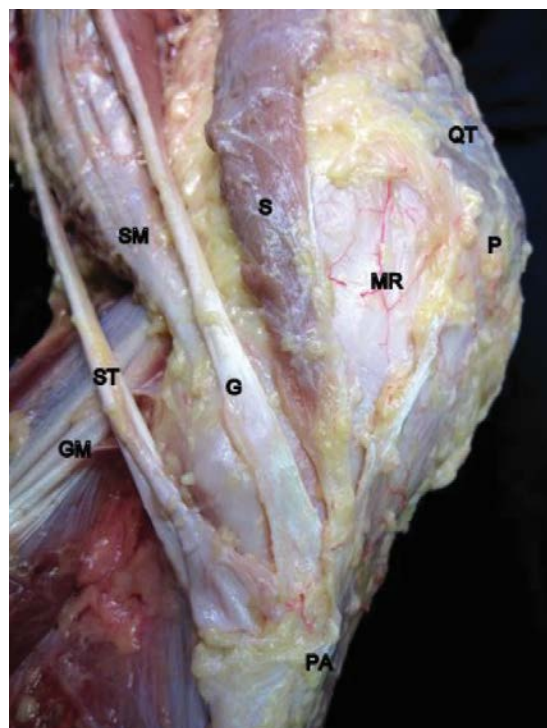
To assess ILTS, clinicians obtain a medical history and carry out a physical examination. Complementary ultrasound can show changes in the ILT echo texture or associated bursitis.

Modification of activity and training habits, stretching of the ILT and strengthening of the gluteus medius and major muscle have been proposed as treatment of the ILTS. A systematic review of prospective RCTs for conservative management of ILTS showed limited evidence for the usefulness of the interventions examined, including NSAIDs, deep friction massage, phonophoresis versus immobilisation and local glucocorticoid injection. Surgery has been advocated for patients refractory to conservative treatment (van der Worp et al, 2012).

5.5.2 Disorders of the extensor mechanism of the knee

The extensor mechanism of the knee includes the quadriceps muscle and tendon, the patella, the patellar retinaculum, the patellar tendon, the fat pads (suprapatellar, prefemoral, infrapatellar or Hoffa's) and the bursae (suprapatellar, pretibial and prepatellar). It constitutes a functional complex that allows extension of the knee joint. The pathology of the patella is included in this section, although obviously related to failure of the extensor mechanism. The quadriceps tendon inserts into the tubercle of the tibia through the retinaculum of the patella, and the patellar tendon then joins with the fascia of the leg as do other muscles in the lower extremity, such as the semimembranosus, semitendinosus gracilis and sartorius (figure 29). These muscles end in tendons and also in fascial expansions to accomplish their function of stabilising the leg.

Figure 29 Anatomical image of the medial knee. G, gracilis; GM, medial gastrocnemius; MR, medial retinaculum; P, patella; PA, pes anserinus; QT, quadriceps tendon; S, sartorius; SM, semimembranosus; ST, semitendinosus. (Image provided as a courtesy of the Faculty of Medicine (Bellvitge), University of Barcelona, Spain.)



As an example, jumper's knee classically refers to an insertional tendinopathy of the posterior aspect of the patellar tendon at the enthesis into the inferior patellar pole; but jumping pathology may also include tendinopathy of the insertion of the patellar tendon into the tibial tuberosity, or tendinopathy of the attachment of the quadriceps tendon, because all these tendons and others are involved in jumping. Acute trauma, overuse injuries and chronic degenerative diseases are the most common pathology found in the extensor mechanism, ranging from minimal damage to complete tendon tears.

5.5.2.1 Jumper's knee

Jumper's knee is seen in young athletes as a result of repetitive microtraumas and can be considered a predisposing factor for patellar tendon rupture.

5.5.2.2 Patellar tendon rupture

Patellar tendon rupture may also occur as a consequence of degenerative tendon or systemic diseases, with local or systemic glucocorticoid injections being a controversial predisposing condition. The rupture can be partial or complete and localised either at the proximal or distal enthesis or at the mid-point. The most common site is at the osteotendinous junction of the tendon with the lower pole of the patella.

When patellar tendinopathy is suspected, in addition to a history of patellar pain, tenderness to palpation has been shown to be a reliable test without correlation with either imaging or evolution of symptoms. When complete rupture of the patellar tendon has occurred, physical examination shows the presence of a palpable gap inferior to the patella, high-riding patella or 'patella alta', weakness on the knee joint extension and inability to walk.

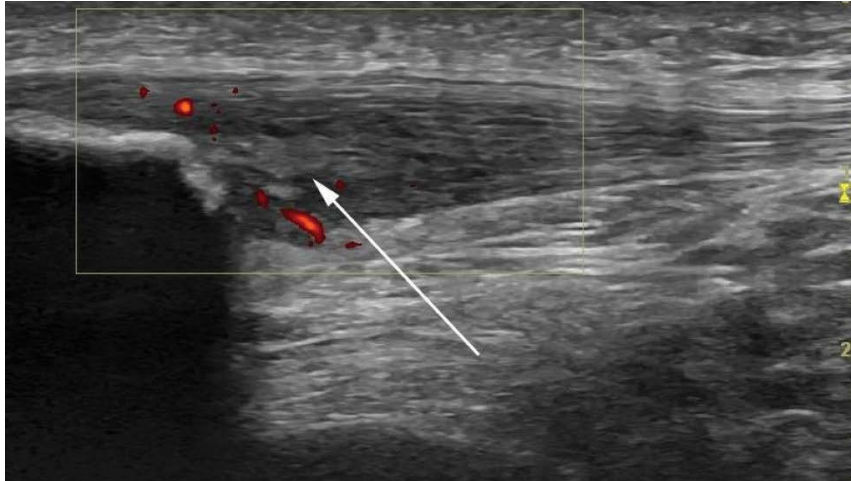
Imaging is recommended to confirm the diagnosis. Ultrasound evaluation of the patellar tendon can ascertain the presence and location of either degenerative changes and a partial or complete tear, although the correlation between these findings and the symptoms is not clear. A Doppler signal can show evidence of neovascularisation in a variable percentage of patients with vessels entering into the tendon from the dorsal side. The presence of a Doppler signal in patients with chronic disease tends to be associated with lower functional scores and more pain (Hoksrud et al, 2008) (figure 30).

In complete tendon tear the radiographic presence of 'patella alta' in a lateral view of the knee in slight flexion with infrapatellar soft tissue swelling confirms the physical assessment.

Management. Controlled loading of the tendon—for example, by an eccentric decline squat regimen, is the central component of treatment. Controlling pain through analgesics, massage, ESWT and biomechanical alterations should also be considered. Glucocorticoid injections are contraindicated and evidence for other

injection therapies is not strong. Surgical repair is the most common treatment for complete patellar tendon rupture with different techniques described in the literature.

Figure 30 Proximal patellar tendinopathy. The ultrasound image shows hypoechoic thickening of the proximal aspect of the patellar tendon (arrow).



5.5.2.3 Quadriceps tendinopathy

Quadriceps tendinopathy is less common than patellar tendinopathy and can be seen in older patients, who usually have an underlying systemic disease. Tears often occur in a weakened degenerative tendon during eccentric contraction, since as the muscle lengthens so to do the higher forces needed. Clinical history and physical examination shows pain and limitation or the impossibility of actively extending the knee, whereas active flexion remains preserved; when the retinaculum is intact, the patient can extend the knee. Therefore, it is necessary to compare the damaged extremity with the opposite leg. If the classic sign of a suprapatellar gap is masked owing to the presence of swelling, active flexion of the hip improves visualisation of the tendon defect. The patient may be able to move about.

The most common abnormalities seen on radiography are inferiorly displaced patella, suprapatellar mass due to retraction of the ruptured tendon, calcifications and alteration of the tendon shadow.

In addition to the high degree of sensitivity and specificity shown by ultrasound in assessing complete tendon tears, dynamic ultrasound shows the tendon gap and can be used to follow up the postoperative repaired tendon. The treatment combines local measures, immobilisation, exercise and knee aspiration to evacuate the traumatic haemarthrosis, if needed. Early surgical repair is suggested in acute complete rupture to achieve good functional outcome; in cases of chronic complete rupture, the surgical results are less satisfactory.

5.5.2.4 Pes anserinus bursitis

The pes anserinus refers to the conjoined tendons of the sartorius, gracilis and semitendinosus at their insertion into the proximal tibia. The tendons run superficial to the medial collateral ligament. A bursa located

distal and anterior to the medial collateral ligament bursa can be irritated and inflamed with repetitive microtrauma. The underlying factors of this condition include factors such as valgus stress, osteophytes, exostoses, tendon tightness, obesity and diabetes. The pain can be located or vague around the medial aspect of the knee (figure 31), being more intense while ascending or descending stairs.

Figure 31 Area of tenderness associated with *pes anserinus tendinopathy* (right knee, medial aspect). (Courtesy of Professor J A P Da Silva. Reproduced with permission from da Silva and Woolf. *Rheumatology In Practice*, Springer, 2010*.)



Ultrasound (figures 32A–C) can identify pes anserinus bursitis in its location. The treatment includes stretching of the adductor and quadriceps muscles and/or local injection if the pain is persistent.

5.6 The foot and ankle

The hand and foot are different structures having different functions—an obvious statement coming from Wood Jones, but fundamental to understanding foot pathology. The foot has been designed for support and locomotion. For these reasons the muscles of the leg and foot have wide and powerful insertions through fascias to large areas favouring the increase of its strength and stability. The calcaneal or Achilles tendon is the largest and strongest tendon in the human body. It is formed as the conjoined tendon of the gastrocnemius and soleus, with its fibres arranged in a spiral form being more superficial than those provided by the tibial side of the muscle. Some of the superficial fibres of the Achilles tendon become continuous with the plantar aponeurosis or plantar fascia (figures 33 and 34).

Figure 32 (A) *Pes anserinus*. Longitudinal image of the medial collateral ligament insertion. 1, medial collateral ligament; 2, sartorius; 3, tibial bone; 4, inferior medial geniculate vessels; 5, soft tissue. (B) *Pes anserinus* bursitis. Longitudinal image of the sartorius tendon proximal to the *pes anserinus* insertion. 1, bursa; 2, sartorius; 3, tibial bone. (C) *Pes anserinus* bursitis. Transverse image. 1, bursa; 2, sartorius tendon; 3, tibial bone.

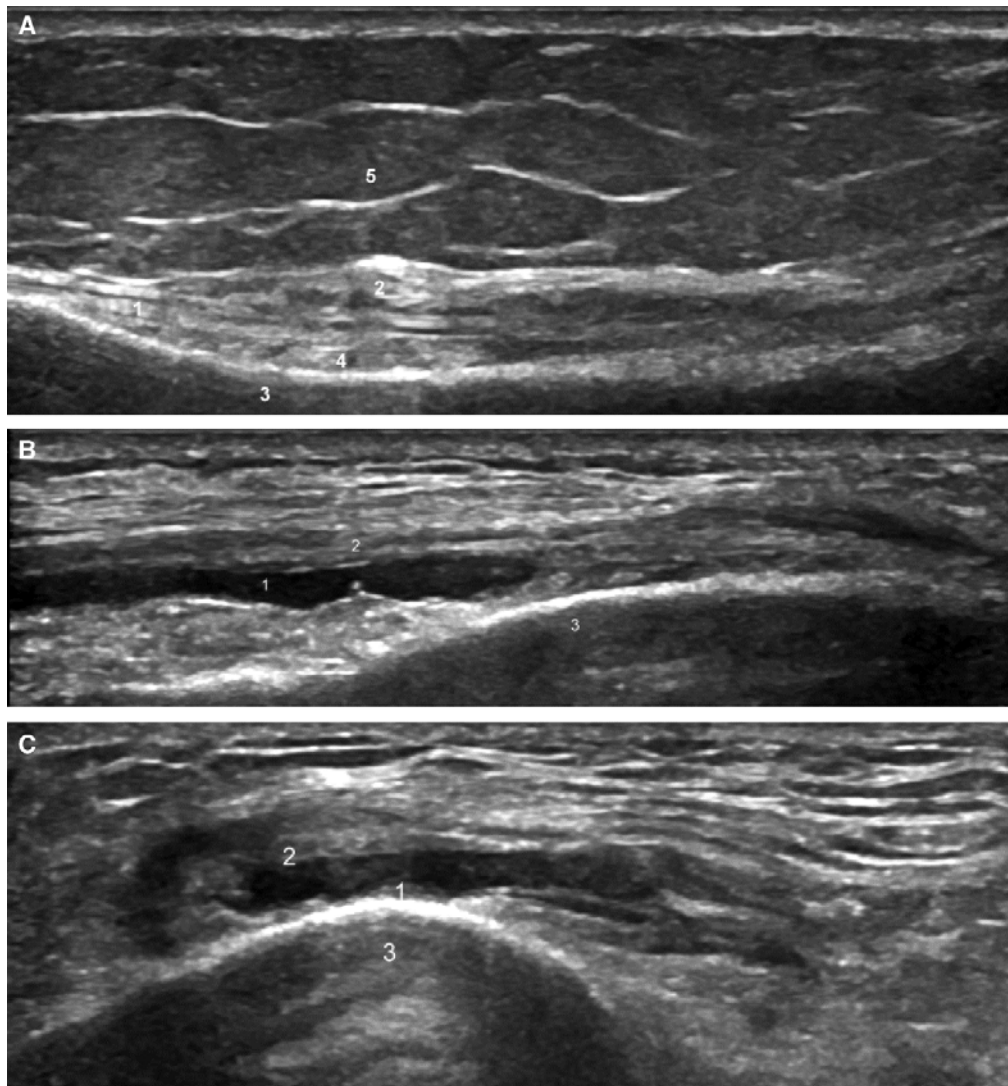
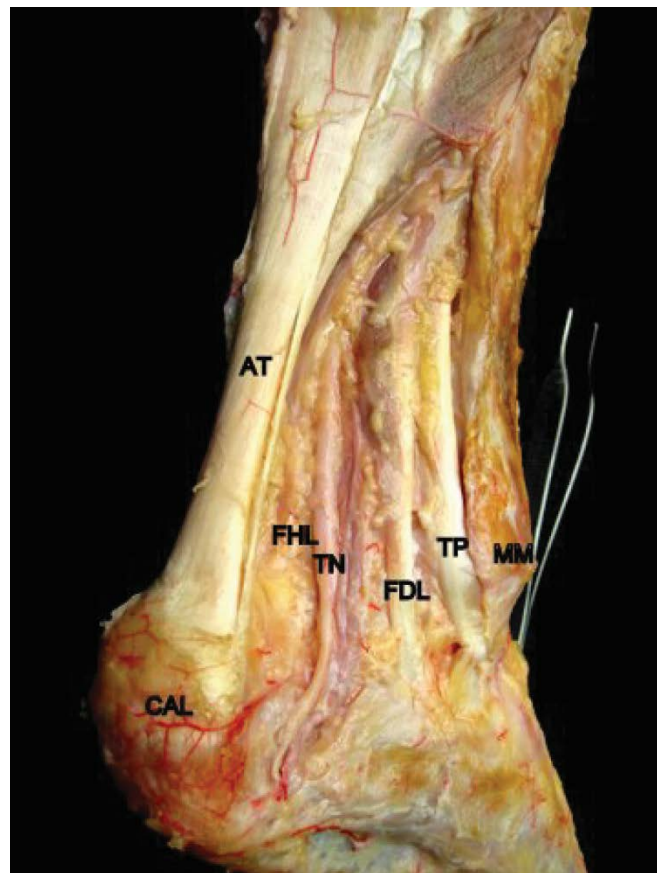


Figure 33 Anatomical image of the posterior aspect of the leg. A, Achilles tendon; G, gastrocnemius; S, soleus. (Image provided as a courtesy of Professor Maribel Miguel, Human Anatomy and Embryology Unit, Department of Pathology and Experimental Therapy, Faculty of Medicine (Bellvitge), University of Barcelona, Spain.)



Figure 34 Anatomical image of the posterior medial ankle. AT, Achilles tendon; CAL, calcaneus; FDL, flexor digitorum longus; FHL, flexor hallucis longus; MM, medial malleolus; TN, tibial nerve; TP, tibialis posterior. (Image provided as a courtesy of the Faculty of Medicine (Bellvitge), University of Barcelona, Spain.)



5.6.1 Achilles tendon disorders

As a consequence of its large size and immense functional demands, the Achilles tendon is susceptible to a wide spectrum of acute and chronic injury along its entire length, which will be considered in this section.

5.6.1.1 Paratenonitis, tendinosis and enthesopathy

Most cases of Achilles paratendonitis and tendinosis are related to overuse, although there are some exceptions. Although 25–33% of patients are reported to be not actively involved in sport, occupational activities may be implicated in their development. In runners, 55–65% of lesions are peritendinous and 20–25% are insertional. The vast majority (80%) of people affected are men. There are no reports of the relative risk in different sports and there seems to be significant variation between countries.

A number of aetiological factors have been implicated in the development of Achilles tendon lesions, particularly being overweight, repetitive impact loading, biomechanical factors (hyperpronation and leg length inequality) and/or sudden acceleration (ruptures). Oral fluoroquinolones are well recognised as a cause of Achilles tendinopathy and cause a florid inflammatory response. Risk factors include male gender, and the use of systemic glucocorticoid therapy, renal failure, advanced age and hypercholesterolaemia.

For example, both heterozygous familial type II hyperlipidaemia (where there is an increased total and low-density lipoprotein cholesterol value of two to three times normal) and mixed hypercholesterolaemia (increased cholesterol and triglycerides) are associated with tendon xanthomas and Achilles tendinopathy. Indeed, the musculoskeletal complaints may be the presenting features of these disorders. Lipid storage diseases such as cerebrotendinous xanthomatosis are also associated with Achilles tendinopathy.

5.6.1.2 Haglund's syndrome

This is a syndrome of an exostosis of the posterosuperior calcaneum in association with a retrocalcaneal bursitis and Achilles insertional tendinopathy.

5.6.1.3 Ruptures

Rupture of the Achilles tendon is the most common form of spontaneous tendon rupture, affecting men more often than women. Ninety per cent of ruptures occur owing to physical activity. Only 10% of all those who rupture have had previous Achilles tendon symptoms, 30% of whom are only mildly symptomatic. Rupture usually occurs 3–6 cm above the insertion (83%), while 12% occur at the musculotendinous junction and 5% at the insertion (Hattrup and Johnson, 1985). Simultaneous bilateral rupture is rare but successive ruptures are relatively more common. Iatrogenic causes of Achilles tendon rupture must also be considered, including fluoroquinolones and glucocorticoid injections.

5.6.1.4 Diagnosis of Achilles tendon disorders

5.6.1.4.1 History

Symptoms may vary from pain, stiffness and severe inflammation to a minor ache, depending upon the specific disorder. Pain may be worst at the beginning of the day, with start-up pain (difficulty in putting the foot to the floor on getting out of bed). Precipitating factors must be sought, including activities, types of footwear and trauma. In the sporting population a careful history must be taken of training patterns, surfaces, equipment use (including shoes), previous injuries and additional training activities. In acute spontaneous ruptures the history of a loud bang and a feeling as if the patient has been kicked in the back of the leg, with subsequent difficulty in pushing off, is virtually diagnostic. However, pain may be absent and symptoms vague. Partial tears of the Achilles tendon may occur as a result of a distinct episode or a series of pain episodes. In individuals with insertional tendinopathies, a systemic enquiry into the possibility of an associated spondyloarthritis is important (box 9).

Box 9 Enthesopathies: associated spondyloarthritides

- Psoriatic arthritis
- Reiter's syndrome/reactive arthropathy
- Enteropathic arthritis (Crohn's disease, ulcerative colitis)
- Ankylosing spondylitis
- Seronegative enthesopathic arthropathy syndrome
- Undifferentiated spondylitis

5.6.1.4.2 Physical examination

Paratenonitis, tendinosis and tears most commonly occur in the mid-third section of the tendon, where the area is relatively hypovascular. Local tenderness, inflammatory signs and/or a palpable tendon nodule may be evident (figure 35).

Figure 35 Palpation of the Achilles tendon and pre-Achilles bursa. (Courtesy of Professor J A P Da Silva. Reproduced with permission from Da Silva and Woolf, *Rheumatology In Practice*, Springer, 2010*.)



Stiffness of the gastrocnemius–soleus complex is common. The tendon may be swollen and generally tender with crepitus in acute paratenonitis. In acute ruptures, swelling and bruising may be evident and in the chronic ruptures, local thickening of the tendon and peritendinous tissues and muscle atrophy are commonly seen. Achilles tendon rupture can be detected by the angle at which the feet dangle over the end of the examining couch (figure 36). Rupture is confirmed by absence of plantar flexion of the foot when the examiner squeezes the calf. The patient is unable to perform a single heel raise and a palpable gap may be present.

Partial tears are often difficult to diagnose; weakness of dorsiflexion and a failure to respond to conservative management should arouse suspicion but imaging is usually necessary.

Insertional tendinopathy (i.e., enthesopathy) is commonly associated with a retrocalcaneal bursitis and a Haglund's deformity (also called 'pump bump'), particularly in association with a hypermobile rear foot. Insertional tendinitis causes local tenderness, swelling and hyperaemia at the insertion.

Figure 36 Achilles tendon rupture—loss of plantar flexion (right). (Reproduced with permission © Royal College of Surgeons in Ireland Illustrations.)



In retrocalcaneal bursitis, bursal swelling is often seen on both sides of the Achilles tendon, although it is not so obvious in chronic situations. In acute and subacute cases, there is painful swelling and occasionally hyperaemia of the overlying skin in the posterosuperior corner of the calcaneus. Dorsiflexion of the foot is painful.

Predisposing anatomical factors should be sought. Gait should be assessed for hyperpronation, leg length discrepancy and deformities.

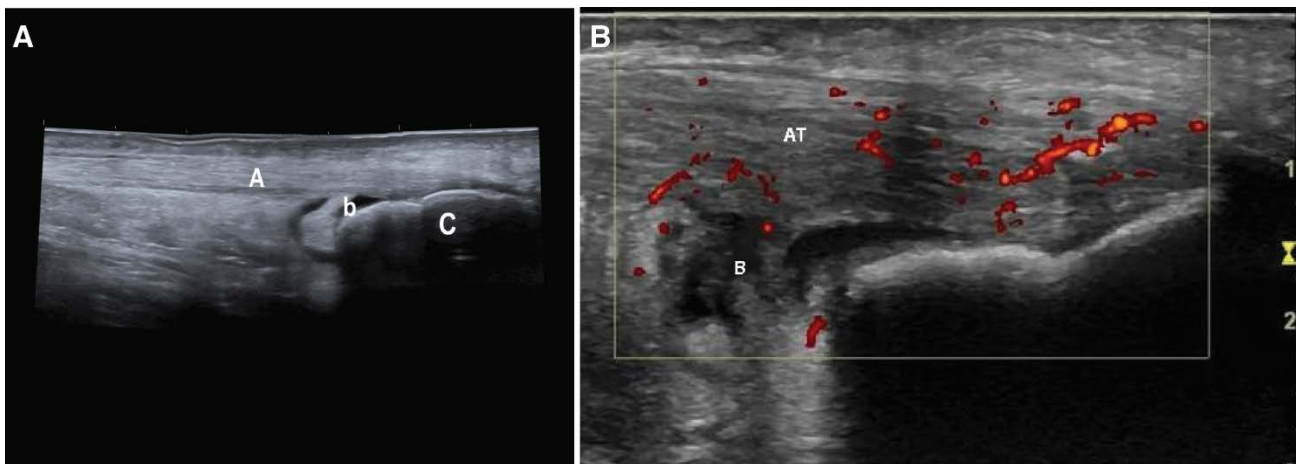
5.6.1.4.3 Imaging of Achilles tendinopathies

Ultrasound should be performed as an extension of the clinical examination. Abnormal findings can be identified at the paratenon, the tendon echo texture and the enthesis. Ultrasound imaging helps to distinguish full thickness tears from other Achilles tendinopathies.

Retrocalcaneal and retro Achilles bursae can also be detected using ultrasound (figures 37A, B). MRI is particularly useful in evaluating the surrounding bony abnormalities and retrocalcaneal pathologies.

Radiography may be helpful in the assessment of a Haglund's deformity, or bony spurs associated with insertional tendon pain.

Figure 37 (A) Longitudinal ultrasound image of retrocalcaneal bursitis (b). (B) Longitudinal ultrasound image of the Achilles tendon presenting increased thickness, a loss of the normal fibrillar structure and positive Doppler sign. The retrocalcaneal bursa (B) is occupied by an inhomogeneous hypoechoic mass. A, Achilles tendon; AT, Achille's tendon; C, calcaneum.



5.6.1.4.4 Management of Achilles tendinopathies

Paratenonitis and tendinosis. The focus, as in all core tendon injuries, is controlled loading. As is the case with so many soft tissue injuries, controlling symptoms to allow rehabilitation is a central goal. In acute and subacute cases, the Protect, Rest, Ice, Compression, Elevation, Support (PRICES) approach is appropriate. Rest is relative; reducing the intensity, frequency and duration of loading activities and cross-training through the adoption of alternative modes of activity that do not stress the tendon (swimming, cycling) is encouraged. In cases of severe inflammatory enthesopathies, in particular, functional casting or, rarely, the use of crutches, may be necessary. Cryotherapy in the form of ice, cold compresses or ice immersion is used to control pain, reduce muscle spasm, oedema, regional blood flow and the metabolic demands of tissue, and thereby prevent further tissue damage.

Topical NSAIDs can help; high drug levels in the tendon can be achieved with a low risk of side effects, local massage of the drug into the tendon itself can provide relief.

Once the very acute symptoms have resolved, early stretching of the gastrocnemius and soleus muscles separately, in addition to hamstring stretching, is important. Heat may be useful later in providing analgesia, reducing muscle spasm, improving tissue extensibility, inducing vasodilatation, and increasing vascular permeability and metabolism. Warm whirlpools, warm packs, hot gels, contrast baths, paraffin wax and infrared may all be used for this purpose.

Local modalities, including ultrasound, deep heat and laser, may be useful but evidence for their effectiveness is limited, and they should not divert attention away from rehabilitation. The use of a dorsiflexion night splint or other orthotics should be considered and gradual strength training of the lower leg musculature should be introduced once the patient is pain free.

Attention to precipitating factors is important, such as exercise concerns or biomechanical factors (e.g., walking patterns, shoe wear).

Where implicated, fluoroquinolones must be withdrawn immediately and treatment of the local disorder is necessary. Where the tendinosis is associated with hyperlipidaemic states, treatment with a statin is indicated.

Appropriate rehabilitation is essential for a successful return to full activities. This includes stretching of the gastrocnemius–soleus complex and hamstrings and gradual strengthening of the calf musculature, the fundamental component being an eccentric muscle training programme, or a similar loading regimen.

Glucocorticoid injections have no role to play, as they are usually ineffective and may weaken the tendon, with resulting rupture.

Although most cases are managed conservatively, surgery may be considered in those people whose movement remains significantly limited despite intensive rehabilitation for 12–18 months. Numerous surgical techniques, alone or in combination, have been advocated, although none have been rigorously evaluated. Surgery in this area may result in significant complications, including poor wound healing, local nerve damage, infection and failure of the repair.

Enthesopathy and bursitis. Treatments are similar to those described above. Relief of friction between the heel counter of footwear and the bursal projection by padding and modification of the shape, height and rigidity of the heel counter are all recommended. ESWT can be useful in cases of calcific disorders or ossification of the Achilles tendon, which most commonly occurs at the insertion.

In acute bursitis with intrabursal fluid, aspiration and glucocorticoid injection can be performed. Haglund's syndrome may take many months to show signs of improvement with conservative measures.

Patients with recalcitrant retrocalcaneal bursitis or Haglund's syndrome may be managed surgically. This may involve debridement or resection of the bursa, or (as appropriate) excision of the posterior superior calcaneus (Haglund's deformity). Calcaneal osteotomy has also been advocated, although this is considerably more invasive.

A seronegative arthritis should be considered in those patients who have persisting insertional Achilles tendinopathy and/or retrocalcaneal bursitis. Ultrasound with a Doppler technique has shown promising results as a diagnostic tool for distinguishing between degenerative and inflammatory (i.e., spondyloarthritis) enthesal involvement.

Rupture. Initial treatment of the acute Achilles tendon rupture requires the PRICES regimen. The options are then early surgical repair and 6 weeks bracing, or bracing for 8 weeks. Re-rupture rate is similar for both approaches but is variably reported to be 0–50%. However, non-surgical management is also acceptable,

particularly for a patient who is less active or not a good candidate for surgery. An aggressive postoperative regimen is commonly followed, with early mobilisation and the start of rehabilitation.

Partial tears. Partial Achilles tears are often classified as tendinosis and are managed in the same way. In the acute stage, management follows the PRICES regimen for 4–7 days, with rest to prevent further tear and the use of a brace support. Surgery is rarely necessary but can be used for those who do not respond to conservative treatment, or for those with substantial tears.

5.6.2 Plantar fasciitis

Plantar fasciitis comprises inflammation of the insertion of the plantar fascia on the medial process of the calcaneal tuberosity (figure 38).

Figure 38 *Palpation of the posterior insertion of the plantar fascia. (Courtesy of Professor J A P Da Silva. Reproduced with permission from da Silva and Woolf. Rheumatology In Practice, Springer, 2010*.)*

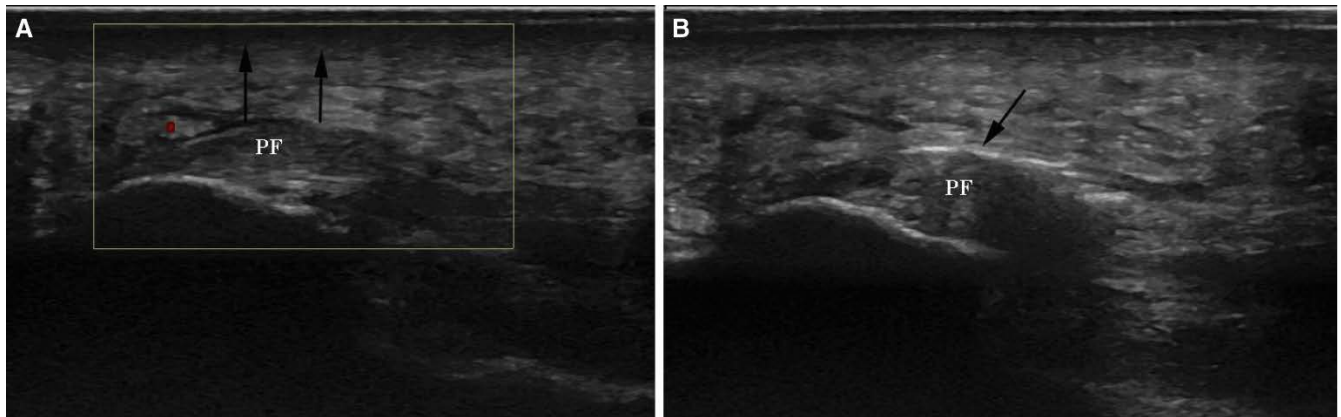


The aetiology is multifactorial but most of the cases are linked to overuse stresses. Possible risk factors include prolonged standing and weight bearing, obesity and heel spurs. Excessive stretching of the plantar fascia can result in repetitive microtrauma of this structure and produce chronic degeneration/rupture of the fascial fibres.

Pain is experienced on the plantar surface of the foot, especially with the first steps after periods of inactivity.

Ultrasonography identifies an increase in the thickness of the fascia, hypoechogenicity and oedema at the level of the calcaneus insertion, as well as loss of definition between the fascia and the surrounding soft tissue (figure 39A). MRI and radiography are useful when other pathologies are suspected.

Figure 39 (A) Longitudinal scanning of the plantar fascia (PF), which has increased thickness and a convex shape (arrows). (B) Longitudinal scanning of the plantar fascia (PF). Glucocorticoid deposition (hyperechoic line, arrow) at the interface between the PF and subcutaneous tissue.



The treatment includes rest and activity changes, ice, NSAIDs, local glucocorticoids (figure 39B), splinting, shoe modifications and orthoses. Some physical therapy programmes, such as stretching, ultrasonography and iontophoresis, may be used as adjuncts.

In refractory cases, apart from surgical procedures, other treatment techniques like PRP injection, glyceryl trinitrate patches and ESWT, have been used.

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SUMMARY POINTS

- Soft tissues, including tendon, muscle, bursa, ligament and fascia, are the most common source of pain presenting to rheumatologists.
- Soft tissue complaints can be due to localised pathology, or related to systemic disease, such as inflammatory arthritides, diabetes, hormonal causes and drugs.
- Establishing a specific diagnosis in a patient with a soft tissue disorder is vital to guide best management.
- The assessment of soft tissue lesions involves taking a careful history and performing a thorough clinical examination, based upon 'Look, Feel, Move, Special Tests'.
- Imaging, particularly diagnostic ultrasound and magnetic resonance imaging, provide information on structural changes in tissues and surrounding anatomy, but should be used only in the context of the clinical picture.
- Musculoskeletal ultrasound is a bedside imaging modality that provides accurate soft tissue diagnoses and guidance for therapeutic injections.
- Rotator cuff disorders are the most common causes of shoulder pain in adults.
- Sepsis and gout should be considered in any patient presenting with an acute red hot bursitis.
- Management of many soft tissue complaints, and in particular those affecting a tendon, involves focused exercise-orientated rehabilitation, facilitated by good management of pain.
- Glucocorticoid injections are often used for soft tissue complaints, but should be reserved for recalcitrant conditions where pain or inflammation is limiting rehabilitation.

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Regional musculoskeletal pain syndromes

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IN-DEPTH DISCUSSION I

**Wrist pain related with ligamentous structures:
Scapholunate ligament pathology**

1.a Introduction

The rheumatologist often cares for patients with dorsal wrist pain or discomfort which is not always inflammatory in nature. The following discussion considers one possible cause: the Scapholunate ligament (SLL) and its pathology.

The wrist is formed by two rows of carpal bones, proximal and distal, joined by a system of intrinsic and extrinsic ligaments enabling the proximal carpal row to act as the link between the static components of the forearm and the distal carpal row. The ranges of motion of the carpal joints are complex and dependent on the integrity of these ligamentous structures. The SLL is one of the most clinically important ligaments of the wrist. SLL clinically relevant anatomy, diagnostic evaluation and treatment will be discussed.

1.b Anatomical details relevant for the diagnostic and treatment.

The SLL is an intrinsic ligament in the proximal row of the carpal bones. The SLL consists of volar (palmar), dorsal and interosseous components. The volar component contributes to rotational motion of the wrist and is highly innervated, thus having a proprioceptive role as well. It is in continuity with the extrinsic volar radioscapholunate ligament. The intermediate component of the SLL is primarily fibrocartilaginous tissue with minimal blood supply which makes it susceptible to the development of degenerative tears or crystal deposition. The dorsal component contributes in the control of the flexion and extension of the wrist joint and is the key component in maintaining the relationship between scaphoid and lunate; the edges blend with the radiocarpal joint capsule and the scaphotriquetral and dorsal intercarpal ligaments. The dorsal SLL is subjected to very strong forces owing to wrist architecture where the scaphoid bone is the link between the proximal and distal row of carpal bones and the movements of radial- ulnar deviation. Flexion and extension occur about the lunate bone. In addition to the SLL, the scapholunate joint also has secondary static stabilizers responsible at the extremes of motion such as the scaphotrapezial-trapezoidal and the radioscaphocapitate ligaments and dynamic stabilizers including the flexor carpi radialis tendon (FCR). The FCR is important during the wrist movements by providing dynamic stabilization of the scaphoid by utilizing its insertion into the scaphoid tuberosity which then extends to its final insertion at the second metacarpal bone. Salva Coll et al (2011) showed that the FCR has capability to extend and supinate the scaphoid and pronate the triquetrum resulting in scapholunate joint junction and dorsal SLL relaxation. This is the basis for the positive effect of FCR re-education in dynamic scapholunate instabilities. Anatomical risk factors for SLL damage are an ulna minus configuration, lunotriquetral coalition and the slope of the radial articular surface.

1.c Diagnostic evaluation

SLL damage commonly results from severe injury or low-grade repetitive trauma. Patients with CPPD deposition disease can have calcium pyrophosphate dehydrate crystal deposition in the fibro-cartilaginous intermediate portion of the ligament with subsequent damage of the SLL. Injuries in the dorsal portion of SLL are related with symptoms whereas tears of the fibro-cartilaginous portion are mostly asymptomatic. Injuries of the volar component are potentially associated with damage to the volar radioscapholunate ligament. These patients present with tenderness located in the region of the scaphoid and lunate bones at the radial side of the wrist. They may experience a painful clicking with decreased grip strength. This may be the result of severe direct trauma or repetitive low-grade trauma with the wrist in hyperextension. A tender point may be noted at the proximal end of the snuffbox just distal to the Listers's tubercle.

Testing the movements of the wrist joint include positions that combine flexion-extension and radial-ulnar deviation. When there is a SLL injury, there is an increase of the scaphoid motion but not of the lunate motion that leads a change in the functional arc of wrist motion used in activities of daily living. The Watson test is a provocative test for detecting damage at the dorsal component of the SLL. The patient will have dorsal subluxation of the proximal scaphoid over the dorsal end of the radius while the wrist is radially deviated; the clinician will notice patient's painful click while doing the test (1).

Villiers (1998) showed that the dorsal ganglia of the wrist appear related with dorsal SLL defect with a communication between the ganglion and SLL.

In presence of severe trauma, the patient can present not only SLL injury but also with injuries to various ligamentous structures including the radiocapitate, radiotriquetral and dorsal radiocarpal ligaments or associated non-ligamentous injuries such as radial styloid fracture or scaphoid fracture.

Other diagnostic possibilities in a patient with dorsal wrist pain include: ulnar translocation syndrome, posterior interosseous nerve neuroma, physiologic scapholunate separation, distal radioulnar joint instability and triangular fibrocartilage complex tears.

Ulnar translocation syndrome occurs when the lunate is displaced in an ulnar direction. It is a frequent cause of radiocarpal instability. Although ulnar translation can be seen in advanced rheumatoid arthritis or in Madelung's deformity, abnormal translation of lunate in ulnar direction is pathognomonic of ulnar translocation syndrome. On X-ray, the lunate is positioned distal to the ulna and the distance between the radial styloid process and the scaphoid can be widened (type I) or normal (type II) with a gap between scaphoid and lunate. The patient presents with the carpus and hand offset in an ulnar direction.

Complementary imaging studies are essential to rule out the diagnosis of SLL damage (2). Dynamic radiographs or cineradiography are the first image choice. Radiographic features include widening of the space between scaphoid and lunate determined in PA view; a gap greater than 3-4 mm is considered to be pathologic (Image a). The width between scaphoid and lunate may also be considered abnormal when the midportion of the scapholunate joint space is larger than the capitulunate or third carpometacarpal joint space widths. Lateral view is important to demonstrate the scapholunate angle which should be less than 70°.

Osteoarthritis can be seen in long standing SLL damage. Initially the radio-scaphoid joint is involved but in advance stages various intercarpal joints can also be involved with the radiolunate joint being the last affected.

When radiographs do not clarify the diagnosis and the patient history and exam suggest a SLL injury, magnetic resonance (MRI) or MRI arthrography help in the treatment decision. Multi-detector CT arthrogram can demonstrate partial tears, abnormal angulations of the scaphoid and lunate bones, changes of the subchondral bone and abnormalities of the cartilage.

According to the Watson classification, there are three stages of scapholunate instability. Pre-dynamic instability, the first stage, is associated with partial SLL tear; although it can be symptomatic, it is not visible on radiographs. The second degree is dynamic scapholunate joint instability when there is a complete tear of the SLL and the third stage is scapholunate joint dissociation when secondary stabilizers are affected. This third stage can lead to degenerative changes with severe osteoarthritis of the wrist. A more detailed six stage classification of Elias et al that take in account prognostic factors that help to assess the probability of a positive post-surgical outcome.

Musculoskeletal ultrasound is helpful in the recognition of dorsal SLL abnormalities and in confirming SLL laxity by placing the probe longitudinal to the dorsal part of the SLL with the wrist in volar flexion while asking the patient to make fist.

1.d Treatment

Treatment should be tailored to each stage of involvement and include: arthroscopic debridement, reconstruction, tenodesis, wrist joint fusion or carpectomy in complete disruption with cartilage loss. (Images b and c) According to Elias et al (3), prognostic factors that may affect surgical outcome of SLL injuries include:

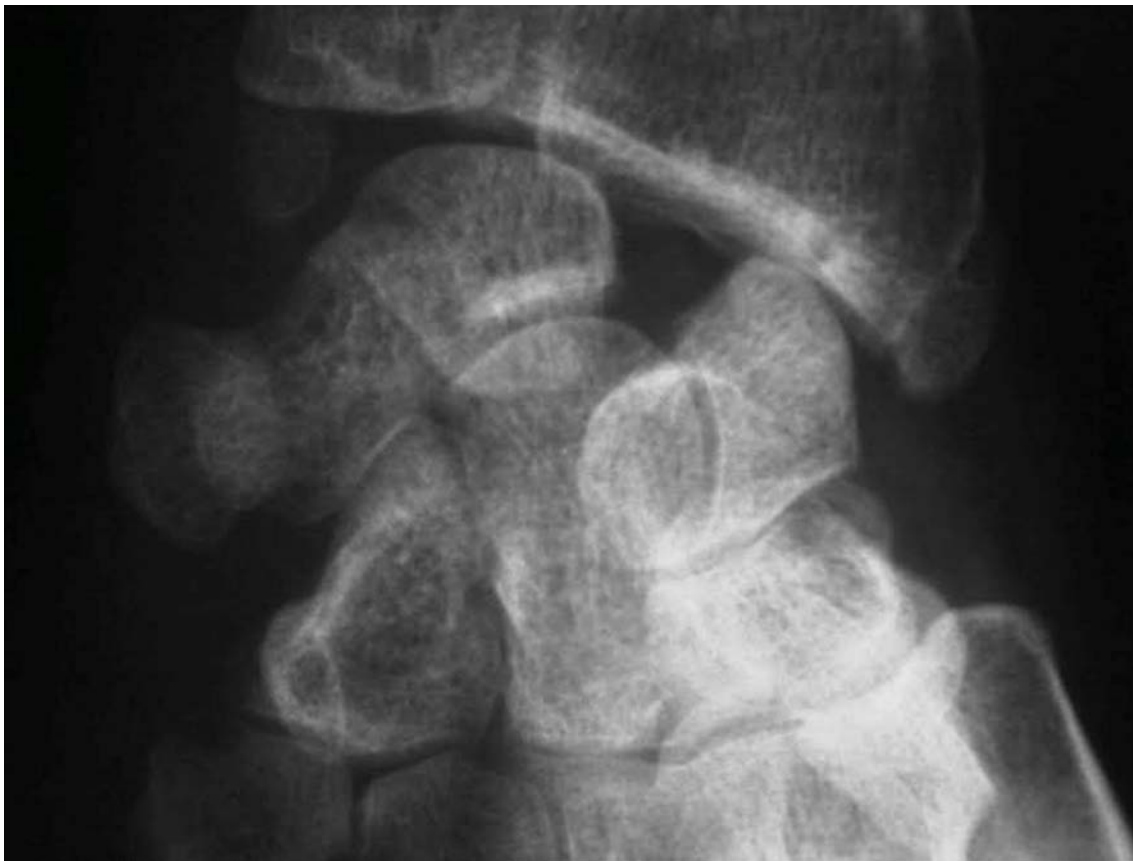
- An SLL tear affecting not only the dorsal portion but extending to the volar and/or fibrocartilaginous layers
- Intra-substance SLL tears are more difficult to heal than the osseous avulsion.
- Condition of the secondary stabilizers of the scapholunate joint.
- Ability to reduce the carpal misalignment.
- The integrity of the radiocarpal and metacarpal cartilages.

- Unfortunately, the level of evidence supporting these various techniques is generally low and does not completely answer questions about their efficacy.

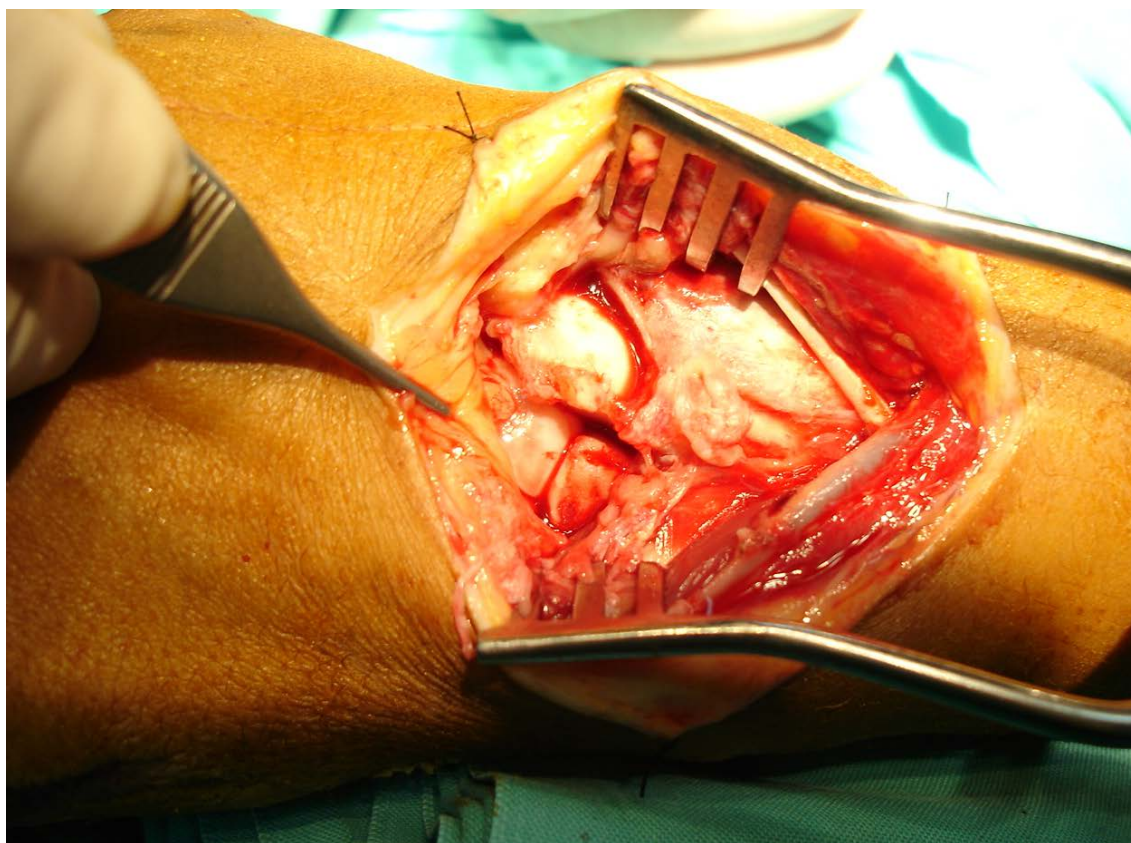
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a- Xrays showing widening of the space between scaphoid and lunate determined in PA view; gap > 4 mm



b- Full thickness tear of SLL; S:scaphoid, C:capitate; L: lunate. Courtesy of J. Palau



c- Surgical treatment of SLL full thickness tear; internal fixation with Kirschner . Courtesy of J Palau





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module

EULAR on-line course on Rheumatic Diseases

Regional musculoskeletal pain syndromes

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A previous version was coauthored by Cathy Speed, Esperanza Naredo, Ingrid Möller



IN-DEPTH DISCUSSION II

Trigger finger

INTRODUCTION

Trigger finger is a common disorder of the hand with an incidence of 2.6% in general population up to 10% in diabetic patients, with higher prevalence in the 6th decade. This disorder is characterized by snapping or locking of the flexor tendons in the affected finger, a phenomenon that generates pain during flexion and extension accompanied by mechanical dysfunction. It occurs more commonly in women, in the dominant hand and most often it affects the third, fourth finger or thumb.

Work activities which imply repetitive gripping of an item or sport activity (e.g. volley) may trigger this pathology but an important percentage of the cases are idiopathic. A tendon sliding deficit generated by a discrepancy between the tendon / sheath size and a hypertrophic A1 pulley underlies this pathology. Still, the pathogenesis is not completely understood and may be multifactorial. A fibrocartilaginous metaplasia of the A1 pulley seems to develop in idiopathic trigger finger with subsequent mismatch between the pulley and underlying tendons.

The most important risk factors are diabetes mellitus, rheumatoid arthritis, hypothyroidism, acromegaly, renal failure with or without amyloidosis and overweight.

Anatomy

The flexor tendon system of the hand consists of flexor muscles of the forearm and the tendinous extensions. At digital level, a specialized digital flexor sheath assures a smooth and rapid flexion of each finger. The flexor muscles of the digits belong to the anterior compartment of the forearm and include the flexor digitorum profundus (FDP), flexor digitorum superficialis (FDS) and the flexor pollicis longus (FPL).

The **FDP** muscle originates from the proximal, anteromedial aspect of the ulna and reaches the distal forearm as a single muscle belly but separates distally in a radial and ulnar bundle. At the musculo-tendinous junction, the radial bundle will form the flexor profundus of the index finger and the ulnar bundle will form the individual profundus tendons of the third, fourth and fifth fingers.

The index and third finger muscles are innervated by the anterior interosseous branch of the median nerve, roots C8 and T1. The ulnar nerve (motor branches, roots C8 and T1) provide innervation for the fourth and fifth finger muscles. The FDP muscles receive blood supply from the ulnar artery, anterior and common interosseous arteries.

The muscular contraction will initiate the flexion of the proximal interphalangeal joint (PIP) and the distal interphalangeal joint (DIP).

The **FDS** muscle originates (ulnar and radial head) from the anterior compartment of the forearm and is located superficial to FDP. At the level of the distal forearm it forms four distinct tendons displaced in 2 layers: superficial (FDS of the third and fourth finger) and profound (FDS of the second and fifth finger). Innervation is provided by the median nerve (roots C7, C8, T1). Blood supply is provided by the branches of the artery of the median nerve, muscular branches of the ulnar and radial arteries.

The **FPL** originates from the mid-anterior aspect of the radius and interosseous membrane. The muscle tendon inserts into the distal phalanx of the thumb and during contraction interphalangeal (IP) and metacarpophalangeal (MCP) joints are flexed. The interosseous branch of the median nerve is responsible for the innervation.

The digital flexor sheath protects the tendons and consists of a membranous and retinacular portion. The membranous portion (synovial lining), made of visceral and parietal layers surround the FDP and FDS and facilitates the smooth gliding of the structures during flexion and extension movements. The retinacular component displays annular, cruciform and transverse fibres forming a pulley system which overlie the membranous portion. Its function is to stabilize the tendons during finger flexion. The pulley system consists of the palmar aponeurosis pulley, 5 annular pulleys and 3 cruciform pulleys. A1 pulley consists of strong, rigid and non-extensible annular bands of connective tissue located at the level of the volar aspect of the metacarpophalangeal joint (MCPj) which are contiguous with the flexor tendon sheath. A1 pulley pathology generates trigger finger.

Clinical presentation

Pain and mechanical dysfunction occur at the base of the digit (volar aspect) during finger flexion attempts while gripping. During flexion, the smooth and rapid tendon sliding is replaced by a delayed, hesitated move of the affected finger, ending with a snap when closed and obstacle is overcome. During extension, a similar phenomenon occurs before the tendon snaps into full extension. In severe cases, the digit remains locked in a bent position and must be manually (passive move) reinstated in full extension or full flexion. With each movement, especially when performing demanding working tasks, the tendon becomes more irritated, inflamed and thicker, aggravating the local situation. The phenomenon is more pronounced in the morning or after a longer interval of finger inactivity (Figure 1).

Figure 1. During digits extension manoeuvre, the affected digit remains locked in a bent position.



Diagnosis

Diagnosis is made on clinical basis after collecting the medical history and performing a physical examination which consists of dynamic manoeuvres of active flexion and extension of the digits, identification of the areas where pain is expressed during motion.

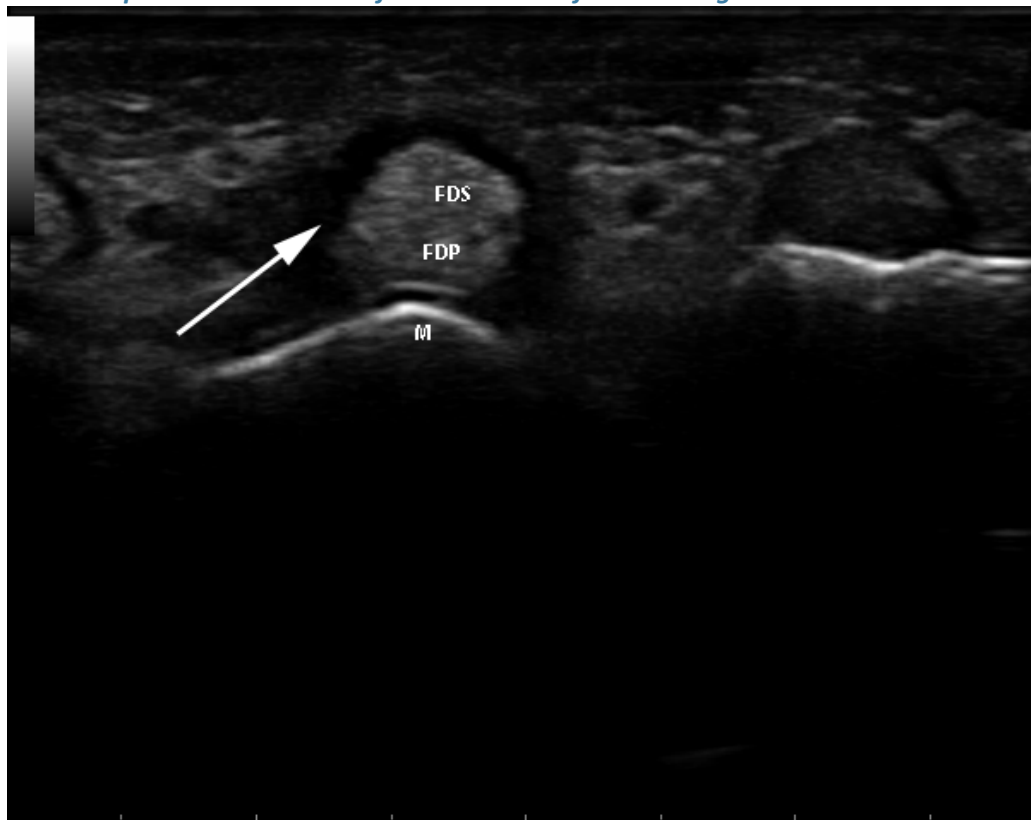
Ultrasound evaluation is an extension of the clinical examination. It can easily help to depict soft tissue underlying lesions. In normal conditions, A1 pulley is depicted as a hypoechoic band superficial to the flexor tendon sheath. In axial plane, marginal shadow artefacts can be depicted because of anisotropy. The tendons (FDP and FDS) have a regular fibrillar structure and slide smoothly when performing dynamic examination (finger flexion).

The ultrasonographic hallmark findings in trigger finger pathology are: hypoechoic thickening of the A1 pulley, tenosynovitis, sometimes nodular thickening of the flexor tendons at dynamic examination (while sliding under the A1 pulley) (Figure 2a, b).

Figure 2a. Volar finger aspect at level of MCP joint, longitudinal scanning. P- A1 pulley (thickened, hypoechoic), FDP- flexor digitorum profundus tendon, FDS- flexor digitorum superficialis tendon. Synovial sheath distension (white arrow).



Figure 2b. Volar finger aspect at level of MCP joint, transversal scanning. M- metacarpal bone, FDP- flexor digitorum profundus tendon, FDS- flexor digitorum superficialis tendon, synovial sheath distension (arrow). At the right side- comparison with normal flexor tendons of another digit.



Treatment

The treatment options are conservative - immobilization, oral nonsteroidal anti-inflammatory drugs (NSAIDs), local US guided corticosteroids (CS) / hyaluronic acid derivate injections and surgical methods like open or percutaneous resection of A1 pulley.

Mild symptoms may benefit from simple measures like avoiding activities which require repetitive gripping, finger exercises in order to preserve mobility, NSAIDs, massage, night splints (rest and maintaining extension position) for some weeks. For moderate to severe symptoms and functional disability, several conservative or surgical options may help. NSAIDs may diminish pain and tendon swelling. Local injected CS (close to the tendon sheath or strictly inside the tendon sheath) may reduce the inflammation and restore the finger movements (Fig 3 a, b). Maximum of efficacy is obtained in early phases when structural tendon and pulley damage is not so evident. In subjects affected by diabetes mellitus, rheumatoid arthritis refractory symptoms imply the repetition of CS injections. Surgical options may be a solution in trigger finger refractory to conservative methods.

Figure 3a. *Volar aspect, free hand corticosteroid injection inside the tendon sheath -transversal scanning position. Needle penetrating inside the tendon sheath- arrow head, FDP- flexor digitorum profundus tendon, FDS- flexor digitorum superficialis tendon, tendon sheath distension- white arrow.*

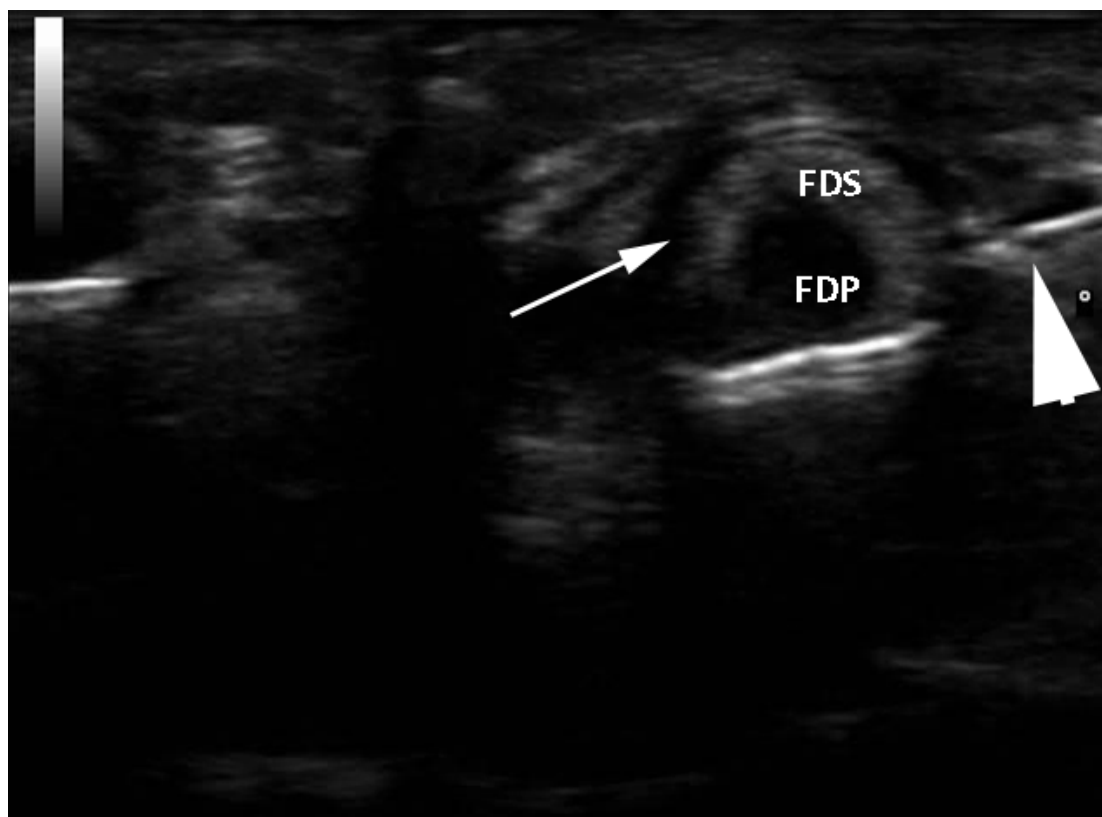


Figure 3b. Post-procedural longitudinal scanning view. Corticosteroid deposition is identified as a hyperechoic mass inside the tendon sheath (white arrow), P- thickened hypoechoic A1 pulley, FDP- flexor digitorum profundus tendon, FDS- flexor digitorum superficialis tendon.



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Generalized pain syndromes

- Including fibromyalgia and chronic fatigue syndrome -

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LEARNING OBJECTIVES

- To describe the epidemiology of generalised pain syndromes—in particular, fibromyalgia and chronic fatigue syndrome (CFS), and their impact on patients, healthcare systems and society
- To recognise and diagnose generalised pain syndromes—in particular, fibromyalgia and CFS
- To select appropriate investigations to exclude differential diagnoses
- To describe and explain the pathophysiological processes that underpin these syndromes and explore their implication on research and clinical practice—in particular, for fibromyalgia and CFS
- To manage patients with generalised pain syndromes—in particular, fibromyalgia and CFS
- To outline recent advances in the diagnosis and management of fibromyalgia syndrome

1 Introduction

Interest in chronic widespread pain has increased considerably in the past decade. Pain has been shown to be the most common reason for medical consultations in the general population. At least 50% of these patients have musculoskeletal pain, which reflects the relevance of this health problem. For the musculoskeletal diseases among these patients, non-articular rheumatic pain syndromes are a major component. These conditions can be regional or generalised. Regional conditions include tendonitis and bursitis, neurovascular entrapment, flatfoot and regional myofascial pain syndromes. Generalised conditions include multiple bursitis–tendonitis syndrome, fibromyalgia and chronic fatigue syndrome (CFS). Multiple bursitis and tendonitis syndrome presents with multiple anatomically localised areas of pain and dysfunction but fibromyalgia tender points are absent. It is likely to respond to local injection therapy. Fibromyalgia and CFS are associated with chronic widespread pain, which results in significant disability and has a major impact on quality of life. They are a major burden on the healthcare system and society. The former chief medical officer in the UK, Professor Liam Donaldson, wrote to all UK doctors highlighting the problem and emphasising the need for more information for doctors and patients.

Fibromyalgia syndrome (FMS) is one of the most common causes of chronic widespread pain. It is characterised by reduced pain thresholds (hyperalgesia) and pain with normally innocuous stimuli (allodynia). Diffuse pain is often accompanied by a wide range of symptoms, including fatigue, sleep disturbance, functional impairment, cognitive dysfunction, variable bowel habits, depression, stiffness and more. One-third of patients with FMS experience significant depression or anxiety. FMS shares many common features, and often coexists, with other syndromes such as CFS, irritable bowel syndrome (IBS), and dysmenorrhoea, leading to the suggestion that it is part of a spectrum of disorders characterised by central sensitisation (Clauw, 2014). FMS also often occurs concomitantly with other conditions, such as rheumatoid arthritis and systemic lupus erythematosus, and other chronic pain syndromes, such as low back pain and headaches. In such cases, the unwary clinician may instigate inappropriate treatment (Atzeni *et al*, 2011). In the past, this has been referred to as secondary FMS, suggesting that these conditions predispose patients to develop FMS. However, this has not been used recently as the precise relationship between FMS and these chronic painful conditions remains unclear.

2 History of FMS

FMS is not a new disease. Froriep described hard places in the muscles of patients with 'rheumatism' which were painful to pressure in 1850 (Froriep, 1850). In 1904, Gowers first coined the term 'fibrositis' in patients who complained of pain on light touch and had fatigue and sleep disturbances in the absence of any signs of local or systemic inflammation. Lewis and Kellgren, in the 1930s, injected hypertonic saline into deep muscle tissue and described referred muscle pain (Kellgren, 1938; Lewis, 1938). Subsequently, fibrositis was

considered a common cause of muscular pain, although many clinicians thought of it as 'psychogenic rheumatism'. The term 'fibromyalgia' was introduced in 1976 by Hench (1976).

In 1977, Smythe and Moldofsky first showed that certain anatomical locations were more tender in patients with FMS than in controls. These 'tender points' were often identical to those points most tender in regional pain conditions such as 'tennis elbow', 'costochondritis' and cervical strain syndromes. Their seminal work has formed the basis of the current classification/diagnostic criteria for FMS. Subsequently, many studies have confirmed the diagnostic utility of tender points, leading to several proposed diagnostic criteria based on presence of pain and tender points, with or without supplementary symptoms, after excluding other rheumatic or systemic diseases. In 1990, the American College of Rheumatology (ACR) criteria for the classification of FMS were published based on comparing patients with age- and sex-matched controls (Wolfe *et al*, 1990). The criteria require the presence of chronic widespread pain, defined as bilateral, above and below the waist, and axial, for at least 3 months and the presence of at least 11 out of 18 tender points. While the primary objective of the ACR classification criteria was to facilitate research so that homogeneous populations of patients could be studied, it is commonly applied in routine practice for diagnosis.

3 Clinical features

3.1 Pain

The most common presenting complaint of patients with FMS is 'pain all over their body', though the severity of pain may vary between patients. Often it fluctuates from one area to another. In some patients, there is a history of chronic regional pain before developing more widespread pain. Pain is often described as a chronic ache with occasional severe sharp spasm or electric shock. Paraesthesia is common. Some patients describe their muscles as tense and 'tied in knots'. Pain is often made worse by exertion or physical activities, although many patients also complain of spontaneous pain without any obvious precipitating factor. Simple analgesics such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) are rarely effective (Clauw, 2014).

One of the characteristic features of FMS is 'tenderness'. Patients often complain that even light touch or pressure is painful: hyperalgesia and allodynia. Hyperalgesia is excessive severe pain induced by a noxious stimulus. Allodynia is defined as the perception of pain induced by an innocuous stimulus. Some patients complain that the slightest touch can make them recoil in pain. Many patients also have a history of other chronic painful conditions such as migraine, non-cardiac chest pain, heartburn, dysmenorrhoea and IBS.

Often patients have severe pain which is disabling. They cannot manage routine household chores, especially shopping and cleaning, and those in employment often find difficulty in coping with work.

Although patients with CFS often complain of chronic widespread pain, it is not universal. Presence of pain is not an obligatory factor for the diagnosis of CFS.

3.2 Fatigue

Fatigue affects 80–90% of patients with FMS. It ranks second after pain as the most disabling symptom by many patients. The severity of fatigue varies but, in general, it is less disabling than in CFS. Patients often describe feeling ‘overwhelming tiredness’ and ‘completely washed out’. Severe attacks may come on suddenly. Some patients find it more difficult to cope with than pain since rest and sleep rarely improve fatigue. When fatigue is overwhelming and the muscular pain less prominent a diagnosis of CFS should be considered (Clauw, 2014; Dailey *et al*, 2014).

3.3 Non-restorative sleep

Over 70% of patients with FMS have poor quality of sleep and do not feel ‘refreshed’ in the morning. Patients often associate poor sleep quality with feeling tired and difficulty in performing physical activity. In addition, some patients with FMS are sleepy during the day. Other patients may have difficulty in getting to sleep or they wake up frequently during the night. Impaired sleep quality was found to be predictive of pain, fatigue and social functioning in one study. Polysomnography has found correlation between sleep disturbance with specific patterns of alpha intrusion and phasic alpha sleep activity. Concomitant restless leg syndrome occurs in 20–40% of patients with FMS. Loud snoring and disturbances of breathing during the night are uncommon in FMS, and the presence of these symptoms should alert clinicians to possible primary sleep disorders, such as obstructive sleep apnoea syndrome (Clauw, 2014).

3.4 Depression and anxiety

Mood disturbance is common in FMS. The prevalence of depression and anxiety in FMS is much higher among patients who attend secondary care (70–80%) than among those in the community (30–50%). Many patients who present to hospital outpatient clinics have a history of depression or anxiety, leading to the view that mood disorders are the cause of FMS. However, mood disorder is not universal and response to antidepressants in patients with FMS has been shown to be independent of any change in mood (Arnold *et al*, 2007). Generalised anxiety seems more common in FMS than depression, and seems to be associated with the distress of the patients with medically unexplained symptoms and chronic pain. This suggests that although depression or anxiety may be the cause of FMS in some patients, it is not the sole pathogenic factor and fibromyalgia cannot be presented as a psychogenic pain condition and masked depression. Patients with depression often have severe fatigue and poor sleep quality. Patients with anxiety often have palpitation and dizziness, sweating, and paraesthesia. In severe cases, some patients may experience panic attacks (Arnold *et al*, 2007; Goesling *et al*, 2013).

3.5 Impaired cognition

Patients with FMS often describe having a 'brain fog,'—that is, cognitive impairment which includes problems with memory, an inability to focus on tasks, retain new information, do mental arithmetic or solve problems. Typically these periods are episodic and last for a few days, although in some cases they may be more prolonged. Impaired cognition is associated with problems coping with work, especially in those patients for whom employment is mentally demanding. It is a major contributor to frustration and psychosocial stress (Clauw, 2014; Dailey *et al*, 2014).

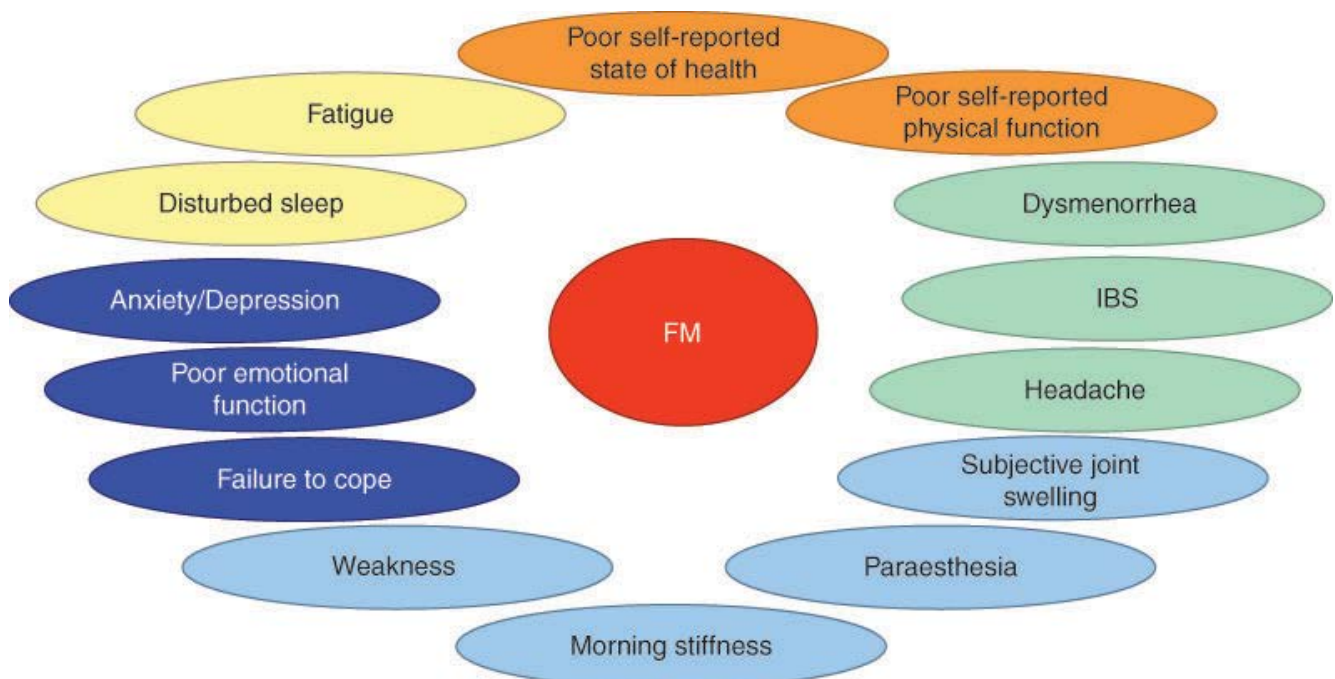
3.6 Morning stiffness

Prolonged early morning stiffness is common in patients with FMS. The duration is variable. For the unwary clinician, it may lead to diagnostic confusion with inflammatory arthritis, especially in those patients with FMS who also have swollen hands or feet. In FMS, stiffness is often not relieved by exercise and objective evidence of synovitis is also lacking.

3.7 Other symptoms

Other common symptoms in FMS include nausea, vomiting, bloating, abdominal pain, diarrhoea and constipation. Concomitant diagnosis of IBS is very common. Uro-gynaecological symptoms are also common, especially urgency, frequency, incontinence, pelvic pain and dysmenorrhoea (figure 1).

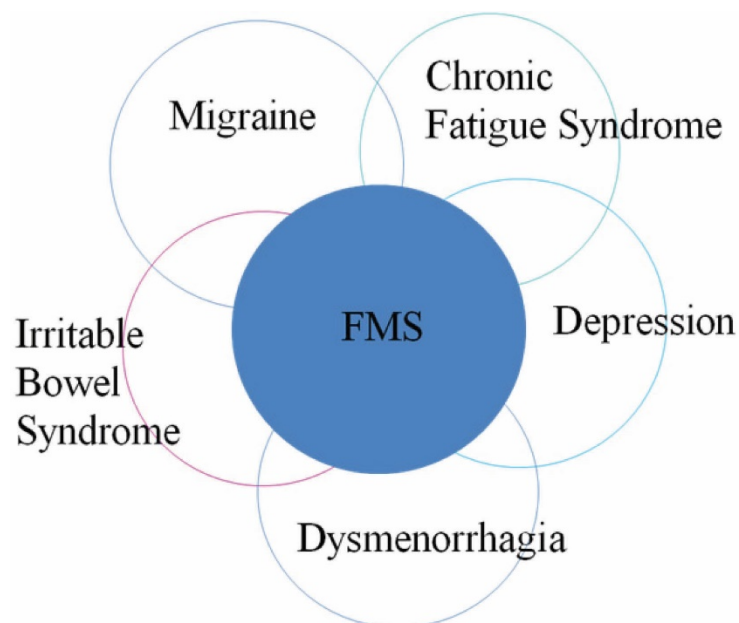
Figure 1 Symptoms associated with fibromyalgia (FM) syndrome. IBS, irritable bowel syndrome.



3.8 Associated conditions and dysfunction syndromes

Psychiatrists have called one group of disorders 'affective spectrum disorders', which often coexist. These include FMS, IBS, CFS, depression and anxiety disorders, and migraine (figure 2), which are all associated with psychological distress. It has been thought that depression may lead to the development of widespread pain, and although it is commonly reported in FMS, it is equally likely that chronic pain results in depression as most patients do not have any psychiatric illness. Furthermore, depression can be treated without improving the pain state. In pain classification, pain states such as fibromyalgia, IBS, CFS and temporomandibular disorders, are included in dysfunctional pain syndromes, characterised by abnormal central sensitisation and pain modulation deficiency.

Figure 2 *Overlap with somatisation disorders. FMS, fibromyalgia syndrome.*



Estimates of the prevalence of IBS in patients with FMS range from 30% to 35% to as high as 70%. A high frequency of FMS was documented in patients with chronic fatigue seen in a primary care practice. Seventy per cent of patients with chronic fatigue had persistent diffuse musculoskeletal pain and the results of their tender point examinations were similar to those of patients with FMS. Clauw (2014) reported that the symptoms of interstitial cystitis and FMS significantly overlap and that patients with interstitial cystitis have diffuse pain, which also is seen in FMS. Fifty-seven per cent of 77 patients with FMS had clinically significant levels of post-traumatic stress disorder. Finally, 22% of female patients with migraine had concomitant FMS (Hausteiner-Wiehle and Henningsen, 2014).

3.8.1 Chronic fatigue syndrome

CFS is also known as myalgic encephalomyelitis, post-viral fatigue syndrome and chronic fatigue immune dysfunction syndrome. Although fatigue is the dominant clinical feature in CFS, there is significant overlap

between CFS and FMS. Patients with CFS and FMS often report similar symptoms, such as pain, fatigue, mood disturbance, cognitive impairment, poor sleep quality and increase in multiple chemical sensitivities (Brown and Jason, 2007). Seventy per cent of patients with FMS and 30% of those with multiple chemical sensitivities met the criteria for CFS. In contrast to FMS, abrupt onset of symptoms is common in CFS, usually preceded or accompanied by a viral or flu-like illness. In many patients, CFS may be precipitated by stress, although the role of infection or stress in its development remains controversial. Some patients with CFS have a gradual onset, and mimic FMS. Features, which are common in CFS, but less so in FMS, include general malaise or influenza-like symptoms, such as sore throat and painful lymph nodes without lymphadenopathy.

As mentioned above, patients often report getting a flu-like or upper respiratory tract infection, from which they seem never to fully recover and, consequently, develop CFS. Hence, the name post-viral fatigue syndrome. However, in some patients, the development of CFS may be preceded by severe adverse stress in the preceding months (Adamowicz *et al*, 2014).

There is no assay or pathological test for CFS; diagnosis is based on symptoms and exclusion of other illnesses. There are many sets of diagnostic criteria for CFS (Bates *et al*, 1994). In general, they include the presence of fatigue which is chronic and/or recurrent for >6 months, which results in substantial reduction in activity, is worsened by exertion and is unexplained by other conditions. Some of these criteria include other symptoms of CFS, such as sore throat, muscle pain, cognitive dysfunction, tender lymph nodes, chemical hypersensitivity, headache and unrefreshing sleep. Exclusion criteria include psychotic, melancholic, or bipolar depression, psychotic disorders, dementia and anorexia or bulimia nervosa.

3.8.2 Differentiating CFS from FMS

Medical opinions are split on relationship between these two conditions. They are similar, and share many clinical features. Some believe the two conditions are the same, while others view them as different. Differentiating the two can be difficult in some patients but the following are helpful. First, pain is the predominant problem in people with fibromyalgia, whereas fatigue is the major complaint in people with CFS. The latter is usually severe and often completely incapacitating. Second, an abrupt onset preceded by a viral infection is more typical of CFS than FM. Third, the presence of sore throat or enlarged or tender lymph nodes would also suggest CFS.

The management of FMS and CFS is similar. Education, exercise and low-dose antidepressant drugs are used to treat both conditions.

4 Diagnosis of FMS

It is important to exclude other rheumatic diseases when assessing a patient who may have FMS (Cazzola *et al*, 2008). Distinguishing patients with FMS from those with early rheumatoid arthritis or connective tissue

diseases may be difficult. Unexplained weight loss or gain and fever are symptoms that strongly suggest alternative diagnoses. Physical examination of patients with FMS is often normal except for the presence of pain on movement and tender points. However, it is important to ensure patients do not have any evidence of synovitis, limitation in passive joint movement, skin rashes or muscle weakness.

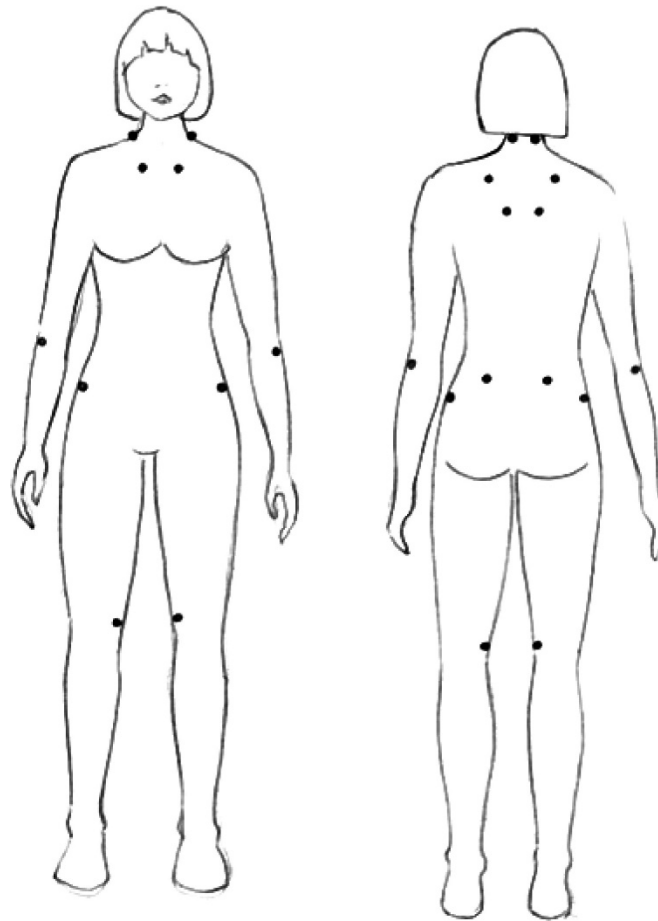
There is no specific diagnostic laboratory test for FMS so blood tests are used to exclude alternative diagnoses. In general, full blood count, biochemistry, erythrocyte sedimentation rate or C-reactive protein and thyroid function tests are all that are necessary. Rheumatoid factor and antinuclear antibodies are typically negative and their determination is not warranted unless the clinical suspicion of rheumatoid arthritis or connective tissue disease is high. Weakly false-positive rheumatoid factor and antinuclear factor are common in normal people and could mislead the unwary. Virological serological tests are usually unhelpful, even in CFS, and are not indicated routinely. They should be considered only when active infection is suspected owing to clinical features such as fever. Similarly, Lyme disease serology is not routinely necessary (Cazzola *et al*, 2008).

Differential diagnoses of FM include osteomalacia, hypermobility syndrome, primary generalised osteoarthritis, polymyalgia rheumatica, rheumatoid arthritis, connective tissue diseases such as systemic lupus erythematosus, Sjögren's syndrome and inflammatory muscle diseases, myopathies, hypothyroidism and malignancies (Atzeni *et al*, 2011).

4.1 1990 ACR classification criteria

The 1990 ACR classification criteria for FMS were developed initially to facilitate research by identifying homogeneous groups to enable results from different studies to be interpreted. They stipulate that essential factors are a history of widespread pain lasting for more than 3 months, defined as pain in both sides of the body, pain above and below the waist. In addition, axial skeletal pain (cervical spine, anterior chest, thoracic spine or low back) must be present. Low back pain is considered lower segment pain. Pain must be present in at least 11 of 18 tender point sites on digital palpation with an approximate force of 4 kg (until the colour under the nail blanches) (figure 3). These must be reported as 'painful' not just 'tender'. The classic tender points of FMS are distributed symmetrically over the occiput, low cervical, trapezius, supraspinatus, second rib, lateral epicondyle, gluteus, greater trochanter and at the medial fat pad of the knee (figure 3). Each point is palpated with the thumb of the examiner, using gradually increasing pressure, until the patient reports the pressure to be painful. A point is considered 'positive' if pressure <4 kg evokes pain by this procedure (Wolfe *et al*, 1990).

Figure 3 Tender point locations for fibromyalgia: occiput; low cervical; trapezius; supraspinatus; second rib; lateral epicondyle; gluteus; greater trochanter; knee.



Box 1 ACR 2010 fibromyalgia diagnostic criteria

Criteria

A patient satisfies the diagnostic criteria for FMS if the following 3 conditions are met:

1. WPI ≥ 7 and SSS score ≥ 5 or WPI 3–6 and SSS score ≥ 9 .
2. Symptoms have been present at a similar level for at least 3 months.
3. The patient does not have a disorder that would otherwise explain the pain.

Ascertainment

WPI

Note the number of areas in which the patient has had pain over the past week (score will be between 0 and 19): left shoulder girdle, right shoulder girdle, left hip (buttock, trochanter), right hip (buttock, trochanter), left jaw, right jaw, upper back, lower back, left upper arm, right upper arm, left lower arm, right lower arm, left upper leg, right upper leg, left lower leg, right lower leg, neck, chest, abdomen.

SS scale score:

1. Fatigue, waking unrefreshed, cognitive symptoms. For each of the 3 symptoms above, indicate the level of severity over the past week using the following scale: 0, no problem; 1, slight or mild problems, generally mild or intermittent; 2, moderate, considerable problems, often present or at a moderate level or both; 3, severe, pervasive, continuous, life-disturbing problems.
2. Considering somatic symptoms in general, indicate whether the patient has 0, no symptoms; 1, few symptoms; 2, a moderate number of symptoms; or 3, many symptoms.

The SSS score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent of somatic symptoms in general. The final SSS score is between 0 and 12.

FMS, fibromyalgia syndrome; SSS, Symptom Severity Scale; WPI, Widespread Pain Index.

4.2 Controversy about the diagnosis of FMS

Although the 1990 ACR criteria were useful for providing homogeneous populations for research and clinical trials, there is significant controversy about the diagnosis of FMS. Some clinicians have argued that FMS is not a distinct disease entity. There is a belief that labelling patients with FMS encourages chronic illness behaviour and increases healthcare use (Hadler and Ehrlich, 2003). However, recent research in the UK showed the contrary to be true. Using the General Practice Research Database, Hughes *et al* have shown that healthcare use among patients with FMS was already very high in the 8 years preceding the diagnosis (Hughes *et al*, 2006*). Interestingly, healthcare use decreased after diagnosis, indicating that diagnosis could be used constructively to reassure and educate patients. A screening test (Perrot *et al*, 2010) (FiRST—Fibromyalgia Rapid Screening Tool) has been developed to detect FMS among patients with chronic widespread pain, based on a list of six questions, with five positive answers detecting FMS with a sensitivity and specificity of more than 80%.

Furthermore, research using neuroimaging to study patients with FMS has shown specific patterns in the brain, associated with central sensitisation. Both single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) have demonstrated reduced thalamic blood flow under resting conditions and also shown that when a pressure stimulus is applied to the thumb nail, responses of patients with FMS in the pain-processing regions of the brain occur at much lower stimulus intensities than in healthy controls (Gracely *et al*, 2002*). Such objective studies showed conclusively that pain is ‘real’ in FMS and further support the diagnosis of FMS.

4.3 Survey base criteria for FMS

Recently, the ACR published survey base criteria for FMS, and a further modified version was published in 2011 (Wolfe *et al*, 2011). The preliminary ACR 2010 criteria for the diagnosis of FMS do not require physical examination, but the requirement for the presence of widespread pain for at least 3 months and that the patient does not have a disorder that would otherwise explain the pain are retained. However, tender point count has been replaced by a symptom checklist which includes the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS). They are now modified with the 2010 modified FM diagnostic criteria available (Wolfe *et al*, 1997*; Wolfe, 2009*; Wolfe *et al*, 2010*; Wolfe, 2011*), see box 1.

In the WPI, patients are asked to indicate the regions (maximum 19 regions) of the body in which pain has been experienced during the past week. Each positive region is given a score of 1 (WPI ranges from 0 to 19).

SSS is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. Each of these three symptoms is scored between 0 and 3 (0 = no problem, 1 = slight or mild problems, generally mild or intermittent, 2 = moderate, considerable

problems, often present and/or at a moderate level, 3 = severe: pervasive, continuous, life-disturbing problems over the past week). The extent of somatic symptoms is also scored between 0 and 3 (0 = no symptoms, 1 = few symptoms, 2 = a moderate number of symptoms and 3 = many symptoms). Permissible somatic symptoms include muscle pain, IBS, fatigue/tiredness, thinking or remembering being a problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhoea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination and bladder spasms. The final SSS score is between 0 and 12.

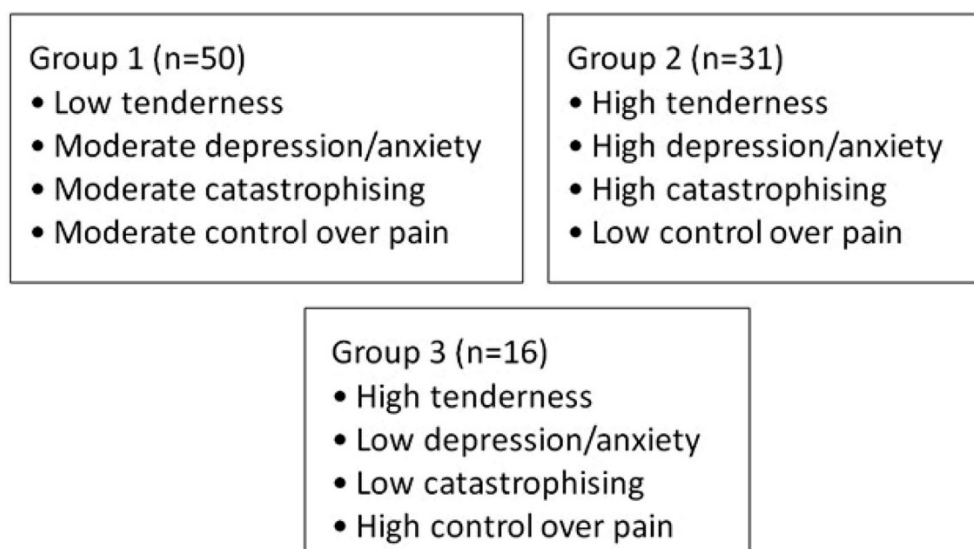
A patient satisfies the criteria for FMS if the following conditions are met: WPI >7 and SSS score >5 or WPI 3–6 and SSS score >9.

Removing the reliance on tender point count is the major advantage of the survey base criteria for FMS. In addition the SSS includes characteristic features of FMS and may be used to monitor disease activity. These criteria are not intended to replace the ACR 1990 classification criteria, but to represent an alternative method of diagnosis.

4.4 Subtypes of FMS

FMS is not a homogeneous condition. Although chronic widespread pain and increased tenderness are universally present, other associated symptoms may not be present in all patients. A study by Giesecke *et al* using cluster analysis suggested that there may be three different subtypes (figure 4) (Giesecke *et al*, 2003*):

Figure 4 Different subgroups of fibromyalgia suggested by Giesecke *et al*. (Reproduced with permission from Giesecke *et al*, *Arthritis Rheum* 2003;48:2916–22*.)



1. Moderate anxiety, depression, catastrophising and poor control of pain, the highest pain thresholds and low tenderness;
2. High levels of anxiety, depression and catastrophising, low pain control and considerable tenderness;
3. Low levels of anxiety, depression and catastrophising, good control of pain but very low pain threshold and the most tenderness.

Another classification shows that patients with FMS can be classified according to the type of pain and sensory profile, and comorbidities (Rehm *et al*, 2010).

In this study, the first subtype was the most common with over half the patients within this group, and therefore was considered to represent 'typical FMS'. It is important to note, however, that the patients in this study were recruited from the community. The proportion of patients in each subtype might change if patients in secondary care were studied since the latter tends to include patients with a higher prevalence of mood disturbance and psychosocial stress.

5 Epidemiology

5.1 Prevalence

Chronic widespread pain is common. The definition of chronic widespread pain according to the 1990 ACR criteria provided uniformity and standardisation for comparing outcomes of prevalence studies around the world. Epidemiological studies reported comparable prevalence rates of chronic widespread pain in the UK, Canada, Israel, United States and Sweden (Neumann and Buskila, 2003). These rates range from 7.3% to 12.9%. This can be compared with chronic regional pain, such as low back pain, which affects 20–25% of the population. Both conditions are more common in women with a female to male ratio of 1.5. In population studies psychosocial distress is associated with the subsequent development of chronic widespread pain (Gupta *et al*, 2007).

In France, using the FiRST screening tool, FM prevalence has been estimated to be 2% of the adult population.

5.1.1 Determination of the epidemiology of fibromyalgia

Several epidemiological studies have examined the prevalence of FMS in North America and Europe—for example, DEFI (Détermination de l'Epidémiologie de la Fibromyalgie) (Perrot *et al*, 2011). The prevalence of FMS in the general population was reported to range from 0.5% to 5% (White *et al*, 1999). In the USA Wolfe *et al* estimated the prevalence of FMS to be 2% overall (3.4% in women and 0.5% in men). In these epidemiological studies patients with chronic widespread pain are identified by pain without determining the presence or absence of 11 out of 18 fibromyalgic tender points which is stipulated by the ACR criteria. In

Europe a population-based epidemiological study, the Feel study (Fibromyalgia Epidemiology European Large-scale survey), found a point prevalence of 7% and 10% in France and Portugal, respectively (Wolfe *et al*, 1995*). FMS is more common in women. In hospital-based studies the female to male ratio was 7:1. In the general population the ratio is 3:1. The incidence of FMS is highest in those aged 20–55 years, but the condition may occur at any age, including childhood. The prevalence of FMS increases with age, reaching 7% in women aged 60–80 years.

The common association of FMS with other pain syndromes, other rheumatic disorders, chronic viral infections and systemic illnesses has been well documented in several studies. The prevalence of FMS in outpatient clinics is much higher than in the general population and ranges from 10% to 16% in rheumatology outpatient clinics. Among patients hospitalised on internal medicine wards, 62% reported musculoskeletal pain, 36% reported chronic regional pain, 21% reported chronic widespread pain and 5% reported transient pain. Fifteen per cent of all the patients had FMS, most of whom (91%) were women.

There are limited data on the prevalence of CFS which is thought to be around 0.4–0.5%, much less than for FMS. It is more common in female subjects and can affect children as well as adults (Branco *et al*, 2005).

5.2 Risk factors

Many studies have shown that psychological conditions, such as somatisation, having a mental disorder, presence of psychological distress, major depression, generalised anxiety, panic disorder and familial major mood disorder, are risk factors for developing FMS. In addition to genetic associations, various external stimuli such as infection, hormonal changes, physical trauma and stress (acute or persistent) have been temporarily associated with the development of FMS (Devanur and Kerr, 2006). McLean *et al* (2005) critically reviewed the literature on motor vehicle collision injury and FMS, using consensus standards developed by the ACR Environmental Disease study group. They concluded that the evidence that motor vehicle collision trauma may trigger FMS meets established criteria for determining causality (Buskila *et al*, 2008).

5.3 Impact on general health and quality of life

FMS varies in severity. However, quality of life in almost all patients with FMS is reduced. Both impaired physical function and emotional impact adversely affect the quality of life of patients with FMS. About 50% of all patients have difficulty with routine daily activities while 30–40% have to stop work or change their employment (Berger *et al*, 2007). The lack of support from family, friends and healthcare system may further compound the problem. Comparison has been made between patients with FMS and other rheumatic diseases, such as rheumatoid arthritis and osteoarthritis, using the Short Form-36. All eight components of the Short Form-36: physical functioning, physical role, social functioning, bodily pain, general health, vitality, emotional role and mental health scores, were significantly lower in patients with rheumatoid arthritis,

osteoarthritis and FMS than in normal healthy controls. Patients with FMS had significantly lower mental health scores than patients with rheumatoid and osteoarthritis (Picavet and Hoeymans, 2004).

5.3.1 Impaired physical function

Physical function is usually impaired in patients with FMS. Most patients reported some disability. They often have difficulty in performing daily activities. Getting going in the morning is often difficult in those patients with early morning stiffness. They require more time to get started and often struggle with tasks that require sustained or repetitive physical effort. Pain prevents them from lifting heavy objects and they often drop things because of poor grip. Walking is often affected. Many patients find their mobility and walking distance reduced. Fear of movement is common and patients often perceived higher ratings of exertion than normal during exercise.

5.3.2 Reduced mental health

As stated above, a major contributor to reduced quality of life in patients with FMS is poor mental health. One study compared the quality of life and general health status of patients with FMS with that of healthy volunteers using the Nottingham Health Profile. Patients with FMS had significantly higher Nottingham Health Profile scores, indicative of poorer general health status. Nottingham Health Profile scores correlated with disease activity as measured by tender point count, Fibromyalgia Impact Questionnaire (FIQ) and Health Assessment Questionnaire score. Patients with depression tended to have a higher Nottingham Health Profile score. This suggested an important relationship between pain, depression and quality-of-life scales in patients with FMS. Moreover, the Nottingham Health Profile score correlated with disease duration, suggesting that chronicity may adversely affect general health and quality of life. A study in Spain based on patients attending a university hospital found that poor quality of life is associated with having a greater number of children, fatigue and depression and a lower self-rated health. Interestingly, the number of specialists consulted before the diagnosis of FMS was associated with a poor quality of life, suggesting that delay in the diagnosis of FMS may adversely affect outcome. Prompt diagnosis and positive management may prevent the development of a vicious cycle leading to the condition spiralling out of control (Castelli *et al*, 2012).

5.3.3 Prognosis

In general, FMS is a long-term chronic illness. Most studies have shown that treatment can significantly improve symptoms, function and quality of life in the short term. The outcome of FMS, in general, is better in children than adults. Prospective long-term outcome studies based in tertiary hospitals in America and Europe found no significant change in disease over a 6–8-year period. Severity of pain, fatigue, disability and quality of life remained unchanged. Furthermore, they found little improvement in health status, health service use and costs, with about 25% of patients with FMS receiving disability or other compensation payments. Health status

as measured by Short Form-36 in patients with FMS is at least as poor, if not worse, than in those with other musculoskeletal diseases such as rheumatoid arthritis and osteoarthritis. Predictors of poor outcome include a history of major disturbing life event or severe disability. However, patients with FMS in the community may have milder conditions and better prognosis than those seen in specialist units.

Because spontaneous remission in FMS is rare, most patients will have a chronic illness. Educating patients to understand they have a chronic illness is important. However, they should be encouraged to adopt a positive attitude and, with the help of healthcare professionals, develop more effective coping strategies to manage their illnesses. Studies have shown that having a positive attitude and an effective coping strategy are associated with better outcome. Different studies have shown that patients with FMS who exercise regularly have a better outcome (Hauser *et al*, 2010). Resolution of stress and promotion of the patient's self-efficacy for control of pain are of pivotal importance in maintaining long-term improvement. Given the absence of a universal panacea, a multidisciplinary approach will be necessary to manage FMS, especially in patients with more severe or a wide range of symptoms. Conversely, a negative approach and over-reliance on medication may lead to excessive self-medication, alcohol or drugs.

5.4 Prognosis in CFS

Prognosis in CFS is similar to that for FMS. Less than 10% of patients experience full remission. Most cases are chronic, although with treatment there is some improvement over time. A study in 2001 found a higher incidence of violent deaths, including suicide and accidents, among people with chronic widespread pain (Gilson, 2001).

5.5 Healthcare burden

Different costs studies have been done among countries (White *et al*, 2002; Annemans *et al*, 2008). In Europe, the direct medical cost of FMS in 2004 was €5241 per patient compared with €2373 in ankylosing spondylitis. In America, the annual total healthcare cost of FMS in 2006 was \$9573 per patient compared with \$3291 in patients without FMS. Secondary care costs, hospitalisation and day care services were the main contributors. In 1997 data from the National Centre for Chronic Disease Prevention and Health Promotion in the USA showed that 7440 hospitalisations were due to FMS. It accounts for 2.2 million ambulatory care visits, 1.8 million physician office visits, 266 000 emergency department visits and 187 000 outpatient department visits. The average patient with FMS makes 10 primary care appointments a year and is admitted to hospital, on average, once every 3 years. The main component of direct medical cost in primary care clinics is diagnostic tests. Patients with FMS are more likely to be referred to hospital specialists and have diagnostic tests. Confronted by such statistics the former chief medical officer in the UK wrote to all the doctors in the UK emphasising the healthcare burden of chronic widespread pain, and urging more research and education to deal with the problem and improve outcome.

The UK General Practice Research Database, a large database covering 5 million patients in primary care, found that healthcare use by patients with FMS was already very high compared with that by disease controls, matched according to diagnosis date, gender and age, up to 10 years before diagnosis. Increased cost was due to a higher rate of referral, clinic visits, prescriptions and diagnostic tests. Patients with FMS averaged 25 visits and 11 prescriptions a year compared with 12 visits and 4.5 prescriptions a year in controls. Following the diagnosis of FMS, the referral rate declined considerably and the number of diagnostic tests and clinic visits stabilised and then declined to 13 per 100 patient-years 4 years after diagnosis. Therefore, the diagnosis of FMS can be used constructively to reduce healthcare expenditure. Modelling based on these data suggests that the diagnosis of FMS can save the healthcare system €200 per patient per year.

5.6 Societal cost

In addition to the direct medical cost of FMS, there are also significant indirect medical costs. Often patients with FMS have to change their work pattern or nature to continue in employment. In North America, 42% of patients with FMS were working and 28% were home-makers. The number of short-term disability days in patients with FMS was 16 compared with seven in patients without FMS. Total annual costs for fibromyalgia claimants were more than twice as high as the costs for the typical insurance beneficiary. Twenty to thirty per cent of patients were receiving disability payment and 16% were receiving social security benefits. In the USA the indirect medical cost per person-year in 1997 amounted to \$3671. The estimated overall annual cost of FMS in the USA is over \$9 billion. It accounts for a loss of 1–2% of the nation's overall productivity. In Europe, a study in the Netherlands reported that average annual indirect medical cost for FMS was €2573 per patient-year. Based on this the estimated total cost of FMS in Netherlands is almost €1 billion a year. In France and Germany total costs were estimated to be around €7000 per patient-year with a higher cost as FM severity increased.

6 Pathophysiology and pathogenesis of FMS

6.1 Perception of pain

6.1.1 History of pain models

Our understanding of pain has made significant advances over the past 20 years. Acute pain is an important protective mechanism and is linked to the stress response and reflex withdrawal to protect from further harm. Excessive tissue damage occurs if pain perception is absent as occurs in Charcot joints. Consequently, pain is inherently perceived as unpleasant, resulting in psychological and physiological stress. These protective mechanisms include avoidance motor reflexes, alterations in autonomic output and increased neuroendocrine response. Hence pain perception has cognitive and emotional components. Natural negative feedback mechanisms, such as central descending pain pathways, regulate the perception of pain.

Conversely, chronic pain is considered as a non-protective mechanism, and the bio-psycho-social model describes it as a specific disease (Phillips and Claw, 2013).

6.1.2 Current pain model

6.1.2.1 Nociceptors

Broadly, pain processing can be divided into four main processes: nociception, transmission, modulation and perception. Nociception is the process whereby a noxious stimulus is detected by a nociceptor which converts this into an electrical impulse. Nociceptors are mostly bare nerve endings which penetrate past the epidermal/dermal junction and are attached to fine fibres. Thin unmyelinated fibres (C fibres) are present in several structures, such as the joint (except in the cartilage), muscles, ligaments and viscera. There are several types of nociceptors which can be classified by the type of stimulus to which they respond: mechanical, thermal, chemical or polymodal (responds to multistimuli).

Until recently, it was thought that nociceptors were only found in the external region but not the internal region. However, recent studies have shown that internal nociceptors are present in the urogenital and gastrointestinal tract, although the density of these receptors is often much lower, which may explain, in part, why visceral pain is often less well localised than somatic pain.

6.1.2.2 Transmission

Transmission is the process whereby the signal of nociceptor activation is transmitted by sensory nerve fibres to the spinal cord from various parts of the body. There are three main types of nerve fibres: A- β , A- δ and C fibres. A- β fibres transmit tactile sensation, whereas A- δ and C fibres transmit pain. All these fibres have a lower threshold for stimulation than mechanoreceptors. Conduction by A- δ fibres (40 mph) is much faster than by C fibres (3 mph). Transmission can be inhibited by local anaesthetics and α -2 δ agonists, which affect calcium transport.

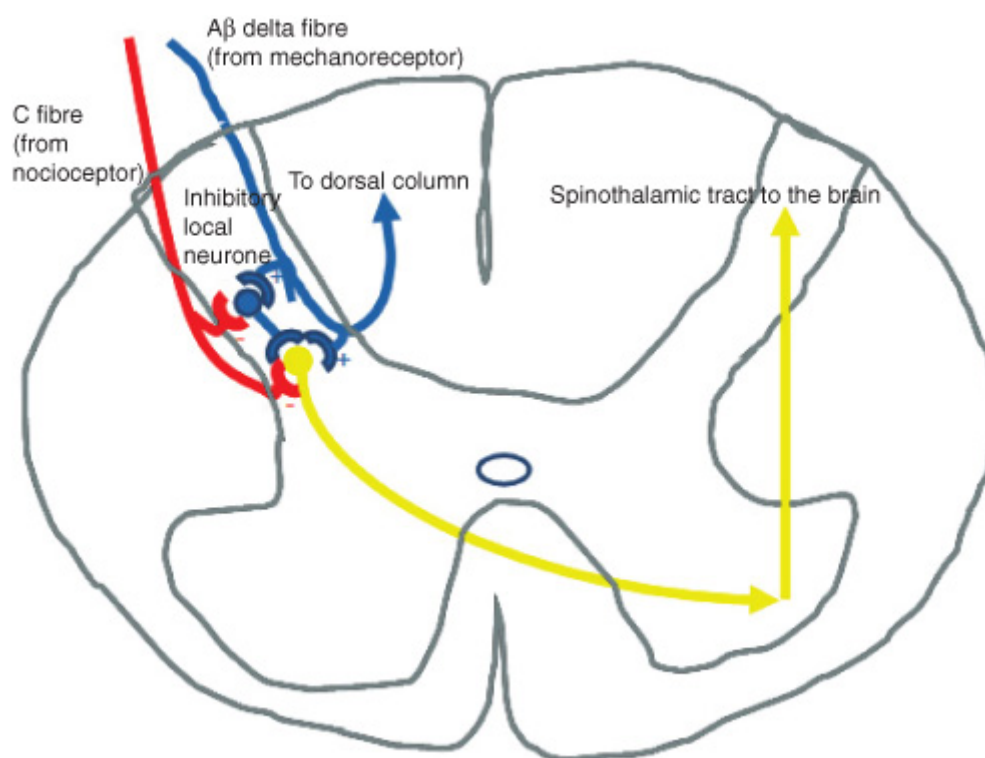
6.1.2.3 Modulation

All sensory information enters the spinal cord via the dorsal root. The dorsal horn of the spinal cord is a vital area for sensory processing and pain perception and modulation. It is divided into laminae I–VI. Sensory nerve fibres synapse via the superficial laminae. Numerous pain neurotransmitters are present in the area. Substance P, aspartate and glutamate are the main excitatory amino acids produced by the afferent neurons. They amplify the pain signals in ascending projection neurons and are the key molecules in pain transmission: this is described as ‘the wind-up phenomenon’.

Pain mechanisms are modulated by two main processes. First, segmental inhibition by a non-noxious stimulus transmitted by large afferent myelinated fibres subserving epicritical sensation inhibitory neurons (figure 5).

Second, 'descending inhibition' from several regions in the brain: peri-aqueductal grey, reticular formation and nucleus raphe magnus, sending inhibitory fibres down the spinal cord to modulate pain at the level of the dorsal horn. They can act either presynaptically on the primary afferent neurons or post-synaptically on second-order neurons. These endogenous inhibitory descending neurons release opioids, serotonin and norepinephrine (NE) to dampen the nociceptive response. Local anaesthetics, α -2 agonists, opioids, NSAIDs, tricyclic antidepressants, serotonin-selective reuptake inhibitors (SSRIs), serotonin NE reuptake inhibitors (SNRIs) and N-methyl-D-aspartate (NMDA) receptor antagonists can affect the balance between pain amplification and inhibition by their effect on pain modulation.

Figure 5 Pain modulation in the dorsal horn of the spinal cord.



The overall pain perception depends on the balance between excitatory and inhibitory neurotransmitters. Such physiological pain modulation is often applied clinically in many musculoskeletal diseases where nociceptors detecting pain are present in structures such as the synovium, joint capsule, bone, muscles and ligaments. When nociceptors are activated, pain signals are transmitted by peripheral nerve fibres to the spinal cord and the brain. These messages can be over-ridden by other signals produced by treatments such as massage, heat or cold packs, transcutaneous nerve stimulation, drugs or even acupuncture.

6.1.2.4 Perception

Perception is the response of the brain to nociceptive signals. Neuronal signals from the dorsal horn of the spinal cord transmit to the specialised areas of the somatosensory cortex via the thalamus. Initially, pain was thought of as a mere extension of the sense of touch. This is clearly too simplistic. Precisely how the brain

perceives pain remains unclear, but the advent of functional neuroimaging using technologies such as fMRI, has allowed greater insight into the perception of pain by the brain. During pain perception, aside from the somatosensory cortex, many areas of the brain become activated (table 1). One area that is strongly activated during pain stimulation is the parieto-insular cortex, which appears to be crucial for pain processing in the brain. Lesions damaging this region in the brain can reduce pain perception. Another important area is the caudal part of the anterior cingulate cortex, which has been implicated in the control of motivational behaviours. Activation of this area is linked to perception of the unpleasantness of pain, and is accompanied by activation in several subcortical sites, such as the amygdala, cerebellum and striatum. Other areas of the brain that are activated include the rostral anterior cingulate cortex, which has been implicated in pain inhibition.

Table 1 Regional cerebral blood flow after various stimuli

Brain region	Stimuli that increase blood flow	Painful or non-painful?
Contralateral primary somatosensory cortex (S1)	Mechanical	Painful and non-painful
Contralateral secondary somatosensory cortex (S2)	Mechanical	Painful and non-painful
Anterior cingulate cortex	Mechanical Catastrophising	Painful
Insula	Mechanical Aversive stimuli Depression	Painful
Thalamus	Mechanical	Painful

Overall, pain processing has huge inter-individual variability—a minimal stimulus in some subjects can cause them to register a large amount of pain, but conversely, a large stimulus in others can result in no pain being registered. Mogil has extensively reviewed this variability, which has been demonstrated both in rodents and humans (Mogil, 2009). Although the relative importance of genetic versus learning in this variability remains unclear, a large body of evidence suggests that genetic factors may have a significant contribution to pain perception. Moreover, pain perception is not ‘hard-wired’ but ‘plastic’. The term ‘neuroplasticity’ is often used to describe the changeability of the response of the nervous system to pain at peripheral and central locations.

6.1.3 Abnormal pain perception in fibromyalgia

Pain perception can malfunction owing to functional abnormality or pathology of the nervous system. Clifford Woolf called such pathological pain ‘maladaptive’. One of the key features of maladaptive pain is increased sensitivity or hyper-responsiveness. Clinically this is often manifested as ‘hyperalgesia’ and/or ‘allodynia’. Hyperalgesia is defined as ‘an increased response to a normally noxious stimulus’. Hyperalgesia can be normal

and transient. Allodynia is defined as painful response to normally non-noxious stimuli. Tender points in FMS are manifestations of allodynia: patients reporting pain when a sub noxious pressure is applied. Both hyperalgesia and allodynia result from similar mechanisms: 'peripheral' and central sensitisation'.

6.1.3.1 Peripheral sensitisation

Peripheral sensitisation is a reduction in threshold and an increase in responsiveness of the peripheral ends of nociceptors. When a noxious stimulus is applied to an area on the skin a small localised area of active tissue hyperalgesia develops owing to sensitisation of local nociceptors. This will spread out to involve a larger area of 'secondary hyperalgesia' over the next few hours. This leads to an increased response to painful stimuli known as primary hyperalgesia or peripheral sensitisation. In the case of inflammation this results from the release of inflammatory mediators by neutrophils, such as prostaglandin E2, which reduces nociceptor thresholds. NSAIDs act by inhibiting cyclo-oxygenase 2 and thereby reducing prostaglandin E2 production. Peripheral sensitisation contributes to the pain hypersensitivity found at the site of tissue damage and inflammation, as exemplified by that occurring in hypersensitivity after sunburn.

Recently, Caro and colleagues showed that the reduction in epidermal nerve fibre density is often (but not always) associated with significant neuropathic pain (hence the name small-fibre neuropathy (SFN)), and it can reasonably be expected to give rise to a clinically detectable loss of skin sensation (so-called negative sensory phenomena) rather than painful peripheral symptoms (positive sensory phenomena). However, SFN is associated with both, and it is thought that the painful peripheral symptoms of SFN are attributable to the disproportionate hyperexcitability of lesioned (but still functioning) primary small nerve fibres surrounded by a structurally normal but physiologically hyperexcitable group of secondary small nerve fibres that respond collaterally (Caro and Winter, 2014).

6.1.3.2 Central sensitisation

Central sensitisation refers to mechanisms that lead to an increase in the neuronal excitability in the central nervous system. Several mechanisms may lead to central sensitisation: action potential windup, receptor field expansion and hyperexcitable neuronal response. Action potential windup results from repeated stimulation of afferent nerve fibres in the dorsal root. This leads to a progressive increase in the number of action potentials generated, prolonging the duration of the discharge by interneurons even after the afferent fibre input has ceased. Receptor field expansion results from activation of neurotransmitter receptors, especially NMDA, leading to adjacent neurons in neighbouring areas becoming responsive to stimuli whether they are painful or not. Hyperexcitability of neuronal responses results from the release of substances that increase neuronal sensitivity. Many molecules have been implicated in the development of central sensitisation, including substance P, glutamate and aspartate. In general, these substances augment membrane excitability by increasing intracellular calcium concentration. For example, glutamate and aspartate activate the NMDA

receptor and resultant intraneuronal elevation of calcium, which stimulates nitric oxide synthase to produce nitric oxide. The latter is a gaseous molecule, which diffuses out from the neuron and stimulates the formation of cyclic guanosine monophosphate in neighbouring neurons, which can decrease the activity of γ -aminobutyric acid—an inhibitory neurotransmitter. Nitric oxide has been implicated in the development of hyperexcitability, resulting in hyperalgesia or allodynia (Phillips and Claw, 2013; Clauw, 2014).

Tender points, which were part of the 1990 ACR classification criteria for FMS, are a manifestation of allodynia. Recent research using more objective assessment has demonstrated a reduced pressure pain threshold over wide areas in patients with FMS not limited to the sites of tender points. It leads to the hypothesis that the pivotal pathophysiology in FMS is central sensitisation.

Furthermore, in patients with FMS, pain elicited from uninjured tissues around the site of pain, secondary hyperalgesia, was found to be increased in comparison with controls. When an electrical stimulus was applied to the skin of patients with FMS they had reduced pain thresholds and pain was noted both distally and proximally to the stimulator lasting for up to 20 min after the stimulation was stopped. Similarly, when hypertonic saline was injected into the anterior tibial muscle to induce pain, patients with FMS had a larger area of pain, which also lasted longer, than that felt by healthy age-matched controls. Pressure pain and the intramuscular summation pain threshold were significantly lower in patients with FMS.

In another study patients with FMS and age-matched healthy controls were given repeated tonic thermal stimuli over the skin stimulation at noxious and subnoxious level (Lautenbacher, 1997). While healthy controls had a significant increase in pain threshold, patients with FMS did not. This failure to down-modulate the pain threshold suggests central sensitisation and failure of the descending inhibitory pathways. An fMRI study comparing patients with FMS and healthy controls found reduced activity in the rostral anterior cingulate cortex, which is linked to the descending pain regulating system (Cook *et al*, 2004). There are two key descending pain regulatory pathways: one involves serotonin/epinephrine and the other, endogenous opioids. A positron emission tomography study showed that patients with FMS have reduced mu-opioid receptor occupancy potential compared with that of normal healthy controls, providing further support for the suggestion that there is abnormal central pain processing in FMS (Harris *et al*, 2007).

The results of these clinical studies are further supported by research using functional neuroimaging. Functional changes in the central nervous system have been investigated by several imaging techniques such as SPECT and fMRI scans. Using the latter, Gracely *et al* (2002)* have shown objectively that fMRI imaging matches the patient-reported pain in FMS. Furthermore, in comparison with normal age-matched healthy controls, patients with FMS have a lower pressure pain threshold. It also showed activation of different parts of the brain, including the thalamus. Acute pain increases thalamic blood flow while chronic pain states are associated with reduced thalamic blood flow. It has been postulated that disinhibition of the medial thalamus

leads to activation of the limbic system. The latter is a complex set of structures that lies underneath the thalamus, just under the cerebrum. It includes the hypothalamus, the hippocampus, the amygdala and several nearby areas. It is primarily involved in emotion and formation of memories. It has been suggested that the limbic system is associated with the descending inhibitory pathway. During acute pain, the limbic system is activated to repress pain signals in the spinal cord. In chronic pain decreased activity in the limbic system leads to hypersensitivity to pain. Mountz *et al* reported that on SPECT imaging, patients with FMS have decreased thalamic and caudate blood flow compared with healthy controls (Mountz *et al*, 1995).

Abnormal levels of neurotransmitters have been reported in patients with FMS. Increased levels of substance P and nerve growth factor in the cerebrospinal fluid have been reported in patients with FMS compared with controls. Substance P is released by afferent neurons in the dorsal horn and lowers the threshold of synaptic excitability, and sensitises second-order spinal neurons. Two studies in patients with FMS have found a threefold increase of substance P in the cerebrospinal fluid. Nerve growth factor is critical for the differentiation and survival of sensory neurons. It increases the production of substance P in afferent nerve fibres, reducing the pain threshold. The nerve growth factor level in the cerebrospinal fluid of patients is up to four times higher in patients with FMS than in controls. Conversely, the neurotransmitter serotonin, released by some inhibitory neurons, has been found to be present at lower than normal levels in patients with FMS.

Taken together there is substantial clinical and neuroimaging evidence to suggest that abnormal pain processing is important in the pathophysiology of FMS, but its specificity is still to be demonstrated.

6.2 Sleep disturbance

One of the most common symptoms of FMS is non-restorative sleep. Moldofsky *et al* first showed that the disruption of stage 4 non-rapid eye movement (non-REM) or deep sleep in normal healthy people by noise stimuli resulted in unrefreshing sleep, variable aching and fatigue (Moldofsky *et al*, 1975). These results have since been replicated by other studies. Sleep studies in patients with FMS have confirmed that poor sleep quality is associated with non-dreaming, non-REM sleep with interruption by alpha waves. Worse tenderness in the morning and cognitive impairment in FMS may be related to chronic sleep disturbance. Phasic alpha sleep patterns are associated with longer duration of pain symptoms, perception of poor sleep and morning pain.

In many patients with FMS improvement of sleep quality often significantly improves other symptoms.

6.3 Hypothalamic–pituitary–adrenal axis

Hypothalamic–pituitary–adrenal (HPA) axis dysfunction has been demonstrated as part of the pathophysiology of patients with FMS. The HPA axis is a critical orchestrator of the body's response to stress. It influences various processes, such as digestion, the immune system, mood and energy. Normally corticotrophin-releasing

hormone produced by the hypothalamus stimulates the anterior pituitary gland to release adrenocorticotrophic hormone (ACTH). ACTH stimulates the production of glucocorticoids by the adrenal cortex. The release of these hormones is under circadian control with rapid increase in cortisol levels shortly after wakening, reaching a peak within 30–45 min. It then diminishes over the day, until rising again in late afternoon. Cortisol levels then fall in late evening, reaching a trough during the middle of the night. Stress-induced release of corticotrophin-releasing hormone from the hypothalamus is influenced by blood levels of cortisol and by the sleep/wake cycle. Increased production of cortisol mediates responses to stress, allowing the body to attempt counter measures. However, chronic excessive production of cortisol can be damaging. Atrophy of the hippocampus in humans and animals exposed to severe stress is believed to be mediated by prolonged exposure to high concentrations of cortisol.

The HPA axis is closely linked with the limbic system, especially the thalamus, amygdala and hippocampus which facilitate activation of the HPA axis. Sensory information arriving at the lateral aspect of the amygdala is processed and conveyed to the central nucleus, which projects to several parts of the brain involved in responses to fear. At the hypothalamus fear-signalling impulses activate both the sympathetic nervous system and the modulating systems of the HPA axis. Deficiencies of the hippocampus may reduce the memory resources available to help a body formulate appropriate reactions to stress. The HPA axis is also linked to the autonomic nervous system, which is involved in modulating sleep, mood, pain and cardiovascular activities (including microcirculation of muscles). Many symptoms of FMS may be explained by sympathetic nerve system overactivity, although more detailed mechanistic studies are needed to confirm a causative relationship.

In patients with FMS, a reduced HPA axis response to stress has been demonstrated. The main HPA abnormalities in FMS are:

- low free cortisol levels in 24 h urine samples;
- loss of the normal circadian rhythm with increased evening cortisol level;
- insulin-induced hypoglycaemia associated with an overproduction of pituitary ACTH;
- low levels of growth hormone;
- reduced adrenal release of glucocorticoids in response to ACTH stimulation.

Patients with FMS often report previous stressful or traumatic events. Some patients consider that such events might have precipitated their illness. A reduced HPA axis response to stress can contribute to the development of FMS or worsening of symptoms. Furthermore, patients with FMS often have worse pain and tenderness in the morning and significant morning stiffness. Often this improves after nights where they have had more

restful sleep. Although a causal relationship has not been established, HPA axis dysfunction may contribute to the development of these symptoms. Alternatively, as a dysfunctional HPA axis has been implicated in the pathophysiology of many disorders, including anxiety, depression, post-traumatic stress disorder, CFS, sleep disturbances and IBS, the HPA abnormalities seen in FMS may reflect other comorbidities.

6.4 Genetics of fibromyalgia

Several polymorphisms have been associated with an increased risk of fibromyalgia. One of the most frequently reported polymorphism is the mutation of catechol-O-methyl transferase, an enzyme-degrading catecholamine. The association of the catechol-O-methyl transferase genotype with psychological distress may identify FMS subgroups.

6.5 Summary of pathophysiology in FMS

Although the pathogenesis of FMS remains unclear, the known abnormalities support the hypothesis that FMS is related to specific pain mechanism abnormalities. Somatosensory abnormalities, cerebrospinal fluid and functional neuroimaging studies all suggest that abnormal pain processing is the central pathophysiological process in FMS.

6.6 Pathophysiology in CFS

The aetiology and pathogenesis of CFS remain unknown, although abnormalities of the nervous, immune systems and HPA axis have been reported. Chronic fatigue is not unique to CFS, and is also present in many chronic diseases. In both instances fatigue limits physical and mental activities.

7 Management

As FMS is a complex syndrome associated with a wide range of symptoms, treatment should be tailored to the individual, dealing with their particular needs and targeting their most distressing symptoms. The best strategy is to use a multidisciplinary approach to treatment, using both pharmacological and non-pharmacological interventions as required (Carville *et al*, 2008; Hauser *et al*, 2009). It is unlikely that a single treatment will target all of the symptoms involved (Clauw, 2014). The different subgroups of patients with FMS are likely to respond differently to treatment strategies, highlighting the fact that patients should be managed according to their individual needs, rather than following a generalised approach. A EULAR task force developed management recommendations for FMS based on a systematic review, which are summarised in table 2.

Table 2 EULAR recommendations for the management of fibromyalgia

Recommendation	Level of evidence	Strength
General		
Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context. Fibromyalgia should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features	IV	D
Optimal treatment requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features such as depression, fatigue and sleep disturbance, in discussion with the patient	IV	D
Non-pharmacological management		
Heated pool treatment with or without exercise is effective in fibromyalgia	IIa	B
Individually tailored exercise programmes including aerobic exercise and strength training can be beneficial to some patients with fibromyalgia	IIb	C
Cognitive behavioural therapy may be of benefit to some patients with fibromyalgia	IV	D
Other treatments such as relaxation, rehabilitation, physiotherapy and psychological support may be used depending on the needs of the individual patient	IIb	C
Pharmacological management		
Tramadol is recommended for the management of pain in fibromyalgia		
Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. Glucocorticoids and strong opioids are not recommended	Ib IV	A D
Antidepressants: amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole, reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia	Ib	A
Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia	Ib	A

Three drugs are licensed for treatment of FMS in the USA: pregabalin (Pfizer), duloxetine (Eli Lilly) and milnacipran (Forrest). However, there are other treatments which have evidence to support their efficacy in FMS.

7.1 Non-pharmacological management

Owing to the lack of a 'gold standard' treatment for FMS, a wide range of non-pharmacological approaches have been tested with varying success and more research will be required to further define the role of some of these treatments in FMS. Non-pharmacological treatments which have been tested in FMS include: exercise, cognitive behavioural therapy (CBT), homoeopathy, physiotherapy, acupuncture, magnetism, dietary alterations and laser therapy. These interventions are generally safe and therefore long-term use is not

detrimental. The potential benefits of non-pharmacological interventions should not be overlooked by practitioners when treating patients with FMS. The list of EULAR-recommended non-pharmacological interventions is given in box 2. They can be implemented in isolation or combined with other non-pharmacological or pharmacological agents, depending on the patients' needs.

Box 2 Non-pharmacological treatment for fibromyalgia syndrome

- Patient education
- Graded exercise
- Heated water therapy with or without exercise
- Cognitive behavioural therapy
- Relaxation
- Rehabilitation
- Physiotherapy
- Psychological support
- Complementary and alternative medicine—for example, acupuncture, dietotherapy, etc

7.1.1 Patient education

As FMS is a chronic condition without a permanent remedy, patient education is an important aspect of management as patients have to learn to manage their pain even if they also receive other treatment. They should also understand that it is unlikely that the symptoms will ever completely resolve. This may help to improve their long-term prognosis by providing more realistic health beliefs.

7.1.2 Graded exercise

Most experts concur that aerobic exercise and strength training are beneficial for patients with FMS and this is supported by systematic reviews (Hauser *et al*, 2010). Patients with FMS can exercise like healthy people, but at levels tailored to each individual. When performing strength training they can achieve the same strength gains, which may in turn lead to functional improvements and better quality of life. It should be noted that exercise may not improve pain, indeed it may become worse at first. However, there is good evidence that it can lead to improvements in physical function, tender point count, aerobic performance and global well-being. Adherence to exercise programmes may be a limiting factor, therefore education on the benefits and risks of exercise should be given. Patients should be advised that exercise is not harmful in FMS and does not cause any muscle damage or worsening of FMS. Long-term exercise is without risks and has other health gains, although programmes should be monitored and graded according to the functional ability of the patient. Education can improve adherence to exercise programmes. Patients should be advised before and during their exercise programme so that they do not have unrealistic treatment goals or worries.

Some patients find that heated pool-based exercise is particularly beneficial; hydrotherapy can be effective for pain relief even without exercise. Buoyancy reduces pressure load from the muscles and the heated water

provides relaxation. Pain relief may only be temporary, but treatment can be maintained long term without any safety concerns. Treatment improves pain, function and reduces tender point count, although availability of a hydrotherapy pool and cost are limiting factors.

7.1.3 Cognitive behavioural therapy

CBT, often including patient education, has been shown to improve pain and function in FMS either as sole treatment or in combination with exercise. It may be particularly beneficial to provide CBT early after diagnosis to help patients understand FMS and learn how to develop more effective coping strategies. Furthermore, encouraging patients to be actively involved in self-management is desirable (Bernardy *et al*, 2013).

7.1.4 Other non-pharmacological treatments

A range of dietary interventions have been studied in FMS, but evidence of their efficacy is limited. Complementary treatments, including homoeopathic remedies and acupuncture, have also been reported to have benefits for pain, tenderness, quality of life and well-being of patients with FMS. There have also been negative studies for acupuncture but it may benefit some patients. A number of miscellaneous treatments have also been used in FMS, including treatment with lasers, magnets, ultrasound and music vibration. The paucity of evidence does not allow firm conclusions or recommendations to be made about these treatments (Cassisi *et al*, 2013).

7.2 Pharmacological treatments

Medication should be used in combination with a non-pharmacological intervention in the management of FMS. As with non-pharmacological interventions a number of pharmaceutical agents have been tested and should be considered for patients with FMS (box 3) (Clauw, 2014).

Box 3 Pharmacological treatment for fibromyalgia syndrome

- Simple analgesics
- Tramadol
- Tricyclic antidepressants
- Serotonin–norepinephrine reuptake inhibitors: milnacipran, duloxetine, venlafaxine
- $\alpha 2$ Agonists—for example, gabapentin, pregabalin

7.2.1 Analgesics

Tramadol is a useful, moderately potent, opioid analgesic that improves pain but not function in FMS. It acts centrally and inhibits NE and serotonin reuptake while also being an agonist for the mu opioid receptor. Most commonly reported adverse events include nausea, somnolence, constipation and dizziness. However, it should be prescribed with caution as typical opiate withdrawal can be experienced when it is stopped—so

careful down-titration must be observed. Dependence and abuse are also potential problems to bear in mind when prescribing. Other systemic analgesics have been used in short-term studies, including lidocaine, ketamine and morphine. While ketamine and lidocaine have received some support for short-term pain relief (after injection), there is doubt about their efficacy for treating a chronic condition such as FMS. Topical analgesics (including xylocaine and capsaicin) are not of benefit in this condition.

NSAIDs may be useful for short-term pain relief when used in addition to other treatments (e.g., stretching exercises). However, they should not be considered as an option for long-term management owing to their gastrointestinal effects. Further to this, most studies of NSAIDs have produced negative results in FMS. In the recent merged German and Israeli guidelines, NSAIDs, strong opioids and benzodiazepines are not recommended (Ablin *et al*, 2013a; Ablin *et al*, 2013b).

7.2.2 Antidepressant drugs

Antidepressant drugs should be considered for patients with FMS (Häuser *et al*, 2014). Tricyclic antidepressants (TCAs), SSRIs, dual reuptake inhibitors, monoamine oxidase inhibitors and serotonin antagonists have all been reported to have benefits. TCAs, such as amitriptyline, are the most widely used in FMS. They inhibit serotonin (5HT₃) and NE re-uptake, but also affect glutaminergic neurotransmission by acting on histamine, acetylcholine and NMDA channels. They can improve sleep, fatigue and pain in FMS (Nishishinya *et al*, 2008). The effect is independent of the drugs' antidepressant action as the doses prescribed are much lower than those for depression. Indeed, in clinical trials, the best result for amitriptyline was for a 25 mg dose rather than 50 mg. Despite the positive results, tolerance is poor, mainly due to the anticholinergic side effects, including dry mouth, digestive and neuropsychiatric disturbances.

SSRIs are better tolerated than TCAs as they have fewer anticholinergic side effects. However, randomised control trials of SSRIs in FMS produced mixed results, requiring higher doses for analgesic effect than for antidepressant effects. Fluoxetine has had some positive results, especially in association with amitriptyline (Don Goldenberg *et al*, 1996).

Dual reuptake inhibitors, SNRIs, seem to have similar efficacy to TCAs without the anticholinergic effects. Their tolerance is good (headaches and nausea are the most commonly reported adverse events) and studies for milnacipran, duloxetine and venlafaxine have all reported positive effects on pain, function, pain threshold, fatigue and quality of life (although the study of venlafaxine was open-label and non-randomised). Duloxetine and milnacipran have recently been licensed for the treatment of FMS by the Food and Drug Administration (FDA) in the USA.

Duloxetine is the first SNRI to be approved by the FDA for the treatment of FMS. In clinical trials, duloxetine 60 mg/day reduced pain and improved function. The recommended starting dose is duloxetine 30 mg once a day

for 1 week; the dose may be increased to 60 mg/day. The most common side effect of duloxetine is nausea. Other common side effects include dry mouth, constipation, decreased appetite, somnolence, increased sweating and agitation. It is contraindicated in patients taking monoamine oxidase inhibitors or thioridazine and patients who have uncontrolled narrow-angle glaucoma.

Milnacipran is the second SNRI approved by the FDA for the treatment of FMS. Like duloxetine, dose titration is recommended. The normal starting dose is 25 mg/day for 2 days. Increasing to 25 mg twice a day for 4 days, followed by the normal maintenance dose of 50 mg twice a day. Similarly to duloxetine, in clinical trials milnacipran reduced pain and improved function. The most frequent side effect adverse is nausea. Noradrenergic side effects such as dry mouth, hyperhidrosis, headache, hot flush and constipation are also common. Increases in blood pressure and heart rate are uncommon but monitoring is recommended. As for duloxetine, it is contraindicated in patients taking monoamine oxidase inhibitors.

Tropisetron and ondansetron are 5HT₃ receptor antagonists which have shown pain and tender point count improvements in patients with FMS but only in short-term studies (5–10 days). A recent study with dolasetron has demonstrated significant effect within a 3-month treatment (Vergne Salle *et al*, 2011).

Although the effects of these drugs for FMS are independent of their antidepressant actions, for those patients in whom depression is the predominant symptom, this should be the first given targeted antidepressant therapy.

A recent meta-analysis reported that TCA, amitriptyline, and the SNRIs, duloxetine and milnacipran, are first-line options for the treatment of patients with FMS, but only a small number of patients have substantial symptom relief with no or minor adverse effects. Moreover, a considerable number of patients drop out of treatment because of intolerable adverse effects or have only a small relief of symptoms, which does not outweigh the adverse effects (Häuser *et al*, 2012).

7.2.3 Other pharmacological interventions

Pregabalin and gabapentin are agonists of the $\alpha 2\delta$ subunit of the voltage-dependent calcium channel in neurons. They reduce calcium influx into the nerve terminals and decrease the release of neurotransmitters such as glutamate, NE and substance P. They were developed as antiepileptic agents initially but recent studies have shown efficacy in FMS. A large recent controlled study of pregabalin in patients with FMS reported good effects for sleep, pain and fatigue and good tolerability, with most adverse events being dizziness or somnolence, mild to moderate in severity. Pregabalin was the first drug which received approval from the FDA for treatment of FMS in the USA. In clinical trials, pregabalin 300 mg/day and 450 mg/day reduced pain and improved sleep quality. The recommended dose is 300–450 mg/day. Doses should begin at 75 mg twice a day and increase to 150 mg twice a day after 1 week. For patients who do not receive sufficient benefit the dose

may be further increased to 225 mg twice a day. Common side effects include dizziness, drowsiness, dry mouth, oedema, weight gain, constipation and increased appetite (Häuser *et al*, 2012).

Gabapentin has also been studied in FMS and produced good outcomes in a number of symptoms, including pain, function and quality of life. These results suggest that the α_2 calcium channel is a good therapeutic target in FMS.

Pramipexole is a dopamine agonist that was developed for the treatment of Parkinson's disease. However, it affects the mesolimbic system (particularly in sleep control), suggesting it might be a useful treatment for FMS. In a randomised control trial, it led to improvements in pain, fatigue, function and global well-being with good tolerance (Holman and Myers, 2005). However, this is based on one study in which patients were allowed to continue with current drug treatment if at a stable dose. Large randomised control trials are needed to confirm the benefits and risks of pramipexole for the treatment of FMS.

Hypnotics, including zolpidem, act on benzodiazepine receptors. In FMS they are effective for sleep and fatigue, but not pain, so should only be used in combination with another approach. Sodium oxybate (a commercial form of gamma hydroxybutyrate, Jazz Pharmaceutical) is known to increase slow-wave sleep and growth hormone levels (both impaired in patients with FMS). It has been shown to improve pain as well as fatigue and sleep in FMS. There is the potential for abuse with this drug, however, and it has been associated with date rape, so its use in FMS should be considered with caution.

Tizanidine, an α_2 adrenergic central agonist, probably acts by reducing levels of substance P in the central nervous system. It has been reported to reduce pain and improve sleep and quality of life in FMS; however, the study was not controlled or blinded. Adverse events can include tiredness, somnolence, dizziness and dry mouth. It should be used with caution in women receiving oral contraceptives, which can reduce its clearance.

Growth hormone has been studied in FMS owing to research showing reduced levels in patients with FMS. Although results were positive for quality of life and tender points, its usefulness is limited by potential side effects and high cost. There has been a suggestion that patients with FMS benefit from thyroid hormone therapy and that perhaps patients (or a subgroup of them) have a subclinical deficiency in this hormone. Three small studies by Lowe *et al* suggest that tri-iodothyronine is beneficial for pain and function after up to 8 months' treatment in euthyroid female patients with FMS. Each of these studies is small and the long-term toxicity of thyroid hormone remains a significant concern (Lowe *et al*, 1997).

7.3 Summary of management

Management of FMS is likely to require a multidisciplinary approach with a combination of pharmacological and non-pharmacological treatments. The goal of treatment is to reduce symptoms to a more tolerable level

as remission is rare. More research into FMS pathogenesis and treatment will hopefully lead to more promising medical development in this area.

Finally, pregabalin, duloxetine, milnacipran and amitriptyline are the current first-line prescribed agents but have mostly had a modest effect. With only a minority of patients expected to experience substantial benefit, most will discontinue treatment because of either a lack of efficacy or tolerability problems (Häuser *et al*, 2014).

7.4 Management of CFS

In the UK, the National Institute of Health and Care Excellence guidance on the management of CFS advise patient education, balanced diet, graded exercise and CBT. Pharmacological treatment such as antidepressant drugs, steroids and thyroxine in euthyroid patients are not recommended as evidence for their overall benefit is equivocal. Patients with CFS should be referred to a specialist within 6 months of presentation for those with mild symptoms, within 3–4 months for those with moderate symptoms and immediately for those with severe symptoms.

7.5 Disease-specific measures

Disease-specific measures are designed to assess specific diagnostic groups or patient populations, often with the aim of measuring responsiveness to treatment or 'clinically important' changes. One obvious disadvantage of some disease-specific measures is that they do not allow comparative judgements between the outcomes of different treatments in patients with different health problems. For example, in resource allocation studies the use of disease-specific measures may be combined with generic measures. However, there are some broad disease-specific measures for FMS, such as the FIQ or the revised FIQ, and the Health Assessment Questionnaire, which include general aspects of functional status together with specific references to states or changes of particular concern to the target population.

Salaffi *et al* validated a Fibromyalgia Assessment Status Index, which is a short and easy to complete self-administered index combining a set of questions relating to non-articular pain (Self-Assessment Pain Scale range 0–10), fatigue (range 0–10) and quality of sleep (range 0–10) that provides a single composite measure of disease activity ranging from 0 to 10. The final score is calculated by adding the three sub scores and dividing the result by three. All three measures are printed on one side of one page for rapid review, and scored by a health professional without the need for a ruler, calculator, computer or website. These disease-specific measures therefore considerably overlap generic measures (Salaffi *et al*, 2009).

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SUMMARY POINTS

- General widespread pain is common and includes conditions such as multiple bursitis–tendonitis syndrome, fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS).
- FMS is the commonest cause of generalised widespread pain and is characterised by reduced pain thresholds (hyperalgesia) and pain with normally innocuous stimuli (allodynia). Diffuse pain is often accompanied by a wide range of symptoms, including fatigue, sleep disturbance, functional impairment, cognitive dysfunction, variable bowel habits, depression, stiffness and more.
- Fatigue is the dominant clinical feature in CFS, but the clinical features of CFS and FMS overlap significantly.
- There is no assay or pathological test for FMS or CFS; diagnosis is based on symptoms and exclusion of other illnesses. For FMS, the American College of Rheumatology (ACR) 1990 classification criteria are commonly used as a diagnostic tool. Recently, the ACR published survey base diagnostic criteria for FMS which include the presence of widespread pain for at least 3 months. However, tender point count has been replaced by a symptom checklist which includes the Widespread Pain Index and Symptom Severity Scale.
- There are many sets of diagnostic criteria for CFS. In general, they include the presence of fatigue that is chronic and/or recurrent for more than 6 months, resulting in substantial reduction in activity, worsens on exertion and is unexplained by other conditions. Some of these criteria include other symptoms such as sore throat, muscle pain, cognitive dysfunction, tender lymph nodes, chemical hypersensitivity, headache and unrefreshing sleep. Exclusion criteria include psychotic, melancholic or bipolar depression, psychotic disorders, dementia and anorexia or bulimia nervosa.
- FMS is common, affecting 2% of the population with a female to male ratio of 7:1. Impaired physical function and reduced quality of life are common and comparable with diseases such as rheumatoid arthritis. Medical costs are high, up to 10 years before diagnosis. The societal cost of FMS due to reduced productivity is high. Constructive diagnosis can reduce healthcare costs.
- FMS is heterogeneous. Although depression is common, it does not always occur and mood should be assessed in all patients. Patients with moderate to severe depression, especially those with suicidal thoughts, should be referred to a psychiatrist for further assessment and management.
- Physiological pain is important in protecting the organism from harm while maladaptive (pathological) pain injury is caused by functional abnormality of the nervous system. FMS is characterised by maladaptive pain which has been demonstrated by functional MRI scan and detailed somatosensory testing.
- Sleep disturbance is common in patients with FMS. Polysomnography has confirmed reduced deep quality sleep and increased wakefulness. In healthy volunteers, selective deprivation of non-rapid eye movement sleep can induce symptoms and hyperalgesic tender sites of FMS.
- Non-pharmacological interventions for FMS, such as graded exercise and warm water bath, are important. Patients should be warned that pain may worsen transiently when starting exercise but should persevere. Other options include cognitive behavioural therapy, relaxation, rehabilitation, physiotherapy and psychological support, which may be used in some patients.
- Pharmacological treatments for FMS, as described in the EULAR recommendations, may be useful adjuncts to non-pharmacological treatments and should be considered. Choice of drug will depend on clinical manifestations.

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Generalized pain syndromes

- Including fibromyalgia and chronic fatigue syndrome -

Piercarlo Sarzi-Puttini, Françoise Laroche, Serge Perrot

A previous version was coauthored by Françoise Laroche, Serge Perrot, Lucy Coates, Ernest Choy

IN-DEPTH DISCUSSION I

Do we need new classification criteria for fibromyalgia syndrome?

The American College of Rheumatology (ACR) classification criteria for Fibromyalgia Syndrome in 1990 were used as diagnostic criteria for 20 years, although there were developed as classification criteria. These ACR1990 FM criteria had a major beneficial impact on research and clinical practice. They are widely used in research as well clinical practice to diagnose the condition. It stipulates an individual must have both chronic widespread pain involving all four quadrants of the body as well as the axial skeleton, and the presence of 11 of 18 tender points on examination. Since clinical researchers are now using the classification criteria extensively, it allows comparison and pooling of results from different studies. Furthermore, when applied in routine clinical practice, the diagnosis of FMS using the criteria reduces healthcare utilization.

Recently, the American College of Rheumatology published survey base criteria for FMS, a further modified version was published in 2011. The preliminary ACR 2010 criteria for the diagnosis of FMS do not require physical examination but the requirement for the presence of widespread pain for at least three months and that the patient does not have a disorder that would otherwise explain the pain are retained. However, tender point count has been replaced by a symptom checklist which includes Widespread Pain Index (WPI) and Symptom Severity Scale (SSS).

In the WPI, patients are asked to indicate the regions (maximum 19 regions) of the body in which pain has been experienced during the past week. Each positive region is given a score of 1 (WPI ranges 0 to 19).

SSS is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. Each of the 3 symptoms: severity of fatigue, waking unrefreshed and cognitive symptom, is scored between 0-3 (0 = no problem, 1 = slight or mild problems, generally mild or intermittent, 2 = moderate, considerable problems, often present and/or at a moderate level, 3 = severe: pervasive, continuous, life-disturbing problems over the last week). The extent of somatic symptoms is also scored between 0-3 (0 = no symptoms, 1 = few symptoms, 2 = a moderate number of symptoms and 3 = a great deal of symptoms). Permissible somatic symptoms include: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhoea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms. The final SSS is between 0 and 12.

A patient satisfies the criteria for FMS if the following conditions are met: WPI >7 and SS scale score >5 or WPI 3–6 and SS scale score >9.

Removing the reliance on tender point count is the major advantage of the survey base criteria for FMS. In addition the SSS includes characteristic features of FMS and may be used to monitor disease activity. These criteria are not intended to replace the ACR 1990 classification criteria, but to represent an alternative method of diagnosis.

A global survey by the independent polling organization Harris Interactive of 800 patients with FMS and 1,622 physicians from eight countries (the UK, France, Germany, Italy, Spain, the Netherlands, Mexico and S. Korea) found that average time taken to have FMS diagnosed was 2 years while the number of physicians consulted was 3. Yet delay in the diagnosis has been shown to be a factor that is associated with a poor outcome by a study in Spain and also higher healthcare utilization. The global survey also found between 40-50% of primary care physicians and 50-60% of specialists felt FMS is difficult to diagnose.

A study has suggested FMS patients can be divided into three different sub-groups based on their symptoms, coping strategy and tenderness level. These three sub-groups have been discussed in the main review.

Lastly, our understanding of pathophysiology of pain processing has been greatly advanced by the availability of new research techniques. Quantitative sensory testing and functional MRI scan have shown objectively that patients with FMS have reduced pressure pain threshold, and PET has shown that mu-opioid receptor binding is decreased in multiple pain processing regions in the brains. Ideally, any new diagnostic criteria should correspond to the pathophysiology of FMS.

In conclusion, whilst the American College of Rheumatology 1990 classification criteria of fibromyalgia have made a significant contribution to research and clinical practice, the new 2010 modified Criteria will improve diagnosis but also severity assessment for graded management.

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Generalized pain syndromes

- Including fibromyalgia and chronic fatigue syndrome -

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IN-DEPTH DISCUSSION II

Is reduced sleep quality a purely secondary phenomenon in fibromyalgia?

Poor quality, unrefreshing sleep is a prominent feature of fibromyalgia syndrome (FMS). 70-90%^{1,2} of patients diagnosed with FMS complain of some type of sleep disturbance including difficulty getting to sleep, frequent wakening, and light sleep. Daytime sleepiness and morning fatigue, feeling the need to sleep shortly after waking, may occur in 75–80% of patients³. Morning fatigue is a good indicator of unrestorative sleep, where the quantity of sleep may be normal but the quality is reduced.

Many people have felt that this effect on sleep is a secondary phenomenon, and it is clear that pain will negatively effect sleep. The association between the two has been well described not only in populations with chronic rheumatic conditions⁴ but in the general population. A large epidemiological study in Germany found that those with chronic widespread pain were more likely to describe poor sleep than those without⁵. However, as the sleep cycle is better understood it is becoming clear that its role may be primary as well.

The sleep cycle is split into NREM, non-rapid eye movement, and REM, rapid eye movement. Most sleep is NREM in nature. There are 4 types of NREM sleep, N1 at the interface between wakefulness and sleep through to N4, slow wave sleep or delta sleep when it is at its deepest. REM sleep has tonic and phasic components. The phasic component is characterized by rapid eye movements, muscle twitches, and respiratory variability and is sympathetically driven. Tonic REM is a parasympathetically driven state with no eye movements.

It is normal to have predominantly delta waves in N2, 3 and 4 with alpha waves occurring in less than 40% of normal NREM sleep⁶. In studies of sleep in patients with FMS frequent alpha wave intrusions into delta wave sleep, so called alpha delta sleep, have been recorded in stages N2, 3, and 4⁶. Increased amounts of differing alpha EEG sleep types have also been recorded. Phasic alpha sleep in 50% of patients compared to 7 % of normal and tonic in 20% of patients compared to 9%⁷. Sleep with low levels of alpha EEG activity occurred in only 30% of patients compared to 84% of normal. Of these those with the phasic pattern of alpha EEG sleep had an increased incidence of pain, increased tenderness on wakening, poor sleep efficiency and less slow wave sleep than the other groups. FM patients have a higher cyclic alternating pathway (CAP) rate than normal subjects⁷. The CAP rate describes instability of the level of vigilance that manifests the brain's fatigue in preserving and regulating the macrostructure of sleep. Patients with FMS had twice as many arousals per hour of sleep than normal and spent a greater proportion of time in stage 1 of NREM sleep. The CAP rate (total CAP time/non-REM sleep time) was significantly increased in FM patients compared to controls (68 +/- 6% vs. 45 +/- 11%; $p < 0.001$) and this increase correlates with the severity of clinical symptoms in FM patients (tender points index; $p < 0.01$) and with less sleep efficiency (time in bed/time asleep).

These studies suggest that different patterns of sleep may occur in patients who already have symptoms of FMS but a causal link between disturbed sleep and pain has also been demonstrated⁵. Moldofsky took 6 young men with no history of chronic pain and used auditory stimulation to disturb their NREM sleep⁵. Using polysomnography they were monitored whilst sleeping and as they entered stage 4 sleep the auditory

stimulation was used to induce alpha waves but not to wake them. This took place over 3 consecutive nights. During this period overnight increases in dolorimeter scores were recorded and increased musculoskeletal symptoms, and mood disturbance comparable to patients those described by patients with FMS were reported. After a period of “recovery”, undisturbed sleep these symptoms resolved. This evidence which suggests a primary role for NREM sleep disturbance is supported by further studies^{8,9}.

Furthermore, animal studies have looked at the physiological effect of sleep and there is growing evidence of a direct effect on pain control mechanisms. Rat studies have shown that neurons in the pontomedullary raphe magnus (RM) are important in the descending modulation of nociceptive transmission. In unanaesthetised rats thermal stimulation can produce either suppression or facilitation of nociceptive dorsal horn cells and nociceptive reflexes depending on the state of sleep or wakefulness¹⁰. RM OFF cells discharge continuously during slow wave sleep but only intermittently during waking. When discharging during slow wave sleep the effect resembles OFF cell discharge after administration of analgesic doses of morphine. This is hypothesized to inhibit nociceptive transmission within the spinal dorsal horn. In human studies increased threshold of nociceptive flexion reflexes have been observed during sleep, particularly REM sleep¹¹. The nociceptive flexion reflex is controlled by multiple systems including endogenous opioids which are increased during sleep and it has been hypothesised that this may have an inhibitory effect which would be lost if sleep is disturbed. Further studies of sleep/pain physiology are required to piece together the effects that each has on the other.

The mounting evidence supporting the role of sleep in FMS has led investigators to examine whether therapies that manipulate sleep can be used to treat FMS. Previously hypnotics have been found to improve sleep quantity but they have not had a significant effect on somatic symptoms including pain¹². They should only be used in conjunction with other treatments for FMS. Recently encouraging research studying sodium oxybate (SXB) has been reported¹³⁻¹⁵. SXB increases slow wave sleep and reduces nocturnal waking. It also modulates activity of noradrenergic, serotonergic, dopaminergic, cholinergic, and glutamatergic neurons and promotes growth hormone secretion and the production of some neurosteroids. A UK based study has shown that treatment with 4.5g or 6g nightly for 14 weeks significantly improves pain compared to placebo¹⁴. A 30% reduction in pain from baseline was reported in 54.2% treated with SXB 4.5 g and 58.5% treated with SXB 6 g compared with 35.2% for placebo ($P < 0.001$ for both comparisons). This was maintained for 50% and 80% improvements in the 6g group. There were also significant improvements in fatigue, early morning fatigue, and functioning in the 6g group versus placebo. However, sodium oxybate is the sodium salt of c-hydroxybutyrate (GHB), an endogenous metabolite of c-aminobutyric acid (GABA) with central nervous system–depressant properties which is also known as a “date-rape” drug and is potentially open to abuse. In addition, tolerability may be an issue with an incidence of at least twice that of placebo for headache, nausea, dizziness, vomiting, diarrhoea, anxiety, and sinusitis. The 6 g dose was generally associated with a greater incidence of AEs than the 4.5 g dose. However, this study and others do indicate that by exploring treatments that improve the

quality of sleep we may be able to make a leap forward in managing patients with FMS and at the same time gain a better understanding of the pathogenesis of FMS.

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Osteoporosis : Pathogenesis and Clinical features

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A previous version was coauthored by Karine Briot, Christian Roux, Cyrus Cooper

LEARNING OBJECTIVES

- Describe and explain the physiology of bone (bone formation, bone resorption) and bone modeling and remodeling
- Outline the epidemiology of vertebral, hip and non- vertebral non-hip fractures
- Describe and explain the consequences of osteoporotic fractures: mortality, morbidity and risk for subsequent fractures
- Diagnose vertebral fractures
- Identify the role of bone density and T-scores for fracture risk assessment.
- State the role of FRAX calculation
- Perform adequate differential diagnosis for secondary osteoporosis
- Assess the risk of fracture in patients treated with glucocorticoids
- Recognise increased risk of osteoporosis and fractures in patients with inflammatory joint disorders.

This course does not address the treatment of osteoporosis

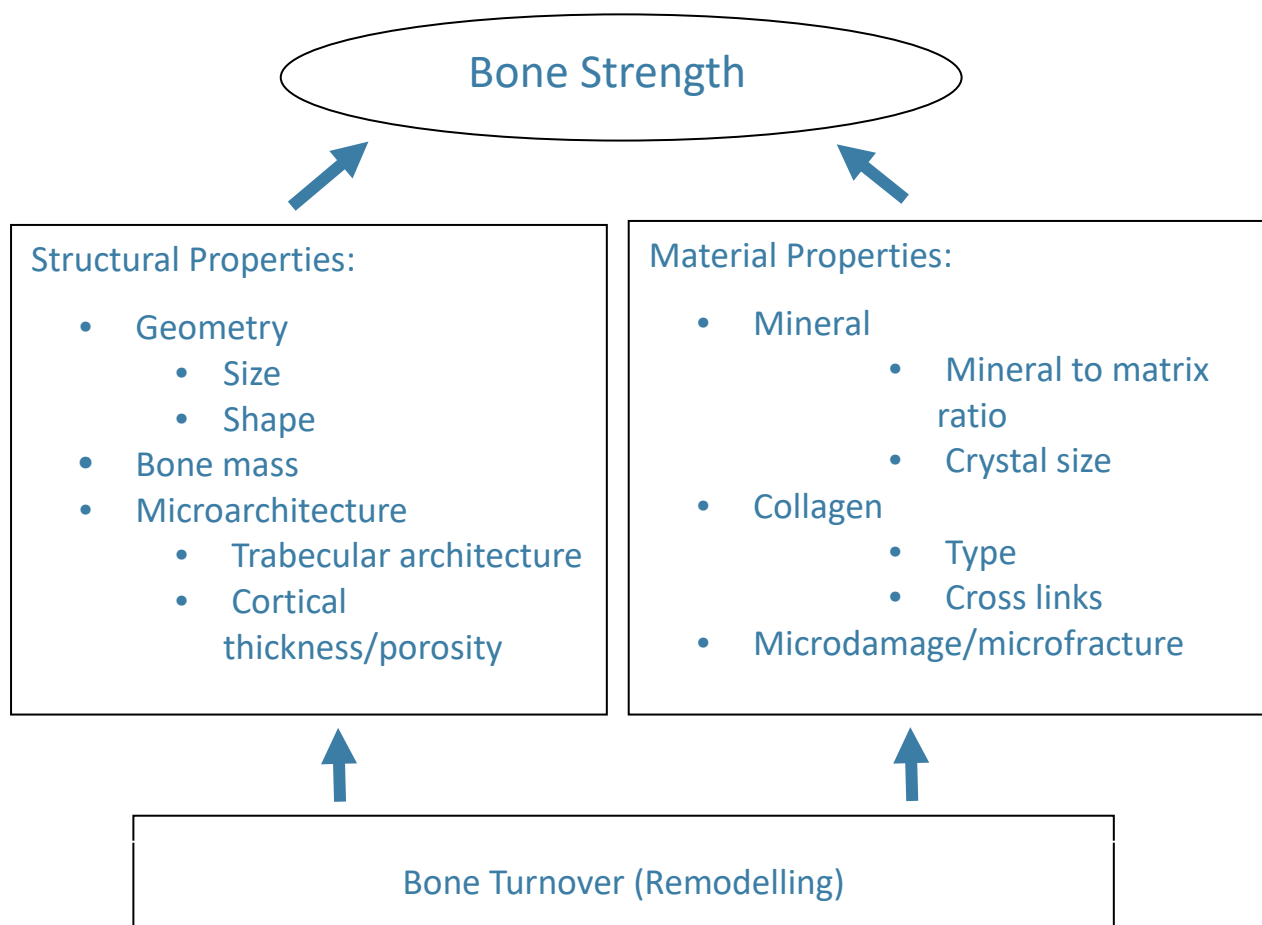
1 Physiology of healthy bone

The skeleton is a metabolically active tissue populated by a diversity of active cells that constantly remodel bone tissue throughout life. These cells activity - including cytokines and hormones production - is essential for various metabolic pathways in the whole body.

1.1 Biomechanical properties of bone

The strength of bone, that is, the ability of bone to resist fracturing, is determined by its structural and material composition, and by the activities of bone cells that determine the level and balance of bone turnover and ability to repair damage (box 1). Bone must be stiff and able to resist deformation, making loading possible. Bone must also be flexible to absorb energy by deforming: to shorten and widen when compressed, and to lengthen and narrow in tension without cracking. If bone is too brittle, the energy imposed during loading will be released by structural failure, initially by the development of microcracks and then by complete fracture. If bone is too flexible and deforms beyond its peak strain, it will also crack and fracture. Furthermore, bone must also be light to facilitate movement, and give room to its host tissue, the haematopoietic cells.

Box 1 Bone strength is related to structure, mass, material properties and turnover



1.2 Macroscopic organisation of bone

The skeleton includes the axial skeleton, with the vertebrae, the pelvis and other flat bones such as the skull and sternum; and the appendicular skeleton, including all the long bones.

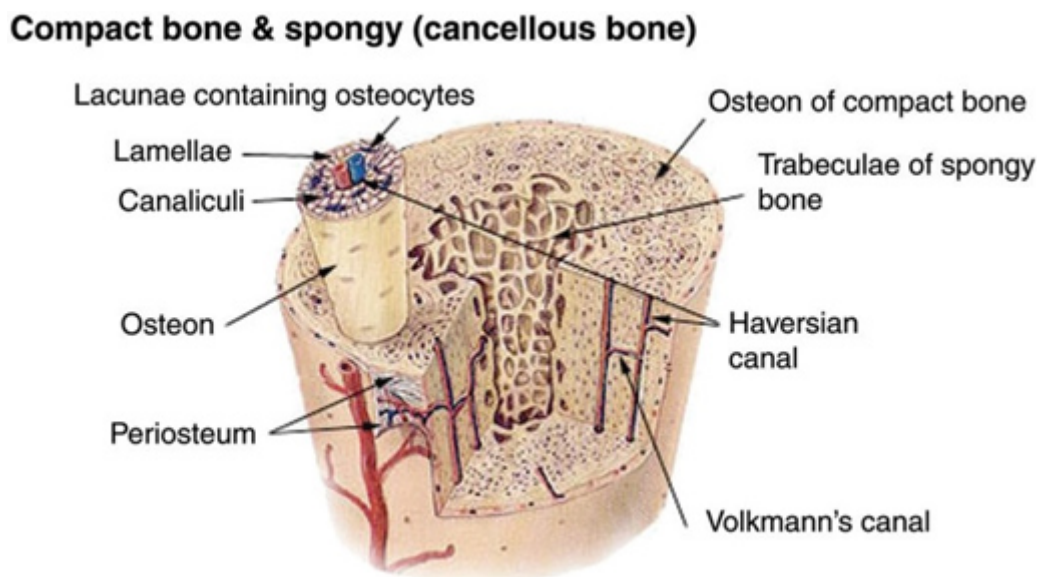
Long bones, e.g., the femur and the humerus, include the diaphysis, with the epiphyses at their extremities. In the diaphysis, the cortical bone (cortex) surrounds the medullary canal. Epiphyses have a thinner cortex and the central area of the bone is filled with trabecular (cancellous) bone. The outer bone envelope is the periosteum, including neurofibres, blood and lymph vessels. The internal surface of cortical bone is called the endosteal surface. The metaphysis is the limit between the diaphysis and the epiphysis, where the growth plate is located in growing children. Although bone length growth stops with growth plate fusion, a slow process of increase in bone width continues throughout life, as a mechanical adaptation to cortical thinning due to aging.

In short, flat and irregular bones, cortical bone surrounds trabecular bone, embedding bone marrow. The periosteal and endosteal surfaces are comparable to that of long bones.

Cortical bone, represents 80% of adult bone mass, and trabecular (cancellous) bone 20% of bone mass.

Trabecular bone has a high surface/bone mass ratio and is in close contact with bone marrow, which is the source of bone cell precursors (figure 1).

Figure 1 Cortical and trabecular bone.



Cortical bone is mainly found in the shafts of long bones (e.g., femur) and the surface of flat bones (e.g., ribs). It consists of overlapping parallel osteons surrounded by interstitial bone and many lacunae containing

osteocytes, which are connected to each other and with the surface cells by numerous canaliculi. These osteocytes are concentrically distributed around the central Haversian canals, which contain blood vessels, lymphatic vessels and connective tissue. Long bones act as levers for loading and movement, with rigidity favoured over flexibility. The presence of a marrow cavity, which hosts haematopoietic cells, ensures structural stiffness and lightness. Cortical bone should not be called 'compact' bone as it is traversed by a huge number of canals (Haversian, Volkmann); these canals provide a large surface area for remodelling. In vertebrae, the cortical shell is very thin, but may bear up to 45–75% of the axial load. At the femoral neck, the cortical compartment is the main contributor to the bending rigidity; removal of trabecular bone from the femoral neck only reduces failure load by 7%.

Trabecular bone is found at the end of the long bones, in the inner part of flat bones and the vertebral bodies. It is a sponge-like, porous structure that functions more like a spring in that it can deform to absorb energy. The interconnecting trabecular plates are orientated according to lines of stress, which favour structural flexibility over stiffness.

1.3 Microscopic organisation of bone

Bone texture

We can distinguish two types of bone textures: woven bone and lamellar bone. Woven bone includes disorganized big collagen fibres and is found in foetal bone, ear ossicles, transiently in fracture callus, and in some conditions like Paget disease of bone and dense bone metastasis. In contrast, in lamellar bone, collagen fibres are organized in lamellae. Within each lamella, fibres are parallel, but form angles around 90° with adjacent lamellae, which is responsible for bone resistance.

Organization of cortical bone

Bone structural units (BSU) correspond to concentric lamellae, surrounding the Havers canal, which contains blood vessels. These canals communicate with transverse canaliculae, the Volkman canals. This cylindrical structure including the Havers canal with its lamellae, is also called an osteon. They lie within interstitial bone, which results from partial osteon remodelling.

Organization of trabecular bone

Trabecular bone is a dense tridimensional network. Bone remodelling produces bone packets, reminiscent of the cortical osteon structure, but open to the bone marrow.

1.4 Bone matrix

The organic bone matrix consists predominantly (90%) of type I collagen. Other non-collagenic proteins include proteoglycan, osteocalcin and osteonectin. Bone matrix also contains growth factors, such as IGF-I and II, for which bone tissue is the largest reservoir. Each unit of collagen is formed as pro-collagen within the osteoblast and consists of two α -1 chains and one α -2 chain twisted together in a triple helix. The formation of cross-links results in the assembly of the triple helix collagen molecules into stable collagen fibrils, which are further grouped into collagen fibres. Collagen fibres are laid down in a regular lamellar (layered) way, - the lamellar bone - and so contribute to the flexibility of bone.

1.5 Bone mineral

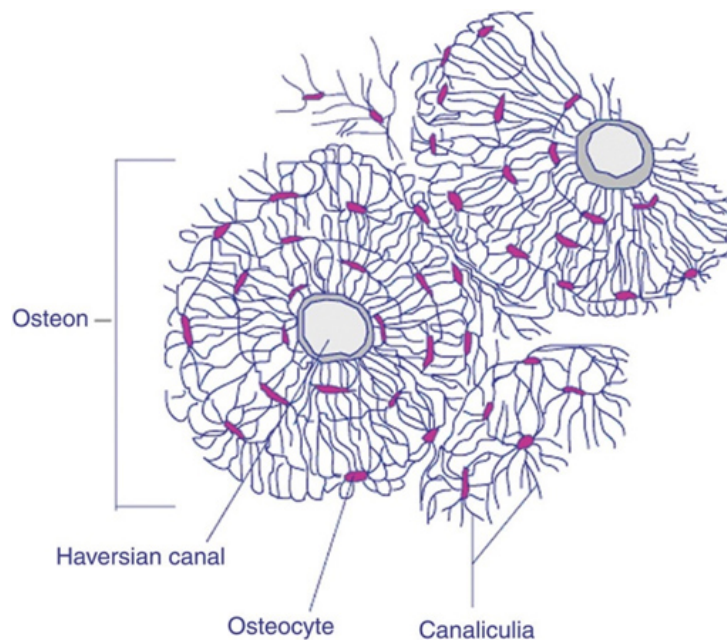
Calcium hydroxyapatite is the main bone mineral and is deposited along the lamellar gaps between collagen fibres. Mineralisation occurs in two phases: an initial phase in which more than 70% of the collagen matrix is mineralised within a few days (primary mineralisation), and a slower, prolonged phase lasting 3–6 months or more, characterised by the maturation of mineral crystals associated with changes in their size, composition and structure (secondary mineralisation). The degree and heterogeneity of mineralisation are two strong determinants of bone stiffness, thus contributing to bone strength.

1.6 Bone cells

Bone consists of four types of cells: osteocytes, osteoclasts, osteoblasts and lining cells. Osteocytes represent the largest number of bone cells (> 75%). Osteoclasts and osteoblasts are few in number and only present at locations with active bone turnover. They are resident cells (as are lining and periosteal cells) and are present throughout the entire bone.

Osteocytes, by far the most abundant bone cells, are derived from osteoblasts lying in lacunae after being embedded in the bone matrix during bone formation. They are small, flattened cells located within the bone matrix, which are connected to one another and to the lining cells on the bone surface by cytoplasmic extensions along tiny canals called canaliculi (some 50 per cell; figure 5). These cells have several functions:

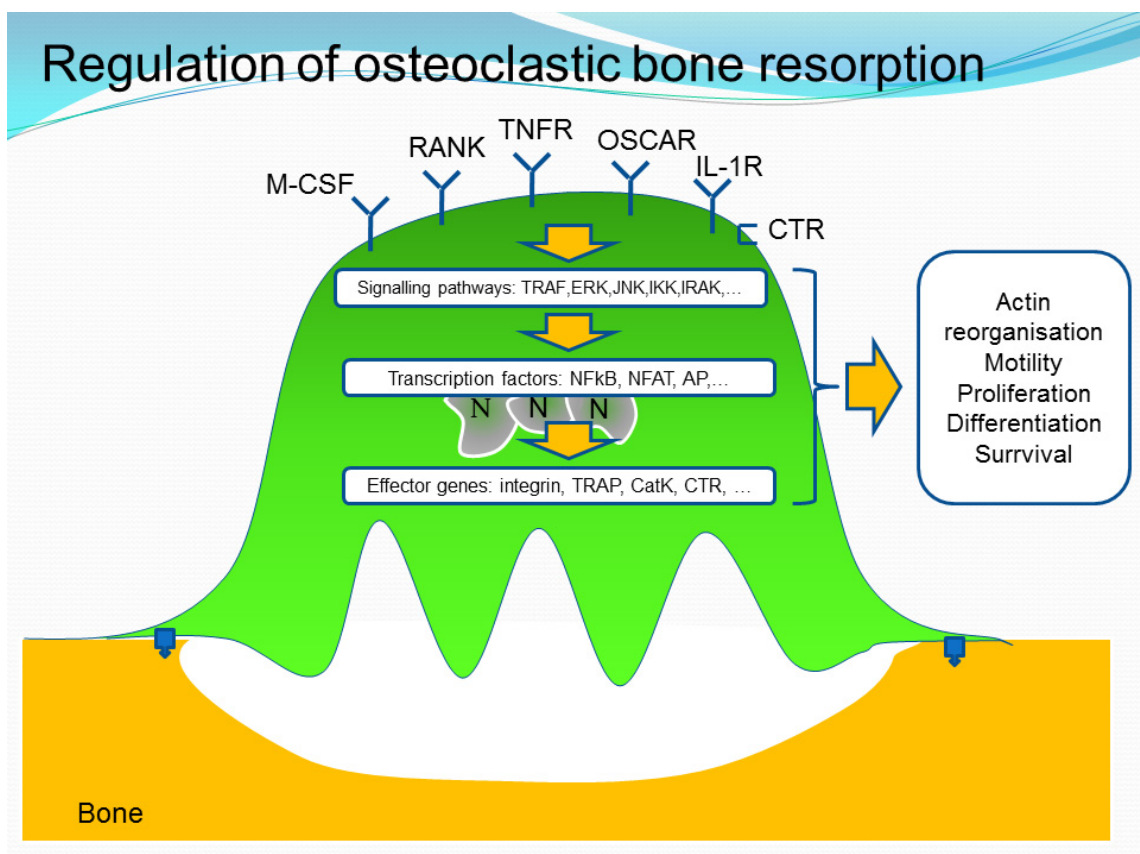
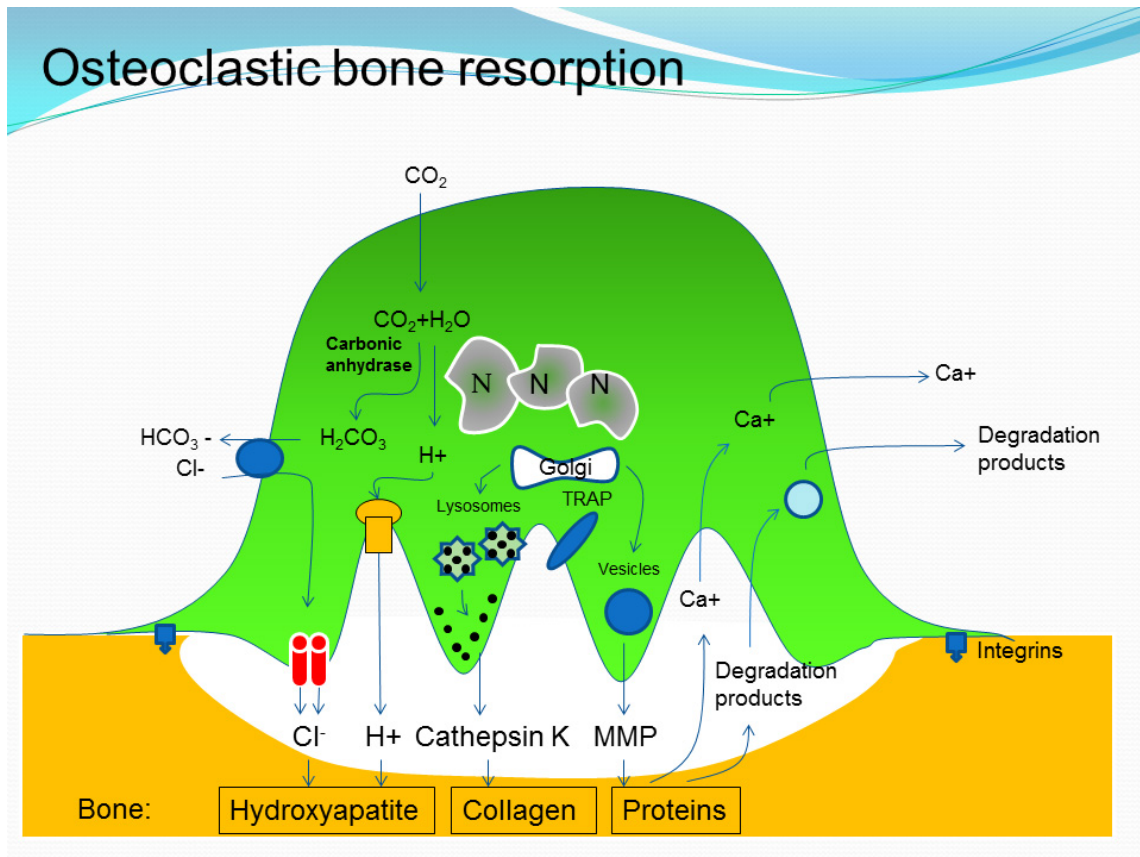
Figure 2 The osteocyte. (Source: Wikimedia Commons, http://en.wikipedia.org/wiki/File:Transverse_Section_Of_Bone.png)



- Osteocytes have an endocrine function by producing hormones, such as FGF23 (which regulates serum phosphate).
- They are the main source of regulators of bone formation (sclerostin, Dkk1) and bone resorption (RANK L).
- Osteocytes are very important in guarding the integrity of the material and structural strength of bone. They sense mechanical strain by mechanically induced cell deformations and/or fluid flows in the canaliculi, thereby signalling the need for adaptive remodelling and distribution to accommodate prevailing loads. The death of osteocytes by apoptosis precedes osteoclastogenesis. Osteocyte apoptosis—which is one of the characteristics of oestrogen deficiency, GC therapy and advanced age—has a more deleterious effect on bone strength than on bone mass.

Osteoclasts are giant multi-nucleated cells that are derived from haematopoietic precursors of the monocyte–macrophage lineage. They are the only cells that are able to resorb mineralised bone tissue. The first part of this process is their attachment to bone mediated by proteins including integrins, osteopontin, fibronectin, collagen and bone sialoprotein. Once attached to bone, they polarise, forming a specialised cell membrane, the ‘ruffled border’, which increases the surface area interface for bone resorption (figure 2). This resorption follows two steps:

Figure 3 The osteoclast. (Top) Activities: binding to bone, and secretion of acid, cathepsin K and metalloproteinases. (Bottom) Receptors for regulators of osteoclast activities activate intracellular signalling pathways, transcription factors and effector genes. (Reproduced with permission of P Geusens.)



- The first step is the dissolution of the crystals. The osteoclasts generate hydrogen ions ($\text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{HCO}_3^- + \text{H}^+$) through the ruffled border into the cavity, which acidifies the area below the cell and dissolves the mineralised bone matrix into Ca^{2+} , H_3PO_4 , H_2CO_3 and water. Hydrogen ions are pumped against a high concentration gradient throughout the cell to the opposite side, thanks to chloride canals.
- The second step is the degradation of the matrix: several lysosomal enzymes (collagenases), such as cathepsin K and matrix metalloproteases (MMP), are released to digest the organic components of the bone matrix (collagen and other proteins). Tartrate-resistant alkaline phosphatases (TRAP) further destroy the bone matrix degradation products.
- The bone resorption pattern consists in the classical resorption pits, but also in resorption trenches. Some osteoclasts move laterally, displacing their extracellular bone-resorbing compartment over the bone surface without disassembling and reconstructing it, thereby generating long trenches. Compared with pits, trenches display more aggressive characteristics: long duration (days), high erosion speed (two times faster) and long-distance erosion

The macrophage colony-stimulating factor (M-CSF) produced by osteoblasts and the receptor activator of the nuclear factor κB ligand (RANKL), which is expressed abundantly by osteocytes, are both indispensable for osteoclastogenesis. RANKL interacts with its receptor RANK, which is expressed on osteoclast precursors and on mature osteoclasts, and promotes osteoclast differentiation and activation. Osteoprotegerin (OPG), present in the bone micro-environment, is mainly secreted by osteoblasts and osteocytes. It is a decoy receptor for RANKL. OPG blocks the interaction of RANKL with RANK and thus acts as a physiological regulator of bone resorption (figure 3).

Many cytokines, 1,25-dihydroxyvitamin D_3 , oestrogens and other molecules are known to affect osteoclastogenesis and bone resorption by influencing the production of RANKL and OPG, thus regulating and affecting the RANKL/OPG ratio: (a) RANKL is upregulated by cytokines like IL-1 β , IL-6, IL-17 and tumour necrosis factor- α (TNF α); (b) 1,25-dihydroxyvitamin D_3 enhances RANKL production; (c) parathyroid hormone (PTH) and glucocorticoids (GCs) enhance RANKL and inhibit OPG production; (d) oestrogens and tumour growth factor (TGF) enhance OPG production; (e) interferon- γ inhibits RANKL-induced osteoclastogenesis; (f) lipopolysaccharide (LPS) enhances OPG production in gingival fibroblasts; (g) ATP up-regulates RANKL expression by human osteoblasts; (h) fibroblasts and activated T cells produce RANKL and the Th17 subpopulation has a key role in osteoclastogenesis; (i) T regulators decrease osteoclastogenesis through CTLA4; and (j) interactions are possible between antibodies (as anticitrullinated protein antibodies) and osteoclastogenesis, through a Fc γ receptor on precursors cells surfaces.

Osteoblasts are plump cuboidal cells organised in continuous monocellular layers along the osteoid, and are derived from pluripotent stromal cells. They are responsible for the formation and mineralisation of bone

matrix. They synthesise and secrete growth factors, such as IGF-I and TGF β , into the matrix. Osteoblast differentiation and function is under the control of the Wnt signalling pathway (figure 4).

Figure 4 The RANK/RANKL/OPG signalling pathway. The mechanisms of action of (A) pro-resorptive and calcitropic factors and (B) anabolic and anti-osteoclastic factors. (Reproduced with permission from Boyle and Simonet, *Nature* 2003;423:337–42.)

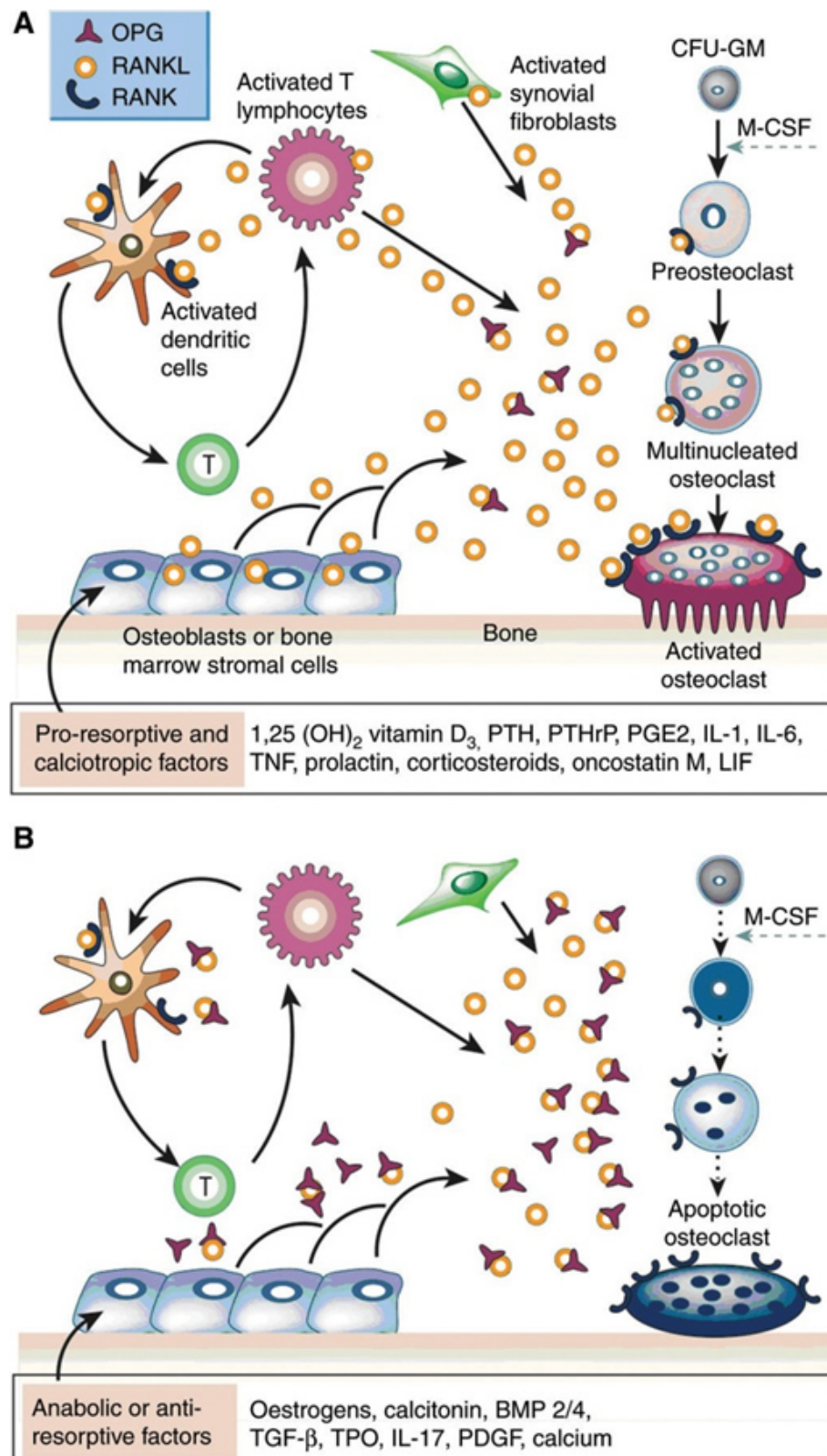
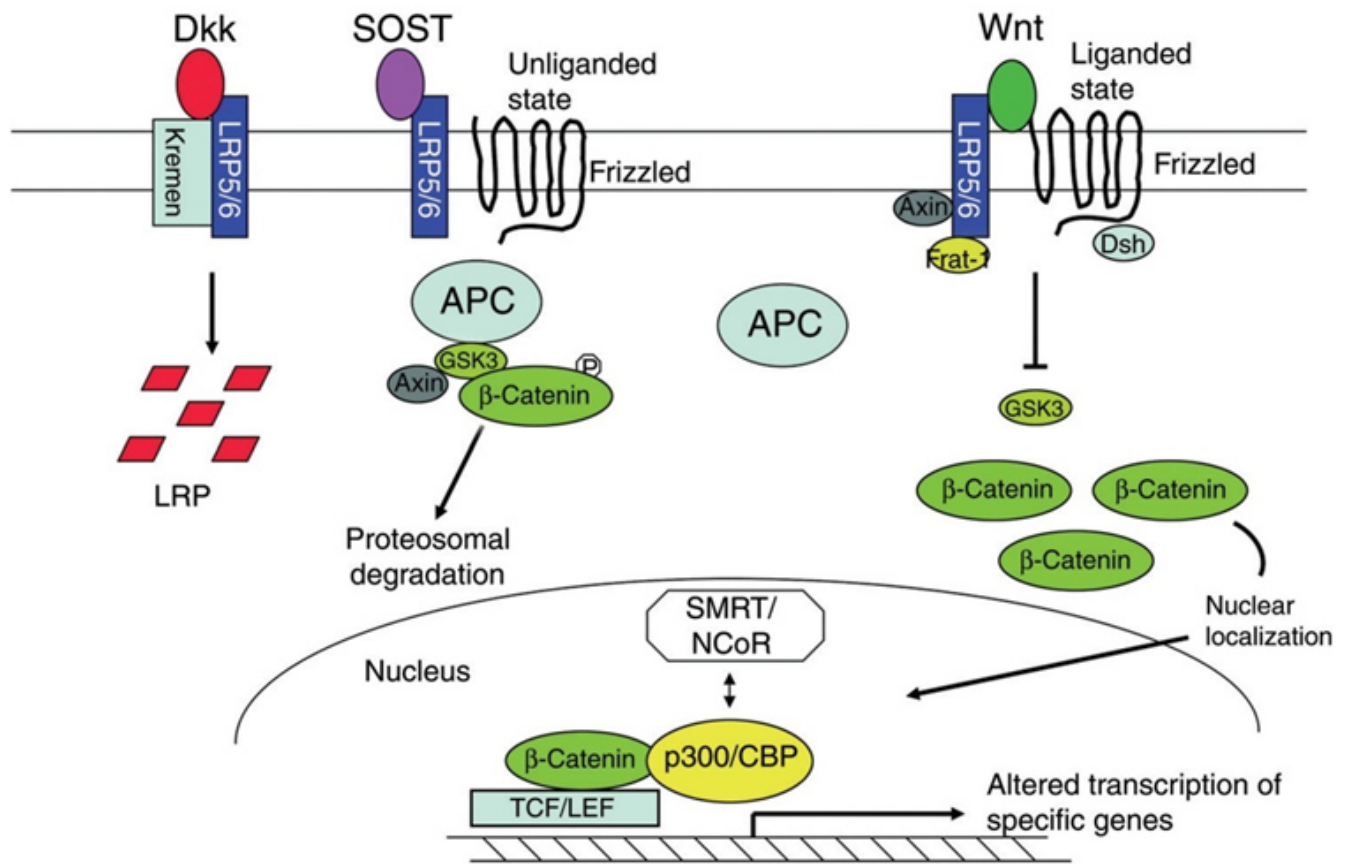


Figure 5 The Wnt signalling pathway in osteoblasts. (Reproduced with permission from Shoback, *J Clin Endocrinol Metab* 2007;92:747–53.)



In some family studies, high bone mass was found to be associated with mutations of LRP5, which had already been observed in animal studies (e.g., mutations in the Wnt signalling pathways are related to the absence of wings in fruit flies) (Krishnan *et al*, 2006*). Wnt molecules bind to the Frizzled receptor at the membrane surface, and need LRP5 as a co-receptor to stimulate osteoblasts by the canonical Wnt signalling pathway which involves β -catenin. Dkk1 (increased in multiple myeloma, rheumatoid arthritis (RA) and during GC treatment) binds to Kremen and LRP, which is internalised, and sclerostin (the protein from the SOST gene in osteocytes) binds to LRP5, thereby inhibiting Wnt from activating the canonical pathway. Thus, osteocytes can actively suppress bone formation through the production of inhibitory proteins, i.e., sclerostin and Dkk1, as inhibitors of the Wnt pathway.

Cross talk: at the local level cell activity is regulated by crosstalk between osteoblasts and osteoclasts.

Osteoblasts block bone resorption by production of semaphorin 3A, which inhibits RANK L-induced osteoclastogenesis, thereby preventing differentiation of monocytes to osteoclasts. Semaphorin 3A has also an autocrine effect on osteoblast differentiation. Moreover, direct contact of cells through ephrins (B₂ and B₄) is part of the crosstalk between osteoblasts and osteoclasts. In turn, osteoclasts secrete clastokines, such as sphingosine-1-phosphate (S1P) which is a coupling molecule. The initial resorption at the tip of the canal is

followed by a period where newly recruited reversal/osteoprogenitor cells and osteoclasts alternate, thus revealing the existence of a mixed "reversal-resorption" phase.

Lining cells cover the surface of the bone that is not remodelled. They are involved in the regulation of bone remodelling but their exact functions remain elusive.

1.7 Modelling and remodelling of bone

The cellular mechanisms responsible for the adaptation of bone are modelling (construction) and remodelling (reconstruction). Bones are shaped by modelling during growth, from the *in utero* period to adolescence, with chondrocyte differentiation, matrix synthesis and calcium deposition. In adults, bone is remodelled, with resorption of old bone and formation of new bone.

Bone modelling produces a change in the size and shape of bone. During this process, formation and resorption are uncoupled. Bone formation and resorption are then associated in time, location, quantity and balance. During bone remodelling, resorption by osteoclasts (lasting about 3 weeks) precedes bone formation by osteoblasts (over the following 3–4 months) through a coupled phenomenon. Osteoclasts and osteoblasts form the bone multicellular unit (BMU) that reconstructs endocortical, intracortical and trabecular bone. At the surface of trabecular bone, the BMU is covered with a canopy, through which passes a capillary that can deliver osteoblasts and osteoclasts, which have been recruited and differentiated from stem cells in the surrounding bone marrow.

During childhood and adolescence, both processes (modelling and remodelling) are involved in establishing peak bone mass (PBM), bone density, macro- and micro-architecture and strength. Bones grow by periosteal apposition (growth in width) and by endochondral ossification in the growth plate (growth in length). During childhood, modelling occurs primarily on the outer (periosteal) surface and is responsible for bone size. Resorption is essential for the excavation of a marrow cavity and the fashioning of cortical and trabecular bone. At puberty, bone thickens because formation can occur on both the outer and the inner (endocortical) surfaces. The modelling and remodelling rates decrease as longitudinal growth ceases with epiphyseal closure.

In young healthy adults, the resorptive phase of the remodelling cycle removes damaged bone, and the formation phase restores the structure. Each cycle is balanced and lasts 90–130 days. Bone resorption and formation are tightly coupled in time, location and quantity. After the remodelling cycle is achieved, mineralisation of new bone will continue. This constant bone turnover is essential: (a) for bone health, preventing the accumulation of old bone, enabling repair of microdamage and changing bone architecture in response to repeated loading; and (b) to provide calcium for calcium homeostasis.

1.8 Building up PBM

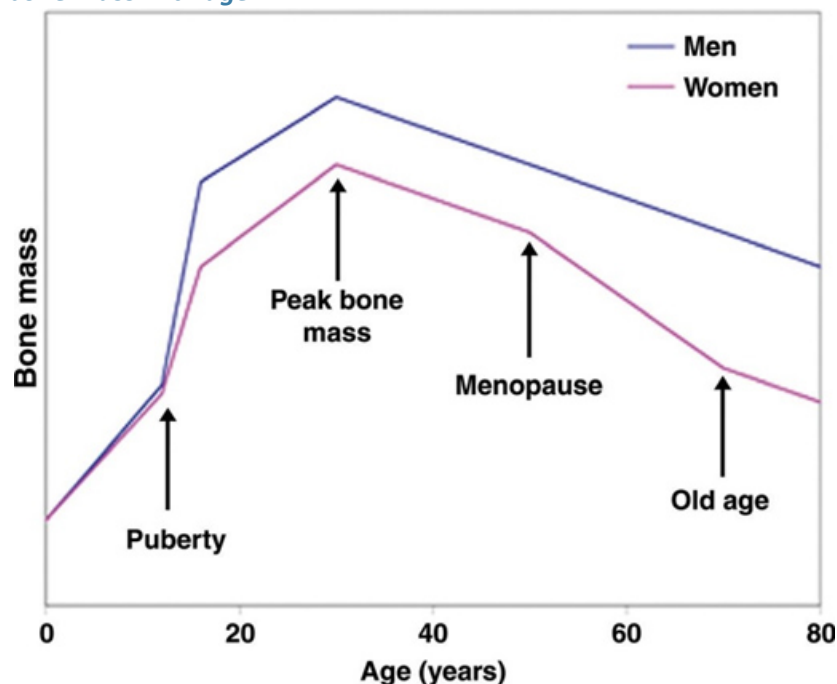
Peak bone mass is the amount of bone acquired at the end of skeletal growth, and it is followed by bone loss throughout the rest of life. Bone mass at a given age is a function of the achieved peak bone mass minus the amount of bone lost later as a consequence of menopause and aging; so the level that can be achieved at the end of bone growth is critical for the future risk of fracture. Peak bone mass, which is reached in early adult life, primarily depends on genetic factors. It is also influenced by dietary calcium intake during adolescence, possible toxic factors such as smoking, drugs and alcohol consumption, as well as by physical activity.

Blacks achieve higher peak bone mass than whites do, who have greater peak bone mass than Asians, particularly Japanese. Twin studies have shown a strong correspondence of peak bone mass in monozygotic twins, who have closer concordance in BMD than dizygotic twins do. Twin and family studies have consistently found that genetic factors account for up to 80% of BMD inter-individual variance. Searches for candidate genes have found that the collagen I α 1 Sp1 polymorphism is moderately associated with BMD and fracture, as shown in a meta-analysis of 13 studies involving 3642 patients. More recently, some variants of LRP5 have been found associated with BMD and fracture. After the candidate gene approach, genome-wide associations studies (GWAS), have helped with identifying genes involved in the regulation of bone strength. Current results from GWAS indicate that genes involved in the RANK–RANKL–OPG pathway (*TNFRSF11B*, *TNFRSF11A* and *TNFSF11* genes), the Wnt– β -catenin pathway (*LRP5*, *LRP4* and *SOST* genes), the oestrogen endocrine pathway (*ESR1* gene) and the 1p36 region (*ZBTB40* gene) are those most strongly associated with osteoporosis. These genetic variants, however, have modest effect sizes, so that we need to better understand the interactions between genes and the environment before they can be tested routinely to assess fracture risk. Building genetic risk scores combining a number of genes to predict fracture may a sensible approach. Dietary calcium intake may be important for attaining optimal peak bone mass. A few placebo-controlled trials in children or in adolescents, including one performed in twins, have shown a modest, but significant increase in BMD in those receiving calcium supplementation. Children with very low calcium intake are more likely to benefit from an increase in calcium intake, preferably from dietary source. A combination of increased physical activity and calcium intake may be more efficient than any factor alone to optimize bone gain during growth. Exercise during growth may contribute to the level of peak bone mass. It has been shown that intensive exercise before puberty may enhance bone acquisition, which might persist in adulthood, but the role of exercise in the normal physiologic range is unknown. In girls, areal BMD gains stop around ages 16-20 and in boys around ages 20-22. During pregnancy, diet, physical activity and toxic substances exposure, including cigarette smoking, may also influence the level of peak bone mass, via the long-term influence of epigenetic regulation.

1.9 Bone loss after menopause and during ageing

Bone loss is an inevitable consequence of ageing at the time of the menopause and continuing throughout life in both men and women, and is the result of persistent hypogonadism in women, emerging hypogonadism in some men, aging and senescence of bone cells and the secondary hyperparathyroidism in the elderly of both sexes that is associated with calcium and vitamin deficiency and reduced mobility (figure 6). It is estimated that approximately 50% of trabecular and 35% of cortical bone is lost over a lifetime in women, with losses in men approximating two-thirds of these amounts. However, keeping in mind that cortical bone is predominant in the skeleton, this means that most of the loss occurs in the cortical compartment.

Figure 6 Changes in bone mass with age.



At the cellular level, two forms of bone loss can be recognised. First, there is an increase in the number of bone remodelling units on bone surfaces, thus increasing the amount of bone undergoing resorption at any one time (increased activation frequency). More densely mineralised bone is removed and replaced with younger, less densely mineralised bone, reducing material stiffness. Excavated resorption sites remain temporarily unfilled and there is alteration of cross-linking between adjacent collagen fibres. Second, bone resorption is more pronounced, resulting in perforations of trabeculae (Seeman and Delmas, 2006*).

In addition, there is a third remodelling imbalance due to age: bone formation is reduced compared with resorption within each remodelling unit. As a result, bone may become too flexible, bend excessively and crack under usual loading conditions.

Since there are a lot of remodelling sites per unit of trabecular bone volume, a great portion of trabecular bone is turned over and lost (trabecular thinning). The deep resorption cavities result in a loss of trabecular

plates and their connectivity, causing greater deficits in bone strength. With continued remodelling, trabeculae perforate and some disappear completely, and remodelling is more active on the endocortical surface. That is why the role of cortical bone loss becomes more and more important with age. Cortical thinning (related to the resorption in the endocortical area) and porosity reduce the resistance of bone to the propagation of cracks. Periosteal apposition partly offsets the loss of cortical bone, more so in men than in women (Zebaze *et al*, 2010*).

1.10 Bone as an endocrine organ

It has been shown in animal models that there is coordinated regulation of bone mass, energy metabolism, and at least in males, fertility. Bone produces at least two hormones, FGF23 that regulates phosphate metabolism and osteocalcin that is involved in insulin sensitivity, energy expenditure and stimulates testosterone synthesis. By its biological connections with the brain, the kidney, the gut and the pancreas, bone physiology is linked to several chronic diseases, that in turn, also influence the skeleton.

2 Pathophysiology of osteoporosis

2.1 Definition and appropriate use of the T-score

The term osteoporosis originally referred to 'porosity of bone', one of the characteristics of bone that contributes to bone's failure to resist fracturing. In 1994, osteoporosis was defined by the WHO as 'a generalised bone disease characterised by a decreased bone mass and a deterioration of bone microarchitecture resulting in an increased fracture risk' (World Health Organization, 1994*). Finally, the National Institute of Health (NIH) defined osteoporosis in 2001 as 'a disease of compromised bone strength, resulting in an increased risk of fracture' (NIH, 2001*). Thus, osteoporosis is both a *disease*, and a *risk factor* for fracture.

Bone strength reflects the combination of bone mass and bone quality. Since there is no current direct and accurate means to measure either bone strength or bone quality, bone mass, assessed as BMD, which accounts for ~70% of bone strength, is used to assess osteoporosis. For epidemiological purposes, osteoporosis has been defined by the WHO as a BMD lower than -2.5 SD below the mean peak BMD in young healthy adults of the same gender, also known and expressed as the T score. This T score definition of osteoporosis (T less than or equal to -2.5) is operational and is the basis of our daily practice in the field of bone diseases.

Thus, to use T-scores appropriately, physicians must understand their disadvantages and shortcomings:

- a) The amount of bone is measured by dual energy X-ray absorptiometry using two-dimensional projection, and BMD is expressed in g/cm^2 , whereas density is expressed in cm^3 .

- b) The bone mass and density measurements do not measure the qualitative parameters of bone, and thus do not reflect all components that contribute to bone strength.
- c) As a consequence, more than half of patients who experience fragility fracture have a T-score above -2.5 ; this is related to the low sensitivity of BMD, and to the association between BMD and risk, which is continuous and does not have a biological threshold. This threshold has been defined on an epidemiologic basis, not on a bone strength estimation (that could be done nowadays by finite element analysis in each individual)
- d) Moreover, T-score calculation was proposed in order to clarify the characteristics of subjects included in clinical studies. Thus the choice of thresholds is arbitrary. The threshold of -2.5 SD below the mean BMD (at the femoral neck) in young subjects produces a 17% prevalence of osteoporosis among women aged 50 years and older, which is similar to the 15% lifetime risk of hip fracture for 50-year-old white women in the USA. Osteopenia has been defined as a T score between -1 and -2.5 , but there is no rationale for the threshold of -1 . The term osteopenia was created to allow comparisons among clinical and epidemiological studies. Osteopenia is not a disease and there is little evidence that it is a risk factor for osteoporosis (i.e., T-scores below -2.5). Osteopenia is frequently seen in patients with fractures (see below). Obviously the threshold for therapeutic decision making is different from the threshold for defining osteoporosis.
- e) The T-score is independent of age, as it refers to PBM, but the interpretation of the T-score for fracture risk is age dependent: for the same T-score, the fracture risk is higher in elderly women than in women in the early postmenopausal phase.
- f) The interpretation of T-scores is not intuitive: a woman with a T-score of -3 has a fracture risk twice that of woman with a T-score of -2 and four times that of a woman with a T-score of -1 , but it does not indicate her absolute risk.
- g) Falls (number, direction of falling, etc.) are of course key determinant of fracture, and independent of BMD.

Thus, the aetiology of osteoporotic fragility fracture is multifactorial and includes bone and fall related risk factors. A low BMD is a strong determinant of risk, but is not present in all patients. Those with prevalent fractures have the highest risk for future fracture.

Large-scale prospective population studies have enabled the identification of risk factors for fractures that are independent of low BMD and the quantification of their relative risks (RR) for predicting fractures. However, RRs are difficult to apply in daily clinical practice as their clinical significance depends on the prevalence of fractures in the general population. From this, and the observation that BMD measurements are not indicated

as a screening tool for the entire population (because of its low sensitivity), the concept of the absolute risk (AR) of fracture has emerged and refers to the individual's risk for fractures over a certain period of time in the context of a more global evaluation of fracture risk. One way of doing this is to use the FRAX case finding algorithm, which will be discussed in section 4 below.

Thus, the diagnosis of osteoporosis can be made on the basis of:

- T score below -2.5 ,
- and/or presence of non-trauma fractures (hip, vertebral...),
- and/or an elevated risk of fracture calculated in AR (such as with the FRAX tool).

Then a decision about treatment can be made, also based on the clinician's judgement concerning the individual risk for the patient, and the benefit of the treatment.

2.2 Postmenopausal osteoporosis

Oestrogen deficiency has been associated with osteoporosis since first suggested by Fuller Albright in the 1940s. It is the main cause of bone loss in women after menopause. Premature menopause—natural or surgically induced—extends the period during which a woman is exposed to a hypogonadal state, thus increasing the total duration of bone loss occurring after menopause.

Oestrogen deficiency is associated with an increase in the activation frequency of bone turnover, resulting in bone loss and structural decay (Rachner *et al*, 2011*). The production of cytokines (IL-1, IL-6 and TNF α) is up-regulated, which, in turn, increases the lifespan and production of osteoclasts. The balance between RANKL and OPG is changed: RANKL is up-regulated, while OPG is down-regulated. Of note, the elevation of FSH linked to oestrogen deficiency may have a direct role in bone loss.

Deeper erosion of bone results in severe loss of trabecular elements, making these trabecular elements less well connected and weaker. On the other hand, loss of oestrogen shortens the lifespan of osteoblasts and osteocytes. This results in the accumulation of apoptotic osteocytes within bone, which may increase bone fragility because of impaired detection of microdamage and suboptimal repair of bone, and may decrease the degree of bone mineralisation. Increased activation frequency has been found until 15 years after the menopause. In many elderly subjects, however, bone turnover, especially bone formation, is low.

2.3 Secondary osteoporosis

The term 'secondary osteoporosis' refers to bone loss, low BMD and increased fracture risk induced by diseases and some medications (table 1). Many patients referred for DXA have known risk factors. However, in the clinical context of DXA referrals, >30% of apparently healthy women with osteoporosis on DXA have

previously unknown secondary osteoporosis. The prevalence of secondary osteoporosis is even more frequent in patients with a recent clinical fracture.

Therefore, screening for secondary causes is indicated in all patients with osteoporosis and in patients with a recent clinical fracture. This includes a thorough history and physical examination and laboratory screening including as a minimum:

- serum calcium, phosphate and albumin: high calcium levels can be found in patients with malignancy and in patients with primary hyperparathyroidism; low calcium levels can be found in patients with osteomalacia.
- alkaline phosphatase: high levels can be found in patients with malignancy, Paget's disease and severe osteomalacia. Hypophosphatasia is very rare but is a contra-indication to anti-resorptive drugs.
- thyroid-stimulating hormone (TSH): hyperthyroidism can be asymptomatic.
- 25-hydroxyvitamin D: to screen for vitamin D insufficiency or deficiency.
- full blood count, erythrocyte sedimentation rate (ESR), and immunoelectrophoresis in case of possible multiple myeloma.
- kidney function must be assessed before prescribing anti-osteoporotic drugs.

Upon indication, other laboratory measurements can be performed, for example:

- PTH
- testosterone levels (in younger men with low bone density)
- tissue transglutaminase antibodies (coeliac disease).
- Serum tryptase (mastocytosis)
- Serum iron, ferritin (haemochromatosis)

Furthermore, X-rays of the spine are indicated when vertebral fractures are suspected (height loss, back pain, etc.). MRI, X-rays and bone scintigraphy are needed when bone metastases are suspected.

In rare situations with severe osteoporosis in individuals younger than 50 but without aetiology after screening, a transiliac bone biopsy for histomorphometric analysis may be performed.

Table 1 Some causes of secondary osteoporosis

Endocrine	Thyrotoxicosis
	Hyperparathyroidism (frequent)
	Cushing's syndrome
	Insulin-dependent diabetes mellitus
	Acromegaly
Hypogonadal	Anorexia nervosa
	Hyperprolactinaemia
	Hypogonadism (Turner and Klinefelter syndrome)
	Bilateral oophorectomy or orchidectomy
Drugs	Glucocorticoids (frequent)
	Aromatase inhibitors, GnRH agonists
	Antidepressants (selective serotonin recapture inhibitors)
	Antiepileptic drugs
	Proton pump inhibitors
Haematological disorders/malignancy	Multiple myeloma (frequent)
	Mastocytosis
	Haemophilia
	Thalassaemia
Nutritional and gastrointestinal disorders	Inflammatory bowel disease (frequent)
	Malabsorption syndromes (coeliac disease)
	Malnutrition
	Gastrectomy
Neurological disorders	Parkinson's disease
	Stroke
	Muscular dystrophy
Other disorders	Rheumatoid arthritis (frequent)
	Ankylosing spondylitis (frequent)
	Chronic obstructive lung disease (frequent)
	Systemic lupus erythematosus
	Chronic renal failure (frequent)
	Immobilisation
	Sarcoidosis
	Amyloidosis
	Haemochromatosis
	Pregnancy-associated osteoporosis
	Organ transplantation

2.4 GC-induced osteoporosis

GC-induced osteoporosis (GIOP) is the most common type of iatrogenic osteoporosis, and a frequent cause of secondary osteoporosis. Approximately 1:200 (0.5%) of the population may be exposed to GCs for a period of at least 3 months. Observational data suggest that 30% of individuals taking long-term GCs for more than 3 years will have evidence of osteoporotic fractures.

From epidemiological studies there is evidence that the increased risk of osteoporotic fractures is:

- proportional to the cumulative GC dose; the risk increases after 3 months of therapy associated with
- increased bone loss, most pronounced in the first year and
- likely to be associated with even low doses of GCs.

Yet few patients taking GCs are evaluated for their skeletal health or receive specific preventive or therapeutic agents.

The pathogenesis of GIOP is a result of several mechanisms. This issue is discussed in depth elsewhere in this module.

2.5 Osteoporosis in inflammatory systemic disorders

There is an increased risk of osteoporosis in patients with RA as well as other rheumatic conditions such as ankylosing spondylitis (AS) and systemic lupus erythematosus (SLE) (see the in-depth discussion on RA and AS elsewhere in this module). Disease activity, immobility and treatment are factors that increase the risk of osteoporosis and fractures, in addition to the background fracture risk. Bone resorption is increased by inflammation and involves many cytokines, such as TNF α and interleukins, RANKL/OPG and Dkk1.

The risk of osteoporotic fractures or low BMD is increased in some SLE patients, since several risk factors may accumulate in these individuals: the use of GCs, female gender, vitamin D deficiency due to sunshine avoidance, chronic kidney disease, amenorrhoea and immobility. Obviously, the use of GCs is one of the most important causes of osteoporosis in patients with SLE. In several cross-sectional studies, it has been found that trabecular and cortical BMD were lower in SLE patients than in healthy controls. In a study from a reference centre in Amsterdam, vertebral deformities were found in 20% of patients, which is remarkable given that the mean age of the patients was only 41 years. It cannot be excluded that, with increased life expectancy for SLE patients treated with GC, combined with other immunosuppressive drugs, the incidence of osteoporotic fractures will increase in (elderly) patients with SLE.

The situation in patients with other systemic inflammatory diseases, such as vasculitis and specifically giant cell arteritis which concerns elderly, is analogous to that in SLE patients. There is no data on fracture incidence,

and BMD may be decreased in particular in GC-treated patients. Since bone loss is highest early in the disease, probably related to a high initial dose of GCs and high initial inflammatory activity, screening for osteoporosis in these patients is mandatory so that anti-osteoporotic drugs can be prescribed early, if appropriate.

2.6 Osteoporosis in men

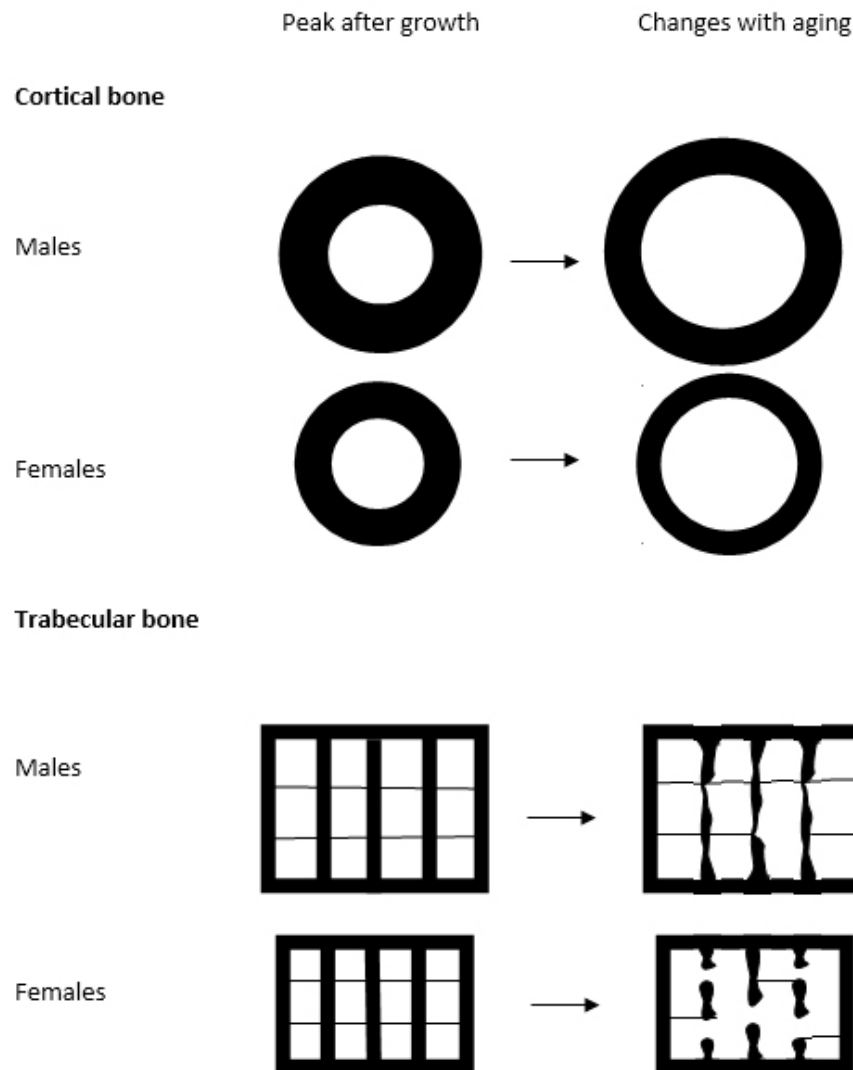
Fractures are more prevalent in men than in women from childhood to middle life, probably because of a higher incidence of trauma. After 40 years of age, fractures are less common in men than in women, but the incidence of fracture as a result of mild trauma increases with aging. The lifetime risk of fracture in men older than 50 years is estimated to be 20%. Fracture risk in men increases from 50 years onwards for vertebral fractures and from 65 years onwards for hip fractures. A key issue is that mortality rates after hip fracture are higher in men than in women, and are related to pre-fracture health status (comorbidities) and post-fracture complications. The prevalence of fractures is lower in men than in women. After the age of 50 years, the incidence of vertebral fractures is about one third to one half of that in women. When assessing the prevalence of vertebral fractures in men, the consequences of trauma at younger ages must be kept in mind.

As in women, osteoporosis in men can result from an inadequate peak bone mass and/or accelerated bone loss. Men build up bigger bones than women, this larger bone size being responsible for the higher bone strength. During aging, bone size may increase in men more than in women by periosteal apposition, increasing even further the gender difference in bone size established during growth (figure 7). Cortical bone loss is less in men because endocortical resorption and cortical porosity are lower. Trabecular bone loss is similar, but trabecular architectural disruption is less in men than in women. Specifically, in aging men, the trabeculae are thinner, whereas they are perforated in postmenopausal women. These structural differences are presumably not captured by measuring BMD, as the absolute risk for fractures appears to be no different between men and women of the same age and BMD, so that the diagnostic threshold for osteoporosis in women can be used in men.

Unlike women, men have no midlife drop in sex hormone production and, thus, no midlife increase in remodelling rate. The andropause occurs at a later age than the menopause in women and only in a subpopulation of men. Aging in men is accompanied by a progressive, but individually variable decline in serum testosterone production: more than 20% of healthy men over 60 years of age present serum levels below the range for young men. Albeit the clinical picture of aging in men is reminiscent of that of hypogonadism in young men and decreased testosterone production appears to play a role in some of these clinical changes in at least some elderly men, the prevalence of androgen deficiency and its association with structural abnormalities is not unequivocally established. In fact, minimal androgen requirements for elderly men remain poorly defined and are likely to vary between individuals. Consequently, borderline androgen deficiency cannot be reliably diagnosed in the elderly.

Hypogonadism is a risk factor for osteoporosis in women. However, as mentioned above, the definition, prevalence, causes and structural consequence on bone of late onset hypogonadism in men are inadequately defined.

Figure 7 Summary of growth and age-related changes in axial and appendicular skeletal mass, size and density in men and women.



In contrast to women, in whom postmenopausal and age-associated osteoporosis is the most frequent cause of fractures, many men with osteoporosis have other causes than hypogonadism and old age: use of GCs, alcohol abuse, current smoking, etc. Contributors to secondary osteoporosis are documented in up to 50% of all cases. A specific problem of secondary osteoporosis in men involves men treated for prostate cancer, in whom androgen ablation therapy results in accelerated bone loss. Idiopathic osteoporosis, defined as osteoporosis that occurs without any known cause of osteoporosis, has been described in men under the age of 70 years. Its prevalence, cause and natural course remain unclear, although the role of inadequate peak bone mass with smaller bones linked to delayed puberty, along with changes in IGF-1 effect have been suspected.

In contrast to the data available in women, there is a lack of data based on randomised placebo-controlled trials of anti-osteoporotic treatments using vertebral, hip or other non-vertebral fractures as an endpoint in men. An increase in BMD and a reduction in vertebral fracture risk has been reported in men with osteoporosis treated with bisphosphonates. PTH therapy in men causes BMD effects similar to those observed in postmenopausal women.

Only a few hundred elderly men have received androgen therapy in the setting of a randomised controlled study, and many of these men were not androgen deficient. The most consistent effects of androgen replacement treatment have been on body composition, but to date there is no evidence-based documentation of clinical benefits of androgen administration to elderly men with normal or moderately low serum testosterone in terms of diminished morbidity or of improved survival or quality of life (QoL). Until the long-term risk–benefit ratio for androgen administration to elderly men is established in adequately powered trials of longer duration, androgen administration to elderly men should be reserved for the minority of elderly men who have both clear clinical symptoms of hypogonadism and frankly low serum testosterone levels.

2.7 Osteoporosis in children and adolescents

Disorders of bone fragility associated with increased fracture risk in children can be divided into primary osteoporosis (osteogenesis imperfecta (OI), idiopathic juvenile osteoporosis (IJO) and osteoporosis pseudoglioma syndrome), where the defect is intrinsic to the bone tissue itself, and secondary osteoporosis (immobilisation-induced disease, inflammatory (rheumatic) diseases and the use of GCs, for example), where the defect arises in a tissue other than bone and adversely affects the skeleton.

In OI, 90% of cases have mutations in one of the two genes encoding type I collagen (COL1A1, COL1A2). The severity ranges from very mild to fatal. Affected individuals experience recurrent fractures resulting in bone pain, deformity and impaired function. The incidence is reported to be approximately 1 in 15 000–20 000. Detection of mild cases in otherwise unaffected families centres on the finding of additional clinical features such as ligamentous laxity, dentinogenesis imperfecta, delayed walking and blue sclerae. These features can also be sought in family members, along with hearing loss and heart valve prolapse. More severely affected children, in particular those with dentinogenesis imperfecta, are at risk of basilar invagination and hydrocephalus. Multiple crush fractures predispose to scoliosis, particularly in early childhood and at puberty. The diagnosis can be confirmed by the finding of a mutation in the type I collagen genes in approximately 90% of cases. Heterozygous mutations in LRP5 have been described in a few cases of juvenile osteoporosis, as well as in children with recurrent fractures and low bone mass. Homozygous mutations in LRP5 result in osteoporosis pseudoglioma syndrome, a severe bone disorder with additional eye defects.

3 Osteoporotic fractures

3.1 Fracture epidemiology

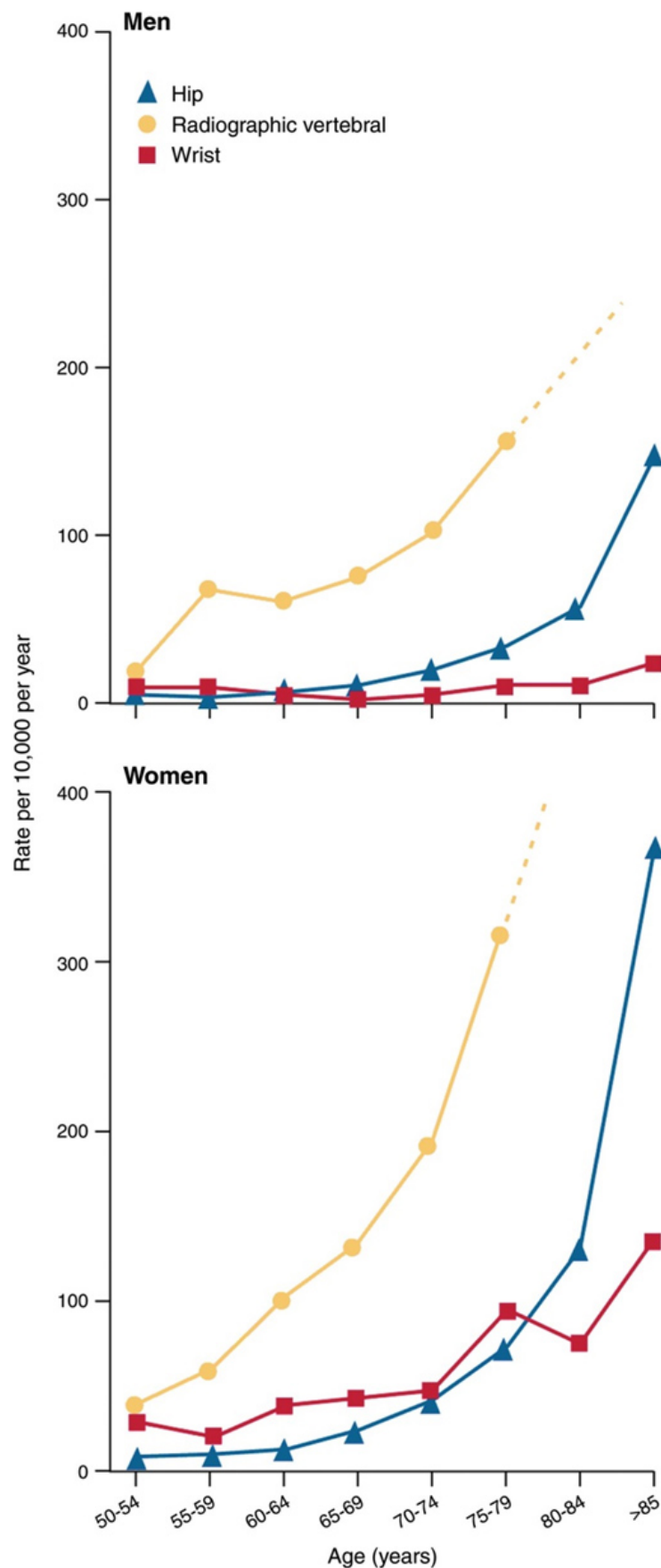
Osteoporosis is a significant health issue because of the fragility fractures and their association with increased mortality and morbidity. That also result in a considerable global economic burden. Osteoporotic fractures predominantly occur in the elderly, and life expectancy is increasing worldwide. The proportion of frail elderly persons at high risk of falls and fractures is expected to rise dramatically in the next decades; in some countries, the number of centenarians is increasing sharply. This has profound implications for societies and individuals who expect to reach old age in good health.

Even if age-adjusted incidence rates for hip fracture tend to decrease slightly in some countries (Western Europe, North America), the estimated number of hip fractures worldwide will rise from 1.7 million in 1990 to 6.3 million in 2050 (Svedbom *et al*, 2013*), due to the increase in the number of elderly at risk. Fractures of the hip, vertebrae and wrist have long been regarded as the typical osteoporotic fractures (table 2). However, the effect of osteoporosis on the skeleton is systemic, and prospective studies have shown that there is an increased risk of almost all types of fractures in individuals with low bone density. Moreover, adults who sustain a fracture are at substantially greater risk of having a subsequent fracture. The RR for a subsequent non-vertebral fracture is doubled after a non-vertebral fracture. After a vertebral fracture, the risk for another vertebral fracture is quadrupled, and the risk for a non-vertebral fracture is doubled. The incidence of vertebral fractures is much higher than that of wrist or hip fractures (figure 8). Some public health problems such as diabetes and obesity are risk factors for various fractures (without decreased BMD), and attention must be paid to the effects of these current epidemics on the epidemiology of fragility fractures.

Table 2 Estimated risks of fractures at various ages. (Reproduced with permission from Van Staa et al, Bone 2001;29:517–22)

	Current age (years)	Any fractures (%)	Radius/ulna (%)	Femur/hip (%)	Vertebral (%)
<i>Lifetime risk</i>					
Women	50	53.2	16.6	11.4	3.1
	60	45.5	14.0	11.6	2.9
	70	36.9	10.4	12.1	2.6
	80	28.6	6.9	12.3	1.9
Men	50	20.7	2.9	3.1	1.2
	60	14.7	2.0	3.1	1.1
	70	11.4	1.4	3.3	1.0
	80	9.6	1.1	3.7	0.8
<i>10-Year risk</i>					
Women	50	9.8	3.2	0.3	0.3
	60	13.3	4.9	1.1	0.6
	70	17.0	5.6	3.4	1.3
	80	21.7	5.5	8.7	1.6
Men	50	7.1	1.1	0.2	0.3
	60	5.7	0.9	0.4	0.3
	70	6.2	0.9	1.4	0.5
	80	8.0	0.9	2.9	0.7

Figure 8 Incidence of osteoporotic hip, vertebral and wrist fractures. (Modified from Van Staa et al, *Bone* 2001;29:517–22, including data from the European Prospective Osteoporosis Study (EPOS) Group, *J Bone Miner Res* 2002;17:716–24.)



3.1.1 Hip fracture

Hip fracture is the most serious consequence of osteoporosis in terms of disability (functional competence and physical functioning markedly diminish after a hip fracture), mortality (20–30% in the first year after fracture), and use of hospital and institutional care (Bliuc et al, 2009*) (box 2). The incidence rises from 1/1000 person-years at age 50–60 years to 30/1000 person-years at the age of 80 in women (0.5/1000 to 19/1000 person-years, respectively, in men). In Westernised countries, data suggest a decrease in the age- and sex-adjusted ratio of hip fracture, but absolute numbers are still increasing because life-expectancy is increasing.

Box 2 Consequences of hip fractures in women

- 20–30% of excess mortality within 1 year
- 20% severely impaired mobility after 1 year, requiring long-term nursing care
- 50% do not regain previous mobility

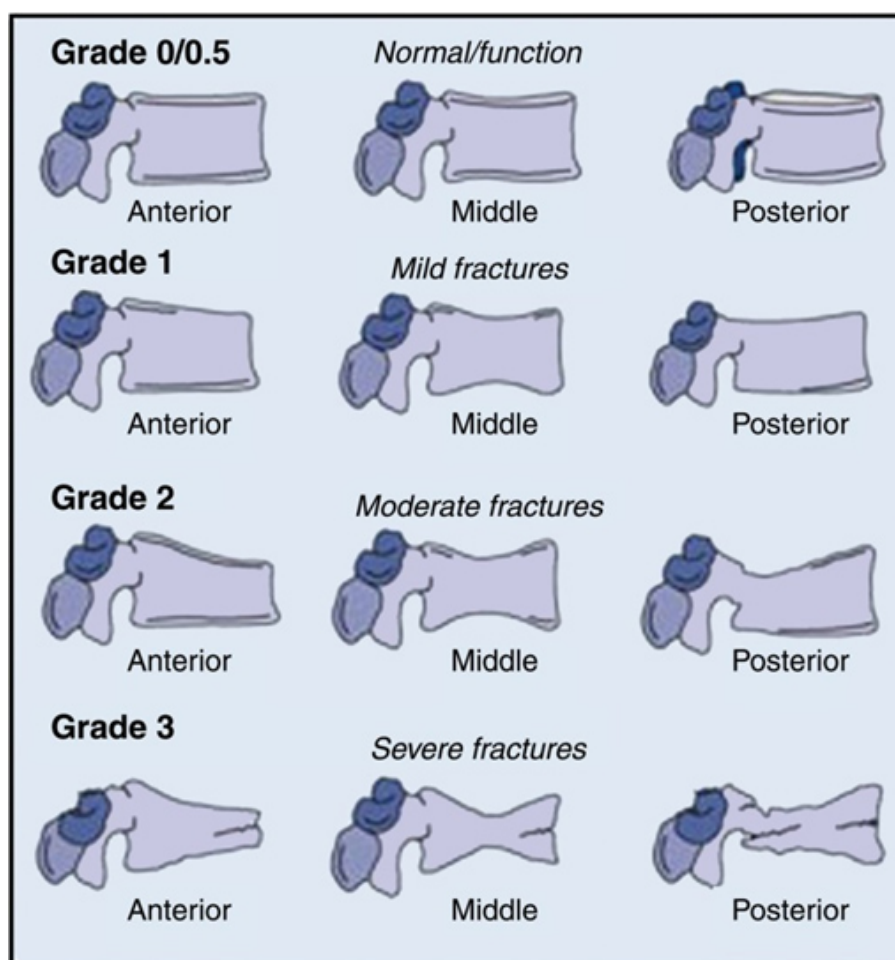
There is a substantial variation in hip fracture rates between populations. In general, people who live farther from the equator seem to have a higher incidence of fracture. The highest rates are seen in Caucasians living in northern Europe, especially in Scandinavian countries. The rates are intermediate in oriental populations and lowest in black populations. The lower incidence rates in the developing countries can be partially explained by lower life expectancy, but probably also by genetic factors associated with bones of higher quality. A hip fracture usually results from the co-occurrence of several risk factors: low bone mass, low bone quality, elevated fall risk, co-morbidity and high age. Data suggest seasonality in these fractures, which occur more frequently in spring, maybe because of reduced concentrations of vitamin D or increased physical activity after the winter. At least half of the hip fractures happen at home or in an institutional setting. Falls are involved in 80–90% of hip fractures; the others are the primary event, related to bone fragility, with fall thereafter.

3.1.2 Vertebral fracture

Vertebral fracture is the hallmark of osteoporosis, but its characteristics impede an accurate assessment of their epidemiology.

- A vertebral fracture is not always a binary phenomenon (fracture yes/no, as for a femoral fracture), but can be of graded severity. This grading is relevant in clinical practice (see below) and was quantified by Harry Genant in 1993 (figure 9). Mild, moderate and severe fractures are those with a decrease of 20–25%, 25–40%, and more than 40%, respectively, of one vertebral body height (either anterior or middle). The classification is based on visual estimation of the decrease, as compared to the expected height, the posterior height of the vertebra (if it is not deformed) or the adjacent vertebrae. This assessment is easy, reproducible and relevant for an appropriate assessment of osteoporosis.

Figure 9 Semiquantitative grading scale for vertebral fractures. (Reproduced with permission from Genant et al, J Bone Miner Res 1993;8:1137–48.)



In contrast, morphometric techniques, which use points positioned on the vertebral bodies for direct measurements of heights, must be avoided in clinical practice as they provide a lot of false positive and false negative results, related to the other causes of vertebral deformities.

- A vertebral fracture can occur without trauma or fall: 40% are related to falls but this proportion is lower in women aged 80 years and more. Vertebral fractures usually occur during daily activities such as lifting, climbing stairs or bending forwards. Neurological involvement after an osteoporotic vertebral fracture is very rare and must lead to a complete investigation for other causes of vertebral fractures (malignancy, etc.).
- A vertebral fracture can be responsible for acute back pain, but symptoms may be mild, and these fractures considered to be 'asymptomatic'. Actually it is estimated that only one third of vertebral fractures come to clinical attention at the time they occur. Loss of height is one of the characteristic of these fractures (figure 10) (Briot et al, 2010).
- Vertebral fractures are overlooked in radiographs. Lack of radiographic detection, and the use of ambiguous terminology (such as 'vertebral deformities') are the two main determinants for failing to

diagnose vertebral fracture. Fractures have to be differentiated from other conditions such as Scheuermann's disease, remodelling and deformities in osteoarthritis, and normal variations in vertebral body height (box 3).

Figure 10 Simple clinical investigation.



Box 3 Why vertebral fractures are often not recognised

- Diagnosing vertebral fractures is more difficult than non-vertebral fractures
- Vertebral fractures are often overlooked on radiographs
- The diagnosis of a vertebral fracture can be over-ruled by another diagnosis
- Missing the clinical relevance of diagnosing vertebral fractures

The prevalence of radiological findings increases with age. The rates vary between populations, with a demonstrated threefold variation across Europe and up to twofold variation within European countries in the European Vertebral Osteoporosis Study (EVOS). Geographical variation in the prevalence and incidence of vertebral fractures seems to be substantially less than that of hip fracture. The age-adjusted and sex-adjusted incidence rates for vertebral deformity are 1% per year among women and 0.6% per year among men from the European Prospective Osteoporosis Study. Similar figures have been found in the USA. The age-standardised population prevalence of vertebral fractures across Europe is 12.2% for men and 12.0% for women aged 50–79 years. In studies where radiographs are performed at baseline and then repeated during follow-up, the incidence of all vertebral deformities has been estimated to be three times that of hip fracture. In Europe, at age 75–79 years, the incidence of vertebral fractures defined in this way is 13.6 per 1000 person-years for men and 29.3 per 1000 person-years for women. This compares with 0.2 per 1000 person-years for men and 9.8 per 1000 person-years in 75–84-year-olds where the fractures were defined by clinical presentation in an earlier study from Rochester, Minnesota. The overall age-standardised incidence in EVOS was 5.7 per 1000 person-years in men and 10.7 per 1000 person-years in women.

Among postmenopausal women referred for BMD measurements, who have risk factors for osteoporosis but T scores above -2.5 , 20% have actually prevalent vertebral fractures. This proportion is higher when assessed at the time of a non-vertebral fracture, particularly in elderly women with a recent hip fracture.

Vertebral fracture assessment (VFA) is a densitometric technique which can be performed easily and quickly at the same time as a BMD measurement. It is important to notice that radiation exposure associated with image acquisition is dramatically lower than that for standard X-rays ($3\text{--}40\ \mu\text{Sv}$ vs $600\ \mu\text{Sv}$). Moreover, standard X-rays are obtained using cone beam X-rays which create parallax distortion within vertebrae located above and below the central point of the beam; VFA uses fan-beam technology and avoids this problem. However, the images obtained with standard spine radiography are less noisy, have a higher spatial resolution, and the legibility of the vertebrae of the upper thoracic spine is better with spine radiography.

3.1.3 Non-hip-non-vertebral fractures

Non-hip-non-vertebral fractures are the most frequent osteoporotic fractures; they carry an increased risk for subsequent fractures. The non-hip-non-vertebral fracture/hip fracture ratio is 20 in women aged 50–60 and 1.5 in the elderly. These fractures must not be neglected, because an opportunity to improve care of osteoporosis is missed.

Wrist fractures have a different pattern of occurrence from hip and vertebral fractures: there is a steep rise in incidence during the early postmenopausal period among women, but a plateau thereafter. In men, there is no apparent increase in the incidence of wrist fracture with age. The plateau may be due to the mode of falls: later in life, a woman is more likely to fall onto her hip than onto an outstretched hand as her neuromuscular co-ordination deteriorates.

The incidence rates of proximal humeral, pelvic and proximal tibial fractures rise steeply with age, and are higher in women than in men.

3.2 Consequences of fractures

Clinical features resulting from osteoporotic fractures include increased risk for new fractures (even within the short term), morbidity (pain, decreased QoL, physical impairment) and excess of mortality, especially after some fractures (table 3).

Fractures of long bones commonly result in acute pain with one or more clinical signs of fracture (swelling, haematoma, deformation, local crepitations, and localised pain on pressure) and are easily confirmed radiographically. Some fractures, such as stress fractures, are more difficult to diagnose, as local clinical signs can be confounded by arthritis or tendinitis, and other imaging techniques may be needed to identify them,

such as MRI and bone scintigraphy. The outcome is dependent on the fracture location, the presence of bone- and fall-related risks, and general health status and co-morbidities before and after the fracture.

Table 3 Clinical features of fractures (functional repercussions: +, yes; –, no)

	Hip	Vertebral clinical	Vertebral radiographic	Wrist
Excess mortality	++	+	+	–
Increased fracture risk	+	+	+	+
Pain				
Acute	+	+	+ or –	+
Chronic	–	+	+ or –	+
Functional decline				
Short-term	+++	+	+	+
Long-term	++	+	+	+
Psychosocial decline	++	+	+	–
Quality of life	+++	++	+	+

3.2.1 Fractures and the risk for subsequent fractures

Epidemiological studies show consistently that patients with different types of fragility fractures are at increased risk of developing subsequent fractures (Van Geel *et al*, 2009*). A previous vertebral fracture carries a 7–10-fold increased risk of subsequent vertebral fractures, a similar order of magnitude to the increased risk associated with sustaining a second hip fracture after a first. Data from Rochester, Minnesota suggest that the risk of a hip fracture is increased 1.4-fold in women and 2.7-fold in men after a distal forearm fracture. The corresponding figures for subsequent vertebral fracture are 5.2 and 10.7. The EVOS study demonstrates that a prevalent vertebral deformity predicts incident hip fracture with a rate ratio of 2.8–4.5. The Dubbo Osteoporosis Epidemiology Study in Australia demonstrated similarly increased rates of refracture in men and women over a 10-year period.

The risk of subsequent fracture is characterised by a time effect and a dose effect:

- *Time effect*: within a cohort of 4140 postmenopausal women in the Netherlands, 54% had refractured within 5 years and 23% had refractured within 1 year of an initial fracture. After the initial fracture, the RR of subsequent fracture declined with time: thus the RR of subsequent fracture in the first year after the initial fracture was 5.3, within 2–5 years it was 2.8, within 6–10 years it was 1.4, and it then dropped to 0.41 for more than 10 years after the initial fracture. Some 20% of postmenopausal women sustain an incident fracture in the year following a vertebral fracture. The risk of hip fracture (adjusted for age and BMD) decreases from 2 at 5 years to 1.4 at 10 years after a vertebral fracture.

Thus, subsequent fractures cluster in time after the first fracture. That means that there is a window of opportunity for treatment in the months immediately following an osteoporotic fracture.

- *Dose effect*: this has been shown consistently for vertebral fractures: the more the number of prevalent vertebral fractures, and the more severe they are, the higher is the risk of incident vertebral and non-vertebral fractures. Even the grade 1 fractures are associated with an increased short-term risk of vertebral fractures (not non-vertebral) in elderly women with low BMD.

3.2.2 Morbidity of osteoporotic fractures

Hip fractures are the most serious consequences of osteoporosis in terms of disability, use of hospital and institutional care, and mortality. They represent 20% of all use of orthopaedic beds in Western countries. At 1 year post fracture, more than 40% of patients cannot walk independently, and more than 50% cannot perform all activities of daily independent living. Age is a major factor here: the proportion of patients being discharged to nursing care is dramatically high in the elderly.

In clinically diagnosed *vertebral fractures*, pain onset varies from gradual to sudden and its intensity from minimal to severe lancing back pain. Pain worsens with movement, coughing or sneezing and is often not relieved by rest. However, pain is sometimes diffuse and not localised to the fractured vertebra. This acute, severe pain episode gradually subsides within 2–6 weeks. Chronic back pain can last for many years. Clinical and radiological vertebral fractures are associated with pain and also with hyperkyphosis, loss of spinal mobility, decline in function, mobility and muscle strength, and an increased risk of falls, bone loss, fractures and loss of independence. Hyperkyphosis results in the typical clinical presentation of a ‘dowager’s hump’. It is a risk factor for falls and subsequent fractures (Roux *et al*, 2010*).

Hyperkyphosis and height loss reduce the distance between the iliac crest and the ribs, resulting in problems with digestion and a protruding abdomen. Functional spine restrictions are associated with difficulty in dressing, fixing hair, standing, lying down, moving in bed, doing housework, walking, climbing stairs, washing, bathing, using the toilet and getting down to the floor, decreases in general health status measures, activities of daily living, balance capability, functional reach, mobility skills, 6-min walk and muscle strength, and a higher level of need for assistance. Lung function progressively decreases with increasing number of vertebral fractures and the degree of kyphosis, probably as a result of increased abdominal pressure.

The presence and number of vertebral fractures are associated with a decrease in QoL and its subdomains (pain, physical function, general health and physical mobility). Lumbar vertebral fractures lead to greater impairment of physical function than thoracic vertebral fractures. Psychosocial outcome is less well documented as many studies did not include a control group. Depression, which is a common mental health

problem in older people, is more frequent in women with osteoporosis and is related to the number and severity of vertebral fractures.

Much less emphasis has been placed on the consequences of *non-vertebral-non-hip* fractures, although their aggregate burden is substantial. Roughly 35% of all healthcare expenditure attributable to osteoporotic fractures in the USA are accounted for by these fractures. They result in more outpatient services than hip fractures. Decrease in QoL has been reported in patients with such fractures. Because they occur more frequently and in younger individuals than hip fractures, patients with these fractures can experience the harmful effects of their fracture for many years.

3.2.3 Mortality following osteoporotic fractures

Increased mortality after some osteoporotic fractures is well recognised, particularly for hip and vertebral fractures, and there is accumulating evidence of increased mortality risk following other types of osteoporotic fracture (mainly humerus and pelvis). Deaths are directly related to hip fracture in 24% of cases, and 28% of deaths among patients hospitalised for vertebral fractures are presumably attributable to the fracture itself. Comorbidities increasingly contribute to mortality as subjects become older and frailer (Bliuc *et al*, 2009*; Roux *et al*, 2012*).

For *hip fracture*, mortality is highest in the first year, and remains elevated in subsequent years. The age- and sex-specific standardised mortality ratios (in Dubbo, Australia) are increased and are 2.43 and 3.51 in women and men, respectively, with hip fracture. A meta-analysis provided data from 22 cohorts in women and 17 cohorts in men, and showed that the relative hazard for all-cause mortality was 5.75 in women and 7.95 in men in the first 3 months after hip fracture, and then decreased but did not return to the expected rates in age- and sex-matched controls. White women having a hip fracture at age 80 years have excess annual mortality compared to controls of 10% within 2 years after the fracture. Importantly, short-term mortality is also increased after a hip fracture in subjects aged less than 80 years.

Both prevalent and incident *vertebral fractures* predict increased mortality, even if the fractures are subclinical, that is they are diagnosed only by imaging. Physical frailty and pulmonary complications are associated with this excess mortality.

Finally, some *non-vertebral-non-hip fractures* (humerus, pelvis, but also lower extremity of the femur and higher extremity of the tibia) are responsible for a fracture–mortality association. A key observation is that refractures contribute substantially to overall mortality.

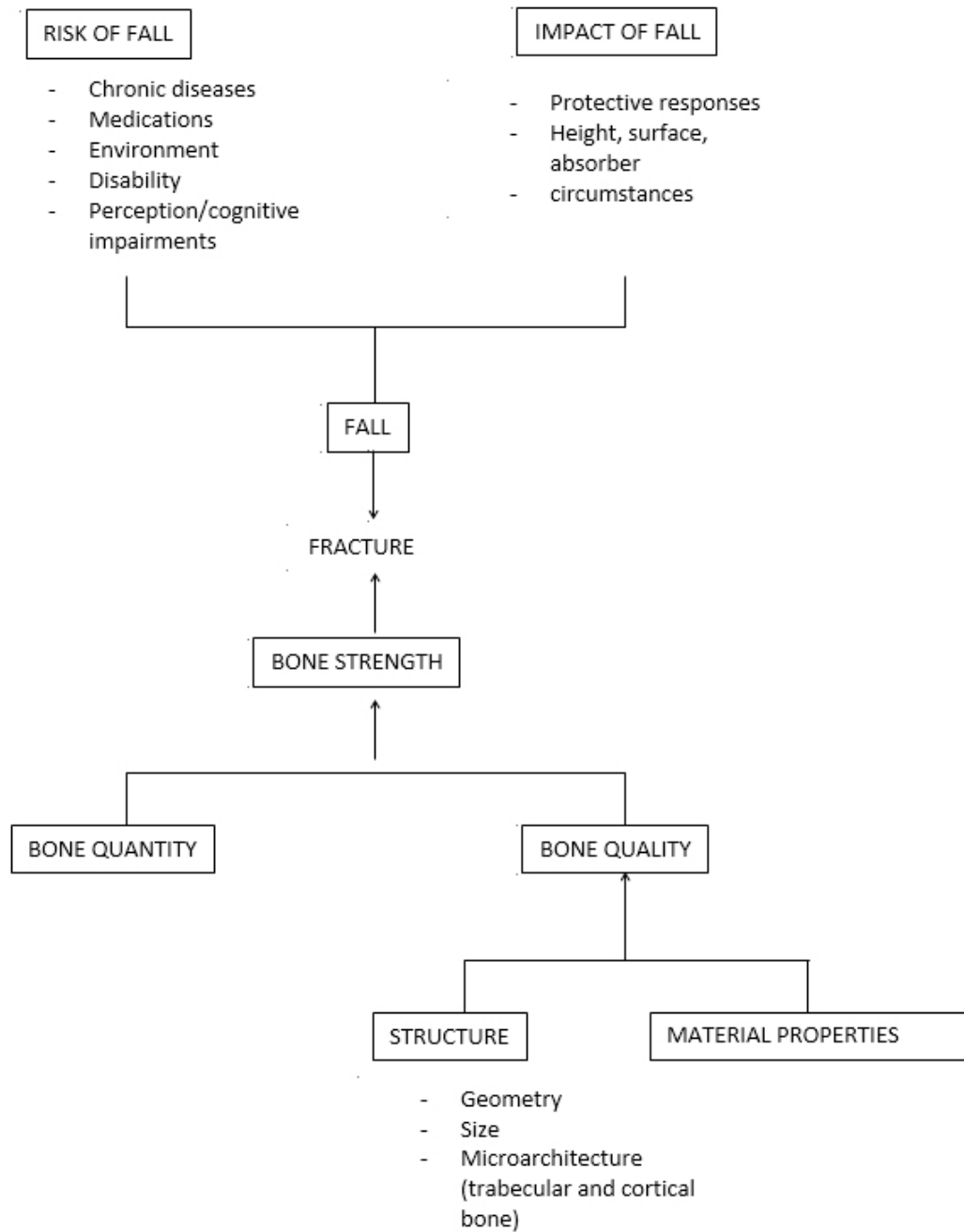
3.2.4 Few therapeutic consequences: the treatment gap

Despite this increased mortality and morbidity after osteoporotic fracture, most patients with fracture - especially severe fractures - do not receive adequate therapy thereafter. It has been shown as soon as the end of 1990s that, even after marketing of several effective therapies for osteoporosis, most patients who have sustained an osteoporotic fracture (forearm fracture, vertebral fracture and even hip fracture) did not receive adequate secondary prevention for future fractures, whereas the risk of repeated fractures is markedly increased, including that of vertebral and second hip fracture. Despite increased attention to this issue, the situation has not improved. In fact, over the past 10 years, the proportion of patients with fracture correctly treated has halved. Now, it is probably not higher than 20-25%.

4 Assessment of fracture risk

The aetiology of osteoporotic fragility fractures is multifactorial and includes bone- and fall-related risk factors, many of which are readily clinically recognisable before a fracture has occurred (figure 11) (Bours *et al*, 2011*). This is best illustrated in studies of risk factors for hip fracture that have shown that low BMD and fall risks are independent risk factors for hip fractures. Compared to controls, patients presenting with a clinical vertebral or non-vertebral fracture had a threefold higher risk for having BMD osteoporosis and a fourfold higher risk for having had a fall, and half of the patients with a recent fracture had both bone- and fall-related risks.

A large number of studies demonstrated that age, low BMD and prevalent fracture are the three main risk factors for sustaining a fracture. RR are difficult to apply in daily clinical practice as their clinical significance depends on the prevalence of fractures in the general population. From this observation and for the purpose of clinical application, the concept of the absolute risk of fracture has emerged and refers to the individual's risk for fractures over a certain time period, for example, over the next 5 or 10 years, a period in which data suggest that anti-osteoporotic treatments are effective.

Figure 11 Risk factors for fractures.

4.1 Bone-related risk factors

4.1.1 Previous fracture

Prevalent fracture is (with age) the most important risk factor for subsequent fracture. Hip and non-vertebral-non-hip fractures are easily diagnosed in contrast to vertebral fracture. Thus, assessment of decreased height, back pain and hyperkyphosis are key for indication of X-rays of the spine, or, if available, a vertebral fracture assessment (VFA) VFA using the low-radiation technology of DXA. In a study of postmenopausal women presenting with a non-vertebral fracture, one out of four had a prevalent vertebral fracture on VFA that was

not recognised previously. This situation of ignored vertebral fractures is an issue in RA, and in patients receiving long-term GCs.

Thus, use of VFA should be encouraged in patients at high risk of having vertebral fractures.

4.1.2 BMD measurements

The limitation of a whole population screening with DXA is its low sensitivity. Moreover, the use of clinical risk factors to trigger a BMD test improves the estimation of fracture risk given by the BMD alone and can guide clinicians and patients in understanding the risk of an osteoporosis-related fracture; it can also inform decisions aimed at mitigating these risks (e.g., initiation of bisphosphonates treatment)

4.1.3 FRAX tool

Several clinical factors are associated with a fracture risk that is greater than what can be accounted for by bone mineral density alone. Fracture risk assessment, therefore, should employ specific risk factors in addition to bone mineral density. On the basis of a series of meta-analyses undertaken to identify clinical risk factors for osteoporosis, the Fracture Risk Assessment Tool (FRAX) was developed and released in 2008. This tool integrates the weight of relevant (and easily assessable) risk factors, with or without BMD, to calculate the individual 10-year probability of major osteoporotic fractures (clinical spine, hip, forearm and humerus) (Kanis *et al*, 2011*). The tool has been constructed using data from nine population-based cohorts (60 000 women and men) around the world, and the mortality data of each country. The variables are:

- gender
- age
- body mass index
- a previous fragility fracture
- parental history of hip fracture
- current tobacco smoking
- ever long-term use of oral GCs
- RA
- other causes of secondary osteoporosis
- alcohol consumption of 3 or more units daily.

Based on the FRAX calculation, the 10-year absolute risk of an individual is calculated. The next question is: when is this risk unacceptably high? Most guidelines consider that the intervention threshold varies by age, from roughly 10% at the age of 50–60 years to 30% at the age of 80–90 years for the risk of a major osteoporotic fracture. This may seem counterintuitive, but is in accordance with the spontaneous increase in

fracture risk with age. USA guidelines use a fixed threshold of $\geq 20\%$ for major osteoporotic fractures based on cost effectiveness criteria.

For example, an 80-year-old woman weighing 50 kg and 165 cm tall with a previous fracture, a mother with a hip fracture, and being prescribed prednisone 15 mg/day for RA, is at particularly high risk for fracture: her 10-year risk of hip fracture is 26% and 28% for a major fracture according to the FRAX algorithm. In contrast, a 55-year-old woman weighing 70 kg and 165 cm tall, without any of the above clinical bone-related risks, is at very low risk of having fractures: her 10-year risk of hip fracture is 0.24% and 2.2% for a major fracture according to the FRAX algorithm. The FRAX-generated risk can be modified in the light of daily steroid dose.

There are several important limitations that need to be considered when FRAX is used as a calculation tool. Other important risk factors for fractures are not included in this calculation tool. These include the serum level of 25-hydroxyvitamin D, physical activity level, risk of falls, number of fractures, cumulative dose and duration of glucocorticoids. Therefore, the calculated risk may be less than the actual risk, which has been shown in several cohort studies. In addition, FRAX does not take into account bone mineral density at the spine or the substantially higher risk of spine fracture among those with a history of vertebral fractures.

4.1.4 Evaluation of bone quality

Given the limitations of the measurement of areal BMD several non-invasive imaging techniques have been developed to overcome this difficulty. They are based on the assessment of bone microarchitecture. While some techniques, e.g., peripheral high resolution peripheral quantitative tomography (HRpQCT), are still research tools, another - the trabecular bone score (TBS) starts to be employed in some areas. This is a texture analysis based on the differences in the levels of grey visible on the image of the lumbar spine by DXA. Recently, this technique has been proposed to adjust the FRAX score.

4.1.5 Synthesis

The optimal strategy must be based on the assessment of risk factors and the prediction of the risk of fracture in the subsequent years (and not a theoretical lifetime risk). This is easy in some situations (elderly woman with very low BMD (T score of -3 or below), and/or prevalent hip or vertebral fracture. Otherwise, the FRAX tool (www.shef.ac.uk/FRAX) can be used. Of note, the calculation on this website must be country-specific, given the variations in epidemiology of fracture across countries.

4.1.5 Bone turnover markers

Markers of bone turnover have been extensively used in clinical research. They reflect the dynamic process of bone metabolism. In untreated subjects, increased markers of bone resorption have been associated with the risk of vertebral and non-vertebral fractures, independently of BMD in population studies. However, their use

in predicting fracture risk in specific patients has not been defined clearly as a result of wide intra-individual variation. Potential uses of bone markers include early prediction of changes in BMD during treatment, monitoring of drug efficacy, and selection of patients for treatment. They have no use in the diagnosis of osteoporosis or prediction of BMD and fracture prediction, but they can have a role in monitoring adherence to therapy.

4.2 Fall-related risk factors

For any given bone density, the risk of fracture is greater in the elderly. The increased frequency of falling, the type of fall that occurs among the elderly, and the loss of protective soft tissue may all explain the larger contribution of age and the less important role of bone mass in the elderly. Among postmenopausal women in the United States, the frequency of at least one annual fall rises from about one in five at 60 to 64 years of age to one in three at 80 to 84 years of age. Propensity for falling has been assessed in several studies with parameters such as gait speed, inability to rise from a chair without using one's arms, and of course, visual impairment. These parameters are associated with a risk of falling. The increase in falling is nevertheless not sufficient to account for the increasing incidence of fractures because only 5% to 6% of falls result in a fracture (1% of hip fractures and 4%–5% for other fractures). Fracture risk is also related to the seriousness of the trauma on the femur and the direction of the fall. Indeed, the risk of hip fracture is 13 times higher when the impact is delivered directly over the hip. A great amount of force can be dissipated by the thickness of soft tissue over the femur, and patients with low fat mass may be at higher risk of hip fracture.

Evaluation of the risk of falls can be time consuming (balance and muscle force tests) but can also be easy: a history of falls and ability to rise from a chair without using one's arms can be assessed in daily practice. A strong risk factor for falls is a fall in the past 6 months. Importantly, this assessment is relevant as it has been shown in a meta-analysis that specific fall-related interventions result in a reduced fracture risk (table 4).

Sarcopenia is considered as a reduction in muscle mass and muscle strength due to age. It is mainly a condition of the elderly, but may also be encountered in people with cachexia, cancer, inflammatory diseases and malnutrition. Muscle weakness is one of the causes of falls, so it also determines part of the risk of fracture. Bone and muscle are also tightly associated, because they both develop from the somatic mesoderm and changes in muscle and bone mass are generally correlated. Bone and muscle mass are influenced by the genetic background, sex steroids, various growth factors and mechanical forces. Both muscle and bone mass may be synchronized, under predominantly muscle influence. The communication between the two tissues probably relies on various paracrine/endocrine factors such as the myokines, which secretion may be triggered by mechanical signals.

Table 4 Risk factors for falling in the elderly

	General problem	Specific problem
Intrinsic factors	General deterioration associated with ageing	Poor postural control, defective proprioception, reduced walking speed, weakness of lower limbs, slow reaction time, various comorbidities
	Balance, gait or mobility problems	Joint disease, cerebrovascular disease, peripheral neuropathy, Parkinson's disease, alcohol, vitamin D deficiency
	Visual impairment	Impaired visual acuity, cataracts, glaucoma, retinal degeneration
	Impaired cognition or depression	Alzheimer's disease, cerebrovascular disease
	Blackouts	Hypoglycaemia, postural hypotension, cardiac arrhythmia, transient ischaemic attack, acute onset cerebrovascular accident, epilepsy, drop attacks
Extrinsic factors	Personal hazards	Inappropriate footwear, clothing
	Multiple drug therapy	Sedatives, hypotensive drugs, glucocorticoids
Environmental factors	Indoor/home hazards	Bad lighting, steep stairs and lack of grab rails, slippery floors and loose rugs, tripping over pets and toys, etc.
	Outdoor hazards	Uneven surfaces, lack of safety equipment, bad weather, traffic and public transportation

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SUMMARY POINTS

- In elderly postmenopausal women, bone resorption and subsequent bone formation are upregulated.
- Low bone mineral density is an important predictor of future fractures, but only a surrogate for bone strength; bone strength is an umbrella term that covers the structural properties of bone, its material properties and bone turnover.
- New data have provided insight into the role of osteocytes in mechanotransduction, and the role of the Wnt signalling pathway in the formation of new bone.
- In patients with rheumatoid arthritis, the RANKL/OPG ratio is upregulated and is related to both local and generalised bone loss.
- Inhibition of bone formation plays a central role in the pathogenesis of glucocorticoid-induced osteoporosis.
- Case finding of postmenopausal women at highest risk for fractures includes the identification of clinical bone and fall-related risk factors and bone densitometry.
- The FRAX algorithm for case finding is available on the web for calculating the 10-year fracture risk in women and men.
- Recognising vertebral fractures remains a challenge, as two out of three do not present with the clinical signs and symptoms of an acute fracture, and requires special attention for other clinical signs and meticulous observation of vertebral shapes on X-rays or DXA-generated lateral images of the spine.

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Osteoporosis : Pathogenesis and Clinical features

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A previous version was co-authored by Karine Briot, Christian Roux, Cyrus Cooper

IN-DEPTH DISCUSSION I

Glucocorticoid-Induced Osteoporosis (GIO)

Introduction

Glucocorticoid (GC) therapy has a strong anti-inflammatory effect, but its long-term use may also lead to side effects: osteoporosis and associated fractures, particularly of the spine and hip, are among the most devastating (1,2). Glucocorticoid-induced osteoporosis (GIO) is the most common cause of secondary osteoporosis and the leading iatrogenic cause of the disease. It is estimated that 0.5% of the adult population chronically uses GC, and that this percentage may even be higher in the elderly, up to 4.6% among postmenopausal women (3). The main causes of GCs use are inflammatory rheumatic disorders (rheumatoid arthritis, polymyalgia rheumatica...) and lung disorders (asthma and chronic obstructive lung diseases). A key point is that the underlying inflammation for which GCs are used has also a role in bone fragility, as there is a strong relationship between inflammatory cells and bone cells. This is one of the determinants of the rapid bone loss occurring at the initiation of GCs.

Pathogenesis

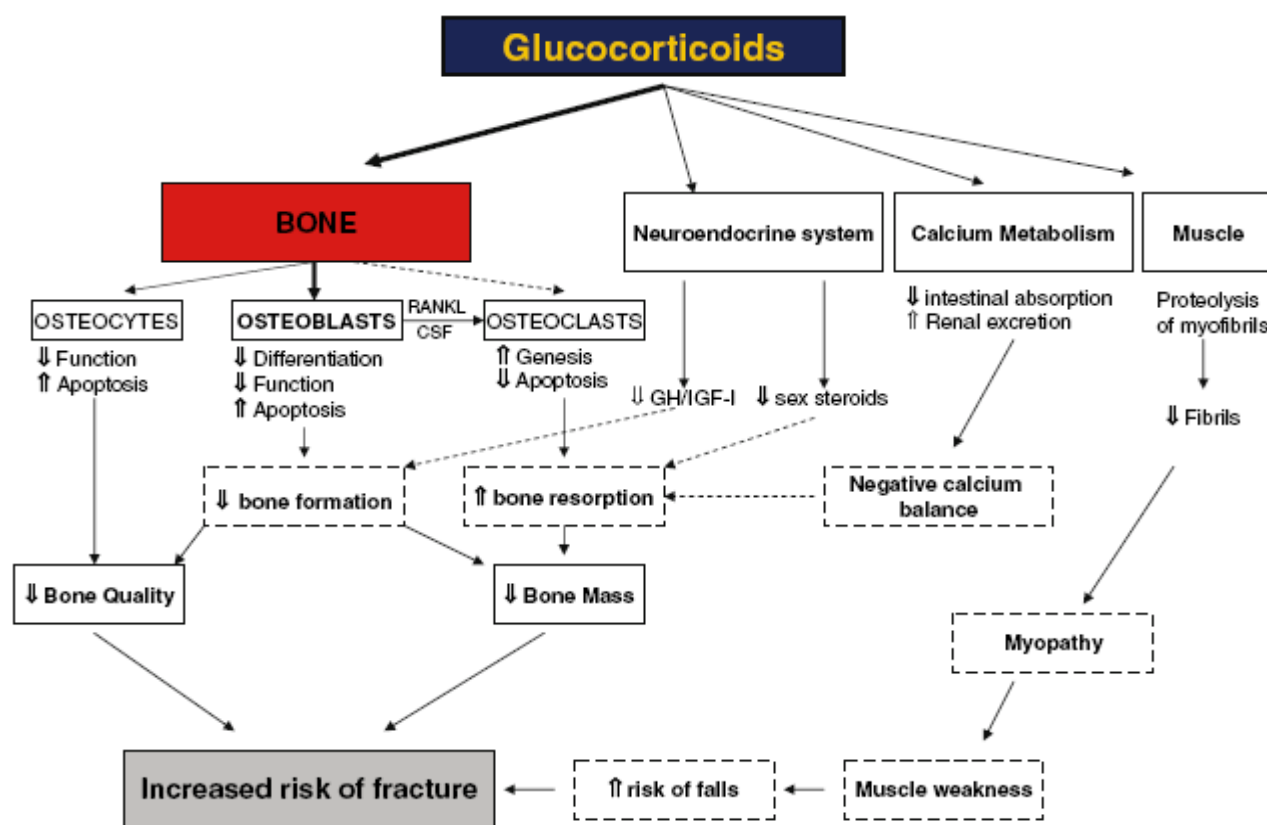
The bone fragility in GIOP is characterized by 2 key points: the early and rapid bone loss at the introduction of the GCs, and the discrepancy between an often unaltered bone mineral density and the risk of fracture. These 2 points can be explained by the pathogenesis of GIOP. While in healthy women bone formation and bone resorption are coupled under normal physiological circumstances, and are upregulated in postmenopausal osteoporotic women, these processes are uncoupled during GC-treatment (4). Bone formation is inhibited during the use of GC, while bone resorption is elevated or unchanged. However, interpretation of bone remodelling in patients receiving GCs should consider the bone effect of inflammation related to the underlying disease. Therefore, studies on the effect of GC on healthy volunteers, without the effects of the underlying disease, are of great interest. In a study in young healthy male volunteers, prednisone (10 mg per day for 1 week), decreased serum osteocalcin (a marker of bone formation) by 22% (6), while no changes were found in pyridinoline and deoxypyridinoline (both markers of bone resorption). A profound decrease of markers of bone formation has been shown also in healthy postmenopausal women receiving 5mg per day of prednisone. GCs have direct and indirect effects on bone turnover (Figure 1). The most consistent skeletal effects of glucocorticoids are to inhibit osteocytes and osteoblasts function. Several mechanisms are involved: decrease in the production of bone anabolic factors (IGF1, TGF β), interference with the Wnt signalling pathway with upregulation of Wnt inhibitors such as Dickkopf-1 and sclerostin. In addition, GCs stimulate apoptosis of osteoblasts and osteocytes: the increased apoptosis of osteoblasts has a negative effect on bone formation, while the increased apoptosis of osteocytes has a strong negative effect on bone strength. GCs have also the potency to stimulate the differentiation of mesenchymal stem cells into the adipocyte pathway, at the expense of differentiation into osteoblasts. Effects on osteoclasts are controversial; GCs upregulate the ratio RANKL/OPG and may increase osteoclastogenesis, as a direct consequence of suppressed osteoblast

differentiation (4). Importantly, glucocorticoid-induced increased collagenolysis by osteoclasts allows continued contact of osteoclasts with mineral, thereby maintaining resorption uninterrupted. As a result, glucocorticoids change the osteoclastic resorption mode from intermittent to continuous, leading to trench-like excavations, rather than the usual round-shaped resorption pits (6). This phenomenon - by impairing quickly the mechanical properties of bone - may explain the rapid rise in fracture risk, despite limited reduction in BMD.

GCs have also a direct catabolic effect on muscle mass and muscle force. The incidence of muscle weakness and myopathy can reach as high as 50% of patients receiving long term GCs and may increase the risk of falls and fractures. Schematically, the complex pathogenesis of GIOP is shown in figure 1.

There is a huge variability of side effects of GCs among individuals including for bone loss, for largely unknown reasons. Attention has been paid to the 11β -hydroxysteroid dehydrogenase (11β -HSD) system, which is a prereceptor modulator of GC action. This system catalyses the interconversion of active/inactive cortisone, and the 11β -HSD1 enzyme amplifies GC signalling in osteoblasts. Interestingly, 11β -HSD, widely expressed in GCs target tissues including bone can be modulated and amplified by pro inflammatory cytokines (7), age, and GC administration itself, suggesting that the mechanism could be a key regulator of GCs effects on bone. Individual GC sensitivity can also be regulated by polymorphisms in the GC receptor gene

Figure 1. Pathogenesis of GIOP, Canalis et al, Osteoporosis Int. 2007 (5).



Epidemiology and risk factors

The use of GCs has not only a devastating effect on bone mass and bone strength, but also on fracture risk. Fracture risk is increased within the first 3–6 months after starting glucocorticoids, the greatest risk being for vertebral fracture. Following withdrawal of glucocorticoid therapy, fracture risk decreases, with the improvement in BMD. A residual risk remains, related to the underlying disorder for which GCs are prescribed. Several large case–control studies have shown strong associations between exposure to glucocorticoids and the risk of fractures. In the largest study, that included >250.000 GC-users and the same number of age-matched controls, the risk of hip and vertebral fractures was elevated in patients treated with high dosages of prednisone, but also in those treated with daily dosages between 2,5 and 7,5 mg per day (8). The risk of hip fractures was doubled, and of vertebral fractures was increased by 2 to 4. GIO mostly affects trabecular bone of vertebrae. In postmenopausal women receiving long term GCs, systematic spine radiographs showed the presence of asymptomatic vertebral fractures in 37% of patients (9). Assessment of vertebral fractures is highly recommended in the management of patients with GCs, considering that these fractures can be asymptomatic because of analgesic effect of GCs.

There is some evidence that high doses of inhaled glucocorticoids may be associated with reduced BMD and a small increase in fracture risk; increased fracture risk has also been reported with intermittent oral glucocorticoid therapy.

Many risk factors are associated with GIO: age, menopause, previous fracture, low body mass index, high GC dose (high current or cumulative dose), underlying disease (rheumatoid arthritis).

Risk fracture assessment in patients receiving glucocorticoid therapy

Fracture risk assessment is recommended for patients starting and/or receiving GCs for at least 3 months. It includes:

- Clinical history with details of co-morbidities, GC use (previous or ongoing, dose, duration and route of administration), fracture history (type and trauma), alcohol intake, smoking, family history of osteoporosis and hip fracture, risk of fall.
- GCs are one of the risk factors in FRAX. However, FRAX underestimates the effect of GCs on the fracture risk because GC use is a yes-or-no question which does not consider the dose and the duration of GCs. The WHO proposed an upward adjustment of risk for patients on 7.5 mg per day of prednisone or more.
- Measurement of the patient's height; height loss suggests the possibility of prevalent vertebral fractures

- There is a mismatch between BMD data and fracture data in patients receiving GCs because of the disparity related to the alteration of bone quality. At similar levels of BMD post-menopausal women taking GCs have considerably higher risks of fracture than controls non-users of GCs (10). Measurement of BMD by DXA at the spine and hip are insufficient to predict the risk of fracture (10). However, the incidence of fractures is higher in patients having $T < -2.5$ and beginning GCs and in patients starting the treatment without osteoporosis. A practical approach is to recommend a BMD measurement in GCs users (optimally at the initiation of treatment) and to consider that patients with $T \leq -2.5$ as those who should receive the highest priority for treatment. But beyond the BMD, a more comprehensive approach of the risk is necessary and clinical judgment remains needed. Lateral imaging DXA with vertebral fracture assessment (VFA) for the detection of existing vertebral fractures; if this is not available, lateral X-rays of the thoracic and lumbar spine should be considered in patients with back pain and/or height loss.
- Laboratory testing should be performed to exclude causes of secondary osteoporosis other than GC use including assessment of vitamin D status and renal function.
- Since bone turnover after long-term glucocorticoid therapy is low, tests bone remodelling markers are not helpful in GIO.

Strategies of prevention and treatments of GIO

1. General measures

General measures are recommended for all patients starting or receiving GCs for at least 3 months. Life-style measures are important, which include adequate levels of dietary proteins and calcium intake and vitamin D supplementation, maintenance of a normal body weight. Tobacco use and alcohol abuse should be avoided. The risk of falling should be assessed in particular in elderly patients, patients with painful joints of the lower limbs, patients with massive doses of GCs... Physical activity or mobilization should be considered, adapted to the underlying condition. Use of alternative immunosuppressive agents enable to reduce the dose of GCs should be considered and alternative routes of administration (e.g. topical, inhaled) or formulations should be preferred. Because glucocorticoid therapy is associated with reduced intestinal and renal calcium absorption and increased urinary calcium excretion, increasing calcium intake seems a logical approach. It is suggested that the total daily intake of calcium should be above 1000 mg. The Cochrane review of these RCTs concluded that sufficient calcium and vitamin D supplements are a prerequisite in patients using GC. Adequate vitamin D levels are not only important for adequate bone mineralization, but also for an optimal neuro-muscular function, as muscles have also vitamin D receptors and low vitamin D levels are associated with an increased the risk of fall. Based on elevated levels of PTH and markers of bone resorption in patients with serum 25 OHD levels up to 50 nmol/L, the cut-off value of adequate serum vitamin D levels is nowadays considered at least 50 nmol/L, but probably should achieve 75 nmol/L in the context of optimal muscle function.

2. Pharmacological interventions

Although several interventions have been evaluated in the management of GIO, the strength of evidence for their efficacy is weaker than that for postmenopausal osteoporosis, since fracture reduction has not been a primary end-point of any study. Bisphosphonates (alendronate, risedronate, zoledronic acid) are considered the first-line treatment option for most glucocorticoid-treated patients at increased risk of fractures (11, 12, 13). However, the anti-resorptive mechanism of bisphosphonates does not address the major pathophysiological mechanisms of impaired bone formation during chronic glucocorticoid treatment. PTH, administered intermittently has effects on bone formation opposite to those of glucocorticoids and therefore is conceptually a more attractive approach. In a 18-month RCT, Saag et al compared the anabolic agent teriparatide with alendronate in 428 women and men with osteoporosis, who received GCs (>5mg per day) for at least three months (14). The increase of lumbar spine BMD was significantly higher in teriparatide group than in alendronate group (7,2% versus 3,4%), with a significant decrease of new vertebral fractures in the teriparatide group (0,6% vs 6.1% in the alendronate group, $p=0.004$). Results were confirmed at 36 months (15). There is no evidence of a positive effect of bisphosphonates and teriparatide on the risk of non-vertebral fractures.

3. Indications of anti-osteoporotic treatments

Because rapid bone loss and increased fracture risk occur soon after the initiation of GCs, anti-osteoporotic treatments should be started at the onset of GCs therapy in individuals at high risk of fracture. Several recommendations elaborated by various international societies, based on the presence of low trauma fracture, age, daily dose of GCs, and the T score have been proposed. The American College of Rheumatology (ACR) last updated their guidelines in 2017 using an approach based on the FRAX calculation of the fracture risk (16). The European Calcified Tissue Society (ECTS), in collaboration with the International Osteoporosis Foundation (IOF), has also published GIOP guidelines (17)

In postmenopausal women and men aged above 50 years, anti-osteoporotic treatments are indicated in case of (one condition required): previous low trauma fracture, age ≥ 70 years, high doses of GCs (≥ 7.5 mg prednisone equivalent) and low T score (17).

Premenopausal women and men aged 50 years or less have a lower risk of fractures than older individuals. Data on the effect of pharmacological treatments are sparse. Anti-osteoporotic treatments can be recommended in patients with a previous low trauma fracture. In the other situations, treatment decisions are based on clinical judgment (17). Bisphosphonates should be used cautiously in premenopausal women, as they cross the placenta and women of childbearing potential should be under appropriate contraception before introducing bisphosphonates

4. Insufficiency of management

Although both effective drugs and several guidelines for prevention of GIOP are available, epidemiological data have shown that adequate prophylaxis is improving over the years. Yet, these drugs are prescribed only in roughly 50% of the GC-treated patients (18). Although an increase in adherence of patients to therapy, which is prescribed for prevention (of fractures) is difficult to achieve, amongst others because anti-osteoporotic drugs are prescribed for prevention (of fractures), this certainly is a challenge for the coming years.

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module

EULAR on-line course on Rheumatic Diseases

Osteoporosis : Pathogenesis and Clinical features

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IN-DEPTH DISCUSSION II

Osteoporosis in inflammatory joint disorders

Introduction

Bone tissue is a target of inflammatory diseases, and bone loss is a complication of persistent inflammation. This chapter focuses on two inflammatory joint diseases: rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Osteoporosis is common in these two inflammatory joint diseases due to the relationships between inflammation, immune system and bone remodelling (1).

Rheumatoid arthritis

Bone complications are the main extra-articular complications of the disease and are described as three different forms: periarticular bone loss (adjacent to the swelling joints), bone erosions, and systemic osteoporosis.

Fracture risk and risk factors

RA is one of the items of the FRAX® to estimate the 10-year risk of fracture in the general population, and the item is stated separately to corticosteroid and other secondary osteoporosis. RA doubles the risk of hip and vertebral fractures, regardless of the use of corticosteroids (2). Vertebral fractures may not come to clinical attention in RA because of analgesics use for painful joints (3). Thus, vertebral fracture assessment (VFA technology on dual X-ray absorptiometry (DXA) devices) should be used in these patients at the time of BMD measurement. Patients with RA are at high risk of osteoporosis and fractures because they have several well-known risk factors: menopause, low BMI, reduced physical activity, and corticosteroid therapy, but inflammatory disease activity may be the most important factor associated with bone loss in RA. Several studies have shown that disability is a risk factor for fractures in RA. The link between orthopaedic surgery and the incidence of fractures in RA has been reported and fall rates in RA patients are higher than in the general population (4, 5). Fall rates in RA patients is higher than in the general population. Falling risk is related to stiff and painful joints, muscle weakness, low postural stability, and reduced physical performance. Accumulated disease activity and inflammation negatively affect lean mass, and sarcopenia/rheumatoid cachexia is a component of the muscle weakness (6). Progressive resistance training programs can be used to prevent part of muscle weakness in RA.

Bone density in RA

Osteoporosis is common in RA, and is obviously one of the determinants of the risk of fractures (7). However, the relationship between decreased BMD and fracture is less clear in RA than in post-menopausal osteoporosis. In RA patients followed prospectively in the 1990s, including patients without corticosteroids, a decrease in spine and hip BMD was reported suggesting that disease activity is the main determinant of BMD decrease, and that suppression of disease activity may prevent the bone loss. Management of RA has changed

over the last years and the objective of the treatments is now the remission of the disease; prevention of bone loss is therefore expected. Observational studies showed that a better control of inflammation corrects the uncoupling of bone resorption (increase in bone resorption and decrease in bone formation) that is observed in RA (8). TNF α blockers are able to arrest BMD loss, supporting a parallel between inflammation control and bone loss arrest in RA (9,10). This arrest of bone loss on TNF blockers is likely to be mediated by a return to a normal bone coupling (11).

Treatment of osteoporosis in RA

As most patients with RA are receiving glucocorticoids, guidelines on the prevention and treatment of glucocorticoid-induced osteoporosis must be applied, including by using bisphosphonates or teriparatide as appropriate. Underlying conditions as menopausal status, level of physical activity, and risk of falls must be assessed for an appropriate prevention of fractures in RA. The different families of biologic therapies can prevent structural damage and also have beneficial effects on bone loss by curbing inflammation and restoring normal bone turnover (12). However, there is no evidence of an antifracture efficacy of these treatments (13). Suppression of inflammation is also the objective for optimal prevention of osteoporosis. Denosumab, that inhibits RANK-L, has been used in patients with RA in several studies. There was no clinical benefit on arthritis, but a reduction of bone damage, a sustained decrease in markers of bone turnover and a 2–4% increase in BMD over 1 year (14).

Ankylosing spondylitis (AS)

Although bone formation is to be the cornerstone of the disease, AS is also associated with a systemic osteoporosis. This osteoporosis cannot be related to the underlying characteristics of the patients like in RA, as AS is typically a disease of young men and glucocorticoids are not used in AS. Patients with AS have an increased risk of osteoporosis which can be observed in the early stages of the disease suggesting that it is not only related to spinal immobilisation observed in advanced cases (15).

Fracture risk in AS

Patients with AS have an increased risk of vertebral fracture, but not of non-vertebral fractures, except in one study (16-17). Vertebral fractures are less frequent than in RA but may lead to major neurological complications, a specific observation in AS. The prevalence of vertebral fractures in AS is very different among studies, and this illustrates the large heterogeneity of the studied populations and the difficulty of diagnosis of these fractures in AS. Spine fractures in AS can be transdiscal, i.e., between two vertebral bodies, in ankylosed spine; although they can occur after a low trauma and reflect bone fragility related to spine stiffness and decreased BMD, they should not be counted among vertebral bodies fractures. Erosions can occur in AS, at the anterior corners of the vertebral bodies, related to the adjacent enthesitis, leading to vertebral deformities,

wedging of vertebrae, and hyperkyphosis in some patients. These deformities, leading to wedging of the vertebral bodies, should not be considered for the estimation of osteoporotic VF prevalence. Using visual or morphometric definitions, prevalence of VFs is 10–30% (18-20). In a retrospective population-based study on clinical fractures, the odds ratio (OR) for clinical vertebral fractures was reported to be 7.7 (4.3–12.6) and even higher in men (18). Patients with vertebral fractures have lower BMD than patients without, and femoral neck is the best discriminant site. However, low BMD is not sufficient for the prediction of fracture in this population. Bone remodelling markers assessment is not indicated for evaluation of fracture risk in SpA.

Risk factors of clinical vertebral fracture in patients with AS are the presence of inflammatory bowel disease (associated with corticosteroid use), subclinical malabsorption, and systemic inflammation. A decreased risk of fracture has been reported in patients with AS taking non-steroidal anti-inflammatory drugs (NSAIDs). Whether the effect is due to a direct bone metabolic effect of NSAIDs or an indirect one through a better physical activity is unknown.

Bone density in AS

Osteoporosis has been reported as an early event in AS. Prevalence of osteoporosis according to bone mineral density (BMD) measurements is 14–27% and 4–14% at the spine and hip, respectively, which is unexpectedly high in these patients aged on average 30-40 years. In a cohort of young patients with early inflammatory back pain suggestive of spondyloarthropathies (disease duration of symptoms 1.6 years), 13% of patients had a low BMD (Z score ≤ -2). The main determinants of low BMD were bone and systemic inflammation as assessed by MRI and biological parameters (23). Presence of bone marrow oedema (BMO) lesions on MRI increases 5-fold the risk of having a low spine BMD and presence of BMO lesions on spine MRI was the single determinant of low hip BMD, suggesting a systemic effect of inflammation. Osteoporosis can occur because of reduced physical activity, decreased spine mobility related to pain, stiffness and ankylosis, and/or subclinical gut involvement. Genetic factors have been suspected, and vitamin D receptor gene may contribute to BMD differences in patients with AS; these polymorphisms are also linked to inflammatory activity. Prospective studies in patients with AS suggest that a decrease in BMD is observed mainly in patients with permanently increased CRP (24-25). In patients receiving anti-TNF therapy, there is an increase in BMD, and a decrease in resorption markers (serum CTX-1). The HLA B27 transgenic rat, a relevant model of AS exhibit decreased bone strength, and increased RANK L/OPG ratio, suggesting the implication of this system in the systemic bone loss (26).

Treatment of osteoporosis in AS

No specific clinical trial has been conducted in this population. In a post-hoc analysis of the ASSERT trial, however, the use of infliximab was associated with restored bone coupling and improved BMD (27). In patients without indication for anti-TNF therapy, current guidelines for treatment of male osteoporosis and

premenopausal women must be applied. In patients with anti TNF therapy and low BMD, it seems logical to assess the benefit given by this treatment before introducing an anti-osteoporotic drug (27-28).

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Osteoporosis: Treatment

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LEARNING OBJECTIVES

- Manage calcium and vitamin D deficiency
- Evaluate the difference between the diagnosis threshold and the therapeutic threshold in osteoporosis
- Critically assess the efficacy of treatments according to their effect on vertebral and/or non vertebral fractures
- Educate patients on persistence and side-effects of treatments

1 General considerations

Provided that the diagnosis of osteoporosis has been properly made and secondary forms of osteoporosis excluded, the treatment of osteoporosis includes non-pharmacological interventions and the use of anti-osteoporotic drugs with proven antifracture efficacy. The general management of osteoporosis includes the elimination of preventable risk factors for osteoporosis and osteoporotic fractures. There are numerous risk factors for osteoporosis and osteoporotic fractures, but only a few can be targeted by interventions (table 1).

Table 1 Preventable risk factors associated with osteoporosis and fragility fractures

Evidence of intervention efficacy	Low evidence of intervention efficacy
<ul style="list-style-type: none"> • Vitamin D insufficiency • Low calcium intake • High risk for falling 	<ul style="list-style-type: none"> • Low body weight or body mass index • Smoking • Alcohol intake

The aim of osteoporosis treatment is the prevention of fragility fractures. A pharmacological intervention is justified when the benefits (decreased fracture risk) outweigh both the side effects and the economic costs of the treatment (i.e., the so-called treatment threshold). Any non-pharmacological intervention for risk factors for osteoporotic fractures (table 1) has negligible costs, might be associated with general health benefits and may be implemented by community interventions (eg, recommending giving up smoking, or increase calcium intake).

2 Non-pharmacological management of osteoporosis

Non-pharmacological interventions are useful for patients with osteoporosis. Also the recommendations discussed below may be applicable for patients with low bone mineral density (BMD) with the aim of avoiding the occurrence of osteoporosis.

2.1 Physical activity

Immobilisation and bed rest quickly lead to muscle weakness and bone loss. For this reason, immobility should be avoided whenever possible. Young individuals practicing weight-bearing sports activities have higher bone mass than controls, particularly at the most stressed skeletal sites, but the effect of physical exercise in postmenopausal women is more controversial as the amount of weight-bearing exercise that is optimal for skeletal health in patients with osteoporosis is unknown. Despite these uncertainties, exercise is an integral component of osteoporosis management because it helps to increase muscle strength and to improve confidence and coordination, thus preventing falls. Mechanical loading also induces new bone formation by preventing the expression of sclerostin, a negative regulator of bone formation produced by osteocytes. Thus, despite a low level of evidence, exercise such as walking, weight bearing, aerobics and resistance exercises

were reported to have an effect on BMD and muscle strength and should be encouraged in osteoporosis management (Howe *et al*, 2011).

2.2 Prevention of falls

The prevention of falls is of crucial importance in the very elderly and the strategies targeted to decrease the most common risk factors for falling (box 1) are recommended. Currently, there is no study showing that it is possible to decrease the incidence of fractures through a fall prevention strategy only. Some interventions for preventing falls in elderly people have been suggested, such as muscle strengthening and balance retraining, home hazard assessment and modification, withdrawal of psychotropic medication, cardiac pacing, and tai chi group exercises. Multifactorial interventions in long-term care populations seem more likely to be beneficial. Frequent fallers and frail individuals must receive the highest priority for osteoporosis treatment (Neyens *et al*, 2011).

Box 1 Risk factors associated with falls

- Age
- Impaired mobility (lower limb osteoarthritis, neuromuscular disorders, etc)
- Impaired vision
- Cardiovascular diseases (arrhythmias)
- History of falls
- Medication
- Cognitive impairment
- Environment (slippery surfaces, inappropriate shoes, carpets, insufficient lighting, etc)

In institutionalised very elderly patients at extremely high risk of falling, hip protectors were shown to reduce the risk of hip fracture, but patient acceptance is rather low and the results inconsistent in patients living in the community (Parker *et al*, 2006; Oliver *et al*, 2007).

2.3 Protein intake

The typical Western diet includes a lot of protein. However, among the very elderly, a diet consisting almost exclusively of carbohydrates is quite common and this is associated with inadequate function of the musculoskeletal system. Correction of poor protein intake can limit the age-related alteration of the growth hormone–IGF-1 axis and improve BMD as well as muscle mass and strength (Rizzoli and Bonjour, 2004; Rizzoli *et al*, 2014*). Increased protein intake has also been shown in patients with a recent hip fracture to improve the subsequent clinical course and reduce the duration of hospital stay.

2.4 Fracture liaison services

As the risk of fracture increases after the first fracture and osteoporosis often goes undiagnosed and untreated in this situation, fracture liaison services may implement clinical pathways in liaison with orthopaedic units for the diagnosis and treatment of osteoporosis in patients with fragility fractures. Such strategies were reported to be cost-effective and are currently being established in many countries (McLellan *et al*, 2011).

3 Calcium and vitamin D

The main nutrients relevant for bone health are calcium, protein and vitamin D. Inadequate intake of these nutrients may occur as a consequence of diseases (eg, intestinal malabsorption), but is also quite common in the elderly. Calcium and vitamin D supplementation has a beneficial effect on bone health and fracture risk, and may be given to prevent and treat osteoporosis, particularly in elderly and institutionalised patients, patients treated for osteoporosis using antiresorptive or anabolic agents, and patients treated with glucocorticoids. However, irrespective of whether or not these nutrients are necessary, they are not sufficient for patients with a high fracture risk.

3.1 Calcium intake

Calcium intake is found to be weakly related to BMD or BMD changes, and in two meta-analyses it was found to be associated with a modest reduction in fracture risk (better effect with high doses of calcium of 1200 mg or more). It was speculated that positive results on bone turnover, bone mass and fracture risk can be expected from using calcium supplements only in patients with inadequate calcium intake (Shea *et al*, 2004; Boonen *et al*, 2007; Nieves and Lindsay, 2007; Tang *et al*, 2007). The recommended amounts of dietary calcium intake are of 800 to 1200 mg/day in adults older than 50. Many dietary recommendations include the consumption of 3 servings of dairy products per day (for example, 1 glass of milk, 1 portion of cheese, 1 yogurt)—an amount that provides most of the Recommended Daily Intake of calcium for the general population. It appears reasonable to use calcium supplements when dietary calcium intake cannot be increased above 800 mg/day. Calcium supplement dose has been inconclusively debated for a long time. The issue is complicated by the observation that the optimal dose of calcium supplements may depend on vitamin D supplementation (see below). It should also be noted that there are fundamental differences between calcium supplied by the diet and that from calcium supplements (table 2), and these should be taken into account for the management of osteoporosis. It is also worth mentioning that all agents registered for osteoporosis treatment have been tested in patients given calcium and vitamin D supplements.

It is currently debated whether the use of calcium supplements may increase the risk of cardiovascular events, in particular the risk of myocardial infarction. Recent additional data suggest that there is no convincing evidence for an increased cardio-vascular risk at the recommended doses of calcium intakes (Harvey *et al*,

2016). Therefore, it appears reasonable to encourage patients to obtain their calcium needs from food and drink and to use calcium supplements only if a calcium intake of at least 1 g per day is not supplied by their diet.

Table 2 Consequences of increasing calcium intake from 400 mg/day to 1400 mg/day with diet (eg, 800 mL of milk-derived products) or with calcium supplements (eg, one tablet of 1 g calcium carbonate)

Increase calcium intake supplied by the diet	Increase calcium intake with calcium supplements
<ul style="list-style-type: none"> • Slow (mainly active) intestinal absorption • Fraction absorbed proportional to 1,25(OH)₂ vitamin D levels • Associated with excess calcium in the large intestine lumen • Decreased absorption by oxalates • Decreased risk of renal calculi • Provide other nutrients (proteins) 	<ul style="list-style-type: none"> • Fast intestinal absorption (mainly diffusion) • Transient hypocalcaemia, suppression of parathyroid hormone secretion and of bone reabsorption • Transient hypercalciuria • Increased risk of renal calculi

3.2 Vitamin D

There are two chemically distinct forms of plain vitamin D, the native compound: vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol), obtained through ultraviolet B (UVB) radiation of the skin (vitamin D3) or through the diet (vitamin D2 or D3). Food and/or supplement intake may provide either vitamin D2 or D3. Sequential hydroxylation in the liver and kidney results in the production of two metabolites: calcidiol (25(OH)D) and calcitriol (1,25(OH)₂D). Vitamin D status must be determined by measuring the serum concentration of the major circulating form of vitamin D, calcidiol (25(OH)D).

Vitamin D deficiency is extremely common in the elderly. The old definition of deficiency and insufficiency was challenged when it was demonstrated that 25(OH)D <50 nmol/L was associated with markers of poor skeletal health (i.e., increased parathyroid hormone (PTH) levels, impaired calcium absorption, lower BMD). These clinical consequences are the basis for switching the definition of vitamin D insufficiency from a biological to a clinical definition—that is, the threshold below which there are consequences for bone (table 3). It was recently recommended that 50 nmol/L (i.e., 20 ng/mL) should be the minimal serum 25(OH)D concentration at the population level and in patients with osteoporosis to ensure optimal bone health. Supplementation with 800–1000 IU/day is recommended for a serum 25(OH)D concentration below 50 nmol/L (i.e., 20 ng/mL), with an intervention threshold that should rise to 75 nmol/L (i.e., 30 ng/mL) in frail elderly patients at elevated risk for falls and fractures (Rizzoli *et al*, 2013*).

On this basis, a large majority of elderly people (40–100% according to several studies) or patients with inflammatory joint diseases, and a high proportion of adults, not taking vitamin D supplements, are vitamin D insufficient (Holick, 2007*). Vitamin D deficiency severely hampers the clinical benefits of antiresorbing therapies (Adami *et al*, 2009*). Vitamin D supplements can also reduce the risk of falling and the risk of fracture through a well-recognised muscle effect. The question of the dose to give is difficult as it depends on the baseline level of serum 25(OH)D and the fat mass of the patient (vitamin D is liposoluble). The optimal dose and dosing is that allowing a circulating level of 25(OH)D of >75 nmol/L. On a daily basis, it is quite difficult to obtain enough vitamin D from dietary sources (even if rich in oily fish). Thus, sensible sun exposure (or UVB irradiation) and the use of supplements (depending on patient exposure to the sun) are needed to fulfil the body's vitamin D requirement. Sunlight is the most important source of vitamin D and stimulates the production of vitamin D₃ in the skin during the summer. During exposure to solar UVB radiation, 7-dehydrocholesterol in the skin is converted to previtamin D₃ and then vitamin D₃. Seasonal variations are observed in serum 25(OH)D, with effects of sunlight exposure that depend on age, skin pigmentation, clothing style and sunscreen use (Lips *et al*, 2014).

Table 3 Vitamin D biological levels

	25(OH) vitamin D	
	ng/mL	nmol/L
Vitamin D deficiency	<10	<25
Vitamin D insufficiency	10–20	25–50
Vitamin D sufficiency	20–30	50–75
Recommended vitamin D level in patients at elevated risk for falls and fractures	30–70	75–175
Possible vitamin D over-dosage	>80	>200

Vitamin D supplements can be given weekly, monthly or at 3-monthly intervals. Except in diseases interfering with vitamin D metabolism (chronic renal or liver failure), there is no justification for using hydroxylated forms of vitamin D (1(OH)D or 25(OH)D or 1,25(OH)₂D) because they expose the patient to an increased risk of hypercalcaemia or nephrolithiasis (particularly for 1,25(OH)₂D). The efficacy of daily administration of vitamin D₂ and D₃ seems to be the same. In case of intermittent administration, vitamin D₃ must be preferred because it induces a longer and more stable 25(OH) vitamin D level than vitamin D₂. To improve vitamin D absorption, it should be taken with a fat-rich diet, such as milk or at the end of the meal. Vitamin D deficiency is so common among elderly people that vitamin D supplements (800 IU/day) can be recommended even in the absence of a measurement of 25(OH)D level, considering that the safety of vitamin D supplements, at doses used in clinical practice, is good. Excess vitamin D, which can cause hypercalcaemia in generally healthy adults, results from a daily intake of >100 000 IU vitamin D, associated with serum 25(OH)D levels of >200

nmol/L, which are far higher than necessary to achieve benefit. Therefore, the use of vitamin D at physiological doses for elderly people without a previous measurement of vitamin D level (i.e., 800–1200 IU/day) is safe.

Two RCT in women showed that high doses of vitamin D (500000 IU of vitamin D per year and 60 000 IU of vitamin D per month, respectively) significantly increase risk of falls (Sanders et al, 2010; Bischoff-Ferrari et al, 2016). Moreover, it was shown that the majority of patients treated with equivalent to 800 IU/day achieve the replete range of above 50 nmol/L 25(OH)D. Therefore, high loading doses of vitamin D are no more recommended. In case of vitamin D insufficiency or deficiency, the recommended daily dose in the average patient (with the target of a serum 25(OH) vitamin D level over the recommended threshold of 50-75 nmol/L) is 800 IU, which can be prescribed in a large variety of compounds from daily to every 3 months administration. If vitamin D deficiency has been documented, the daily dose might be increased to a maximum of 2000 IU/day for one to 3 months before a maintenance dose of 800 IU/day.

3.3 Combining vitamin D with calcium or with bisphosphonates

The addition of calcium is necessary to optimise the clinical efficacy of vitamin D supplementation in terms of reducing fracture risk. The consequences of vitamin D deficiency on PTH secretion are also related to calcium intake. In subjects with a very high calcium intake, moderate vitamin D insufficiency is not associated with secondary hyperparathyroidism. In people with calcium intake as low as 400 mg/day, levels of 25(OH) vitamin D above 100 nmol/L are able to maintain PTH within the normal range, which might be particularly relevant for patients who are unable to increase their dietary calcium and are intolerant of any formulation of calcium supplements (Lips *et al*, 2010).

Vitamin D can be combined with all types of anti-osteoporotic medication. A fixed dose combination of once-weekly alendronate 70 mg and vitamin D3 5600 IU is available for the treatment of postmenopausal osteoporosis.

4 Pharmacological intervention

4.1 Pharmacological treatment threshold

4.1.1 Criteria for treatment threshold identification: BMD, fracture risk factors and FRAX

The aim of osteoporosis treatment is the prevention of fragility fracture. A pharmacological intervention is justified when the benefits (lowering fracture risk) outweigh both the side effects and the economic costs of the treatment. For the latter, treatment threshold may vary according to local health policy (Geusens *et al*, 2008*).

The definition of osteoporosis is based on BMD measurement (Kanis *et al*, 2000). The original World Health Organization (WHO) definition of osteoporosis (a T score of –2.5 or less at any skeletal site) has been recently

adjusted by specifying a reference site (the femoral neck) based on a young normal reference range (WHO, 1994). In clinical practice, the positioning of the area of analysis on the femoral neck is not always easy and the T score of the total hip is an acceptable alternative.

The definition of osteoporosis based on the T score will not change with the use of scores of fracture risk (see below), just as the definition of hypertension has not changed with the use of tools to estimate vascular risk. However, the diagnosis threshold may be different from the therapeutic threshold. Indeed, several factors besides BMD affect the risk of fracture (table 5), so the decision to start an intervention aimed at reducing this risk will be better if it takes all factors into account.

Table 5 Clinical risk factors most widely used for the assessment of fracture probability

Clinical risk factors

- Advanced age
- Female sex
- Low body mass index
- Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture
- Parental history of hip fracture
- Glucocorticoid treatment (>5 mg prednisolone daily or equivalent for 3 months or more)
- Current smoking
- Alcohol intake of 3 or more units daily
- Rheumatoid arthritis
- Other secondary causes of osteoporosis
 - Untreated hypogonadism in men and women; for example, premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism
 - Inflammatory bowel disease; for example, Crohn's disease and ulcerative colitis (risk is in part dependent on the use of glucocorticoids, but an independent risk remains after adjustment for glucocorticoid exposure)
 - Prolonged immobility; for example, spinal cord injury, Parkinson's disease, stroke, muscular dystrophy, ankylosing spondylitis
 - Organ transplantation
 - Type I diabetes
 - Thyroid disorders; for example, untreated hyperthyroidism, over-treated hypothyroidism
 - Chronic obstructive pulmonary disease

Prevalent vertebral and hip fragility fractures, or high steroid doses in postmenopausal women, identify categories of extremely high risk patients for whom many European health authorities grant funding for osteoporosis treatments even in the absence of a DXA (dual-energy X-ray absorptiometry) evaluation (Lindsay *et al*, 2001*).

In other patients, the identification of a treatment threshold based on BMD only is more complicated. Fracture risk may vary markedly among different populations for the same BMD value, according to the presence of other risk factors (table 5). Thus, the combination of BMD and clinical risk factors predicts fracture risk better than BMD alone. Fracture risk increases with advancing age, regardless of baseline T score; for example, a T score of -2.5 is associated with a 10-year fracture probability of 6% in a 50-year-old woman, but with a 10-year fracture probability of 26.5% in an 80-year-old (Kanis *et al*, 2001*). A prevalent vertebral fracture increases the risk of incident vertebral fracture by about fivefold in the year following the primary fracture. Also the occurrence of a recent vertebral fracture is associated with a recurrence in the year following the primary fracture in about 20% of cases (Black *et al*, 1999*).

The 10-year probability of a major osteoporotic fracture (vertebral, hip or forearm) can be calculated in treatment-naïve patients (men and women) using femoral neck BMD and clinical risk factors for fracture with a country-specific adaptation of the WHO fracture risk algorithm (FRAX), available online for public use (<http://www.shef.ac.uk/FRAX>). The risk factors included in FRAX are age, sex, weight, height, previous fracture, parent with fractured hip, current smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and excess alcohol intake (more than 3 units per day). The risk of fracture can also be calculated without BMD.

FRAX has a number of limitations:

- It is not freely available for automatic application to databases or case report forms.
- It does not take into account the 'dose effect' of some risk factors, such as steroid use (dose and duration) or fractures (number, severity or type). A prior clinical vertebral fracture carries approximately a 2 fold higher risk than other types of prior fracture.
- The fracture risk is not adjusted for the perception of the risk, which may vary individually according to age, life-expectancy and other factors (in particular the risk of falls).
- FRAX does not define intervention thresholds, which depend on country-specific considerations.
- FRAX is not available for all countries. When a country does not have a national reference on FRAX, it seems reasonable to choose the reference of a neighbouring country.
- By using femoral neck BMD, FRAX does not allow the taking into account of spine–hip discordances in T score in patients who have a lumbar spine T score lower than their femoral neck T score.
- FRAX does not consider prior treatment

In light of these points, care providers might tailor treatment thresholds individually. Despite the aforementioned limitations, FRAX is likely to become, in many countries, the most popular instrument for identifying patients to be treated and or entitled to drug reimbursement.

4.1.2 Clinical guidelines for treatment threshold for osteoporosis

In the absence of a universally accepted policy for population screening in Europe to identify patients with osteoporosis or those with high risk of fracture, patients are identified using a case-finding strategy based on previous fragility fracture or the presence of significant risk factors.

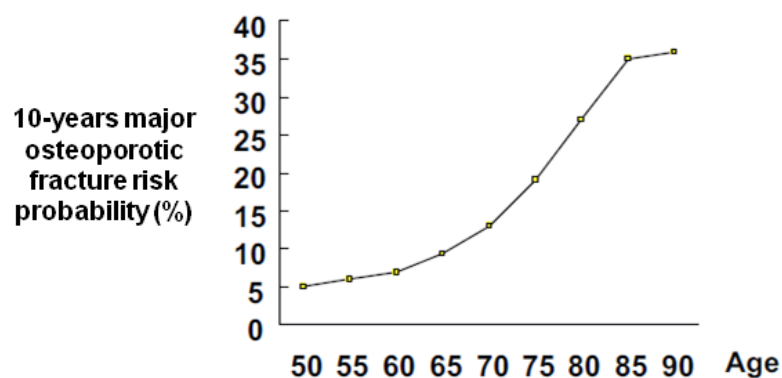
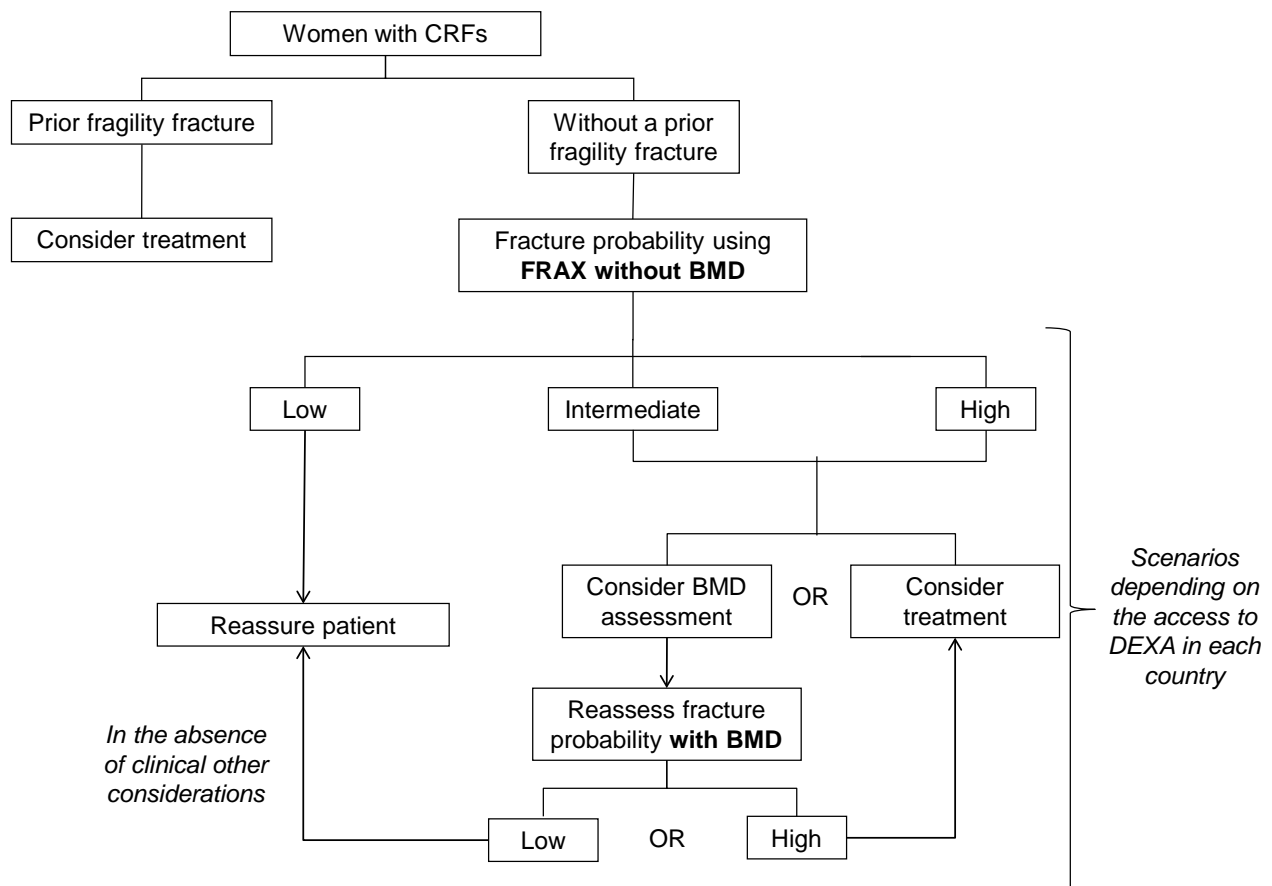
European guidelines for the management of osteoporosis in postmenopausal women were revised in 2012, based on the finding of a previous fragility fracture or the presence of significant clinical risk factors and the use of FRAX (Kanis *et al*, 2013).

The fracture probability at which to intervene, in terms of assessment threshold for BMD testing and intervention threshold for treatment, differs for individual countries according to health economic perspectives and other factors. It is not possible to propose a universal decision threshold for FRAX valid in all countries because the threshold is dependent particularly on each country's healthcare system. In other words, an unacceptable level in one country would be acceptable in another. As an example, in France, in patients without prevalent fractures with a T score greater than -3 , the treatment decision depends on the FRAX probability, and the thresholds for treatment vary with age, as reported in figure 1B (Briot *et al*, 2012). It should be noted that the value of a metatarsal or rib fracture is very different from that of a vertebral or hip fracture. Therefore, no general algorithm can be proposed for use in all countries.

The current treatment guidelines of the US National Osteoporosis Foundation (2014) recommend pharmacological therapy for postmenopausal women and men aged 50 years and older, after appropriate evaluation, presenting with:

- a hip or vertebral (clinical or morphometric) fracture
- a T score of -2.5 or less at the femoral neck, total hip or spine by DXA
- a low bone mass (T score between -1.0 and -2.5 at the femoral neck, total hip or spine by DXA) and a 10-year probability of a hip fracture of 3% or more or a 10-year probability of a major osteoporosis-related fracture of 20% or more based on the US-adapted WHO algorithm. Some situations associated with negative effects on the skeleton require specific approaches, in particular to prevent bone loss and fracture risk associated with aromatase inhibitors (Rizzoli *et al*, 2012a), or in geriatric populations (Rizzoli *et al*, 2014*).

Figure 1 (A) Proposed management algorithm for the assessment of individuals at risk of fracture, to be modified in each country according to local dual-energy X-ray absorptiometry (DXA) access and reimbursement issues. (B) Intervention threshold for osteoporosis treatment described in French recommendations. BMD, bone mineral density; CRF, clinical risk factor. ((A) Adapted from Kanis et al, *Osteoporosis Int* 2013;24:23–57; (B) Adapted from Briot et al, *Joint Bone Spine* 2012;79:304–13.)



4.2 Pharmacological treatment options

The drugs registered in Europe for the treatment of postmenopausal osteoporosis are listed in table 6.

Table 6 Pharmacological agents licensed in Europe for the treatment of postmenopausal osteoporosis

Drug		Bone targets and mechanism of action	Dose in osteoporosis treatment	Effect on fracture risk reduction demonstrated in clinical trials			Side/off-target effects and adverse effects
				Vertebral	Non-vertebral	Hip	
Bisphosphonates	Alendronate	Inhibitors of bone resorption: inhibit osteoclasts activity and induce osteoclast apoptosis	70 mg/week (oral)	+	+	+	Oral bisphosphonates: low bioavailability due to low absorption in gastrointestinal tract (<1%) Long-lasting residual protection of bone Oesophageal irritation Flu-like symptoms after intravenous injection Osteonecrosis of the jaw in patients given high doses Atypical fractures of the femur with long-term use
	Risedronate		35 mg/week (oral)	+	+	+	
	Ibandronate		150 mg/month (oral) or 3 mg/3 months (IV)	+	Post hoc	–	
	Zoledronate		5 mg/year (IV)	+	+	+	
SERMs	Raloxifene	Inhibitors of bone resorption: non-steroidal agents that bind to the oestrogen receptor and act as oestrogen agonists on bone	60 mg/day (oral)	+	Post hoc	–	Decreased risk of invasive breast cancer due to oestrogen antagonist effects Increase in deep venous thromboembolism
	Bazedoxifene		20 mg/day (oral)	+	Post hoc	–	
Anti-RANKL monoclonal antibodies	Denosumab	Inhibitors of bone resorption: humanised monoclonal antibodies binding selectively and with high affinity to RANKL. Prevent the effect of RANKL on	60 mg/6 months (SC)	+	+	+	Possible adverse immune effects (dermatological side effects and skin infection) Hypocalcaemia Possibly associated with osteonecrosis of the jaw and atypical fractures of the femur Possible rebound of bone turnover and BMD loss after

		osteoclast differentiation, activation and survival					discontinuation
Parathyroid hormone	Teriparatide	Activators of bone formation: intermittent administration of PTH increases the number and activity of osteoblasts	20 µg/day (SC)	+	+	–	Contraindicated in conditions with abnormally increased bone turnover (pre-existing hypercalcaemia, primary hyperparathyroidism, Paget's disease of the bone, unexplained elevation of alkaline phosphatase) in patients with prior radiation therapy to the skeleton, skeletal malignancies or bone metastases Duration of treatment limited to 24 months (=duration of trial)
	PTH 1-84		100 µg/day (SC)	+	–	–	

The main mechanisms of action together with the clinical evidence of efficacy are reported.

IV, intravenous; RANKL, receptor activator of nuclear factor kappa B ligand; SC, subcutaneous; SERMS, selective oestrogen-receptor modulators; +, effect on fracture demonstrated; –, effect on fracture not demonstrated.

Most of these drugs decrease osteoclastic activity (bisphosphonates, denosumab, selective oestrogen-receptor modulators). The only bone anabolic agent registered for the treatment of osteoporosis is PTH, either the first 34 amino acids or the full molecule. The fundamental differences between these two classes of agents are illustrated in figures 2–4.

Figure 2 Components of spine bone mineral density (BMD) changes during therapy with antiresorptive drugs. The initial rapid increase in BMD is explained by the rapid reduction in the number of bone metabolic units (BMU). The decreased bone turnover associated with inhibitors of bone resorption permits a higher degree of secondary mineralisation (continuous process of mineralisation of mature bone tissue).

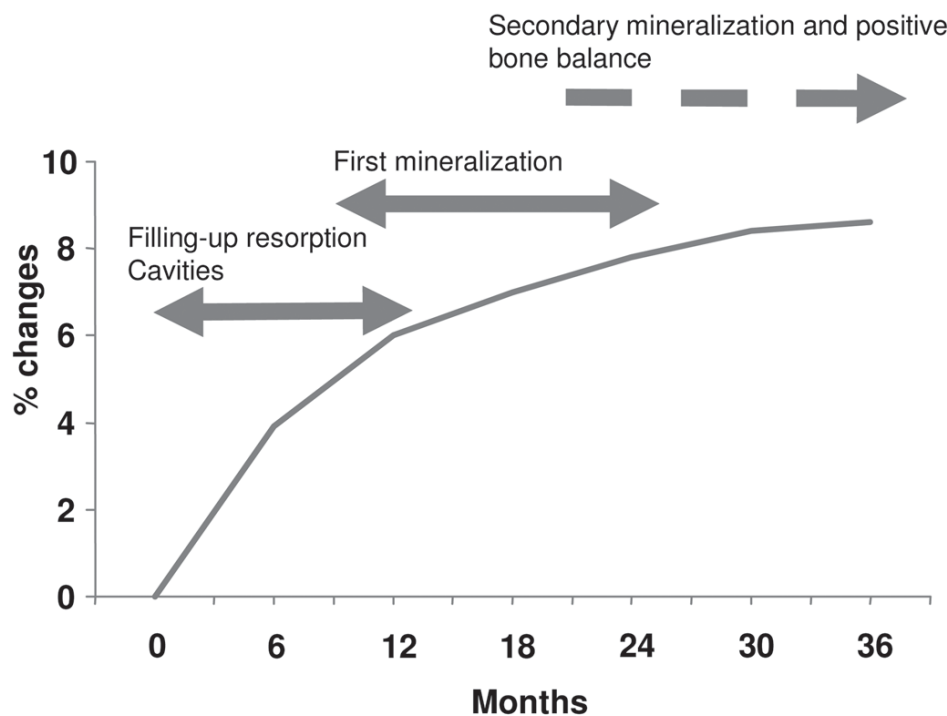


Figure 3 Changes in bone turnover markers during therapy with antiresorbers. The antiresorbers, such as bisphosphonates, rapidly decrease osteoclastic activity and bone resorption. This is associated with a later decrease in osteoblastic activity and bone formation. The lag time to new coupling between bone resorption and formation represents the therapeutic window, during which bone tissue is growing.

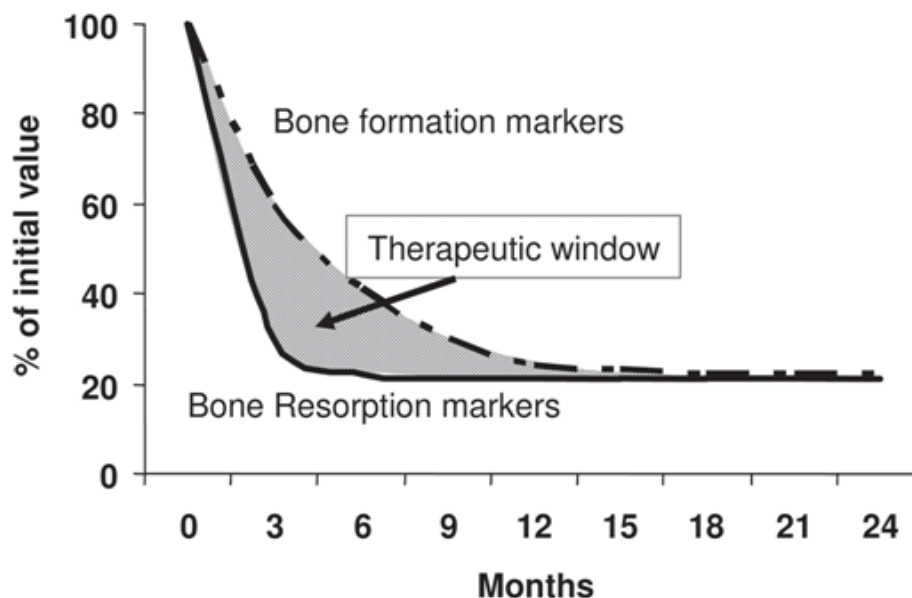
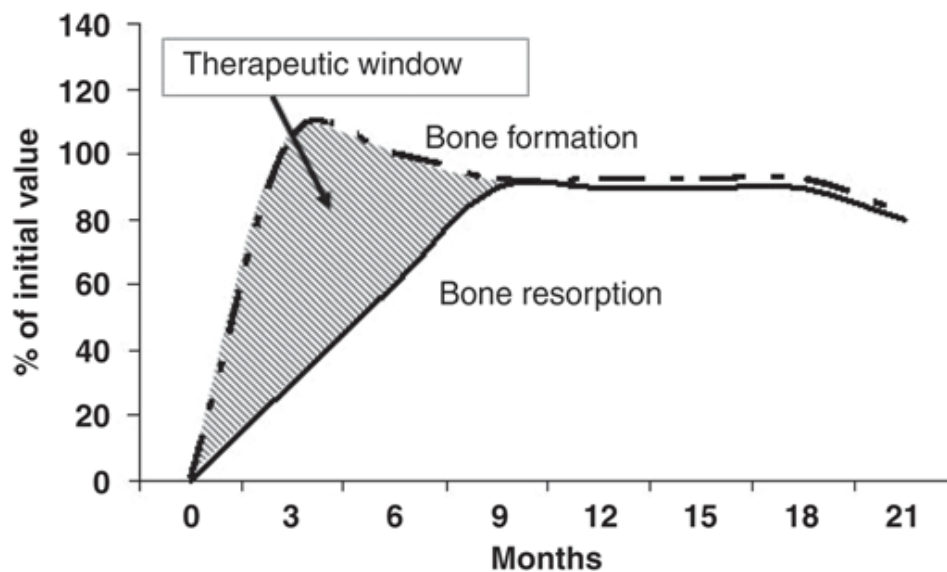


Figure 4 Changes in bone turnover markers during therapy with parathyroid hormone (PTH). PTH is the only bone anabolic agent so far available. It rapidly increases osteoblastic activity and bone formation. This is associated with a later increase also of osteoclastic activity and bone resorption. The lag time to new coupling between bone resorption and formation represents the therapeutic window, during which bone tissue is growing.



4.2.1 Bisphosphonates

Bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid; see table 6) are the accepted first-line therapy for most patients with postmenopausal osteoporosis. Drugs in this class increase bone strength and reduce fracture risk by inhibiting osteoclast activity and inducing osteoclast apoptosis, thereby reducing bone resorption and increasing BMD (Rodan and Reszka, 2002). Oral formulations are available for administration daily (alendronate, risedronate), weekly (alendronate, risedronate) and monthly (ibandronate, risedronate). Oral bisphosphonates are poorly absorbed (<1%) and might be associated with oesophageal irritation/gastrointestinal symptoms when used in clinical practice. They must be taken with plain water on an empty stomach after an overnight fast, with a post-dose fast and upright position for 30 min (alendronate, risedronate) or 60 min (ibandronate). Two intravenous bisphosphonates are approved by the European Medicines Agency (EMA) for the treatment of postmenopausal osteoporosis: ibandronate and zoledronic acid. The major side effect of these formulations is the occurrence 24–36 h after the first infusion, in a large proportion of patients, of flu-like symptoms or acute phase reaction (Rizzoli *et al*, 2011). The symptoms are almost invariably self-limiting, can be easily controlled with simple analgesics, and tend not to occur with subsequent infusions. In a few cases the symptoms might be long lasting and rather severe. This condition can be easily resolved with administration of paracetamol for 1–3 days.

A clinical entity termed osteonecrosis of the jaw (ONJ) has been described mostly in patients with malignancy given high intravenous doses of bisphosphonates (Cartsos *et al*, 2008). It is defined as necrotic bone exposed in the maxillofacial region lasting for more than 8 weeks in patients treated with bisphosphonate or

denosumab who have not undergone head and neck radiation therapy. The syndrome is characterised by difficulty in eating and speaking, oral pain, infection and bone necrosis. The condition commonly manifests as a painful exposed non-healing bone and is a challenging clinical and surgical management problem. Risk factors for the development of ONJ are: cancer and anticancer therapy, dental extraction, oral bone manipulating surgery, poorly fitting dental appliances, intra-oral trauma, duration of exposure to bisphosphonate treatment, glucocorticoids, alcohol and/or tobacco abuse, and pre-existing dental or periodontal disease (Khosla *et al*, 2007). ONJ can also occur, extremely rarely, in patients receiving oral bisphosphonates for osteoporosis treatment, but its incidence even in high-risk patients (see above) is not known. Since ONJ is likely to be associated with actinomyces infection, the empiric recommendation is to perform intensive antiseptic (both local and systemic) treatment whenever a patient who has been on treatment for a long time with bisphosphonates has to undergo an invasive mouth intervention.

The long-term use of bisphosphonates has also been associated with atypical fractures of the subtrochanteric region and diaphysis of the femur. These fractures are considered as stress or insufficiency fractures, which do not normally heal. Suppression by antiresorptive therapy of intracortical remodelling at the site of the stress fracture impairs the processes by which stress fractures normally heal, and lead to progress to full fracture. The absolute risk of these fractures in patients on bisphosphonates is low, ranging from 3.2 to 50 cases per 100 000 person-years, but long-term use may be associated with higher risk (100 per 100 000 person years) (Shane *et al*, 2014*). When an atypical subtrochanteric fracture is found, it is recommended to image the contralateral side at the same time.

The efficacy of the different bisphosphonates is globally comparable, regardless of their mode of administration, bearing in mind that:

- ibandronate has demonstrated its ability to reduce the risk of non-vertebral fractures only in a subgroup of patients with higher risk, but has shown no significant effect on the risk for hip fracture alone
- zoledronate has shown a reduced risk of clinical vertebral fractures, non-vertebral fractures and hip fractures. It has also demonstrated its efficacy for preventing clinical fractures after a first hip fracture, and showed that this reduction was associated with reduced all-cause mortality (Eriksen *et al*, 2009).

These two points are summarised in table 6. Different intermittent dosing, mode (oral or intravenous) and frequency of administration (mainly weekly or yearly), provide several options for bisphosphonate treatment and more patient and physician choice. This issue is important to limit poor adherence to treatment.

4.2.2 Selective oestrogen-receptor modulators

Selective oestrogen-receptor modulators (SERMs) are non-steroidal agents that bind to the oestrogen receptor and act as oestrogen agonists or antagonists, depending on the target tissue. Raloxifene (60 mg/day) was the first SERM available for the prevention and treatment of postmenopausal osteoporosis. It demonstrated effects on fracture prevention that are restricted to vertebral fractures (table 7). It should therefore probably not be considered as first-line therapy in women at high risk of non-vertebral fracture (particularly hip fracture). Other third generation SERMs have been developed, and bazedoxifene and lasofoxifene are now approved for the treatment of postmenopausal women in the EU (Silverman *et al*, 2008; Cummings *et al*, 2010). They decrease the incidence of vertebral fractures; a decrease of non-vertebral fractures was also demonstrated with lasofoxifene (at a dose of 0.5 mg/day), and in a subgroup of women at high risk of fractures (T score below -3 and/or one or more moderate or severe vertebral fractures) with bazedoxifene 20 mg/day (but not 40 mg/day).

Table 7 Raloxifene risk-benefit

Raloxifene benefit	Raloxifene risk
<ul style="list-style-type: none"> • Vertebral antifracture efficacy • Marked reduction in the risk of breast cancer • Cost-effectiveness profile 	<ul style="list-style-type: none"> • Lack of effect on non-vertebral fractures • Increased incidence of hot flashes • Risk of venous thromboembolism

The main adverse event of SERMs is an increase in deep venous thromboembolism. Particularly in early post menopause, climacteric symptoms may worsen. This is balanced by a decreased risk of invasive breast cancer (Barrett-Connor *et al*, 2006). Raloxifene does not significantly affect the risk of coronary heart disease and more generally of cardiovascular diseases. According to these data, raloxifene is considered to have a favourable risk:benefit ratio in the treatment of osteoporosis in early postmenopausal osteoporotic women at risk of vertebral fractures.

4.2.3 Denosumab

Denosumab is the latest antiresorptive agent approved for osteoporosis treatment in the EU. Denosumab is a humanised monoclonal antibody that binds selectively and with high affinity to the receptor activator of nuclear factor κ B ligand (RANKL, a member of the tumour necrosis factor (TNF) family). This is a major cytokine involved in osteoclast activation and bone remodelling expressed by osteoblasts, synovial fibroblasts and activated T cells. RANKL binds to RANK, a receptor on osteoclast membranes, and induces differentiation, activation and survival of osteoclasts. A regulator of the RANK–RANKL interaction is the soluble cytokine osteoprotegerin (OPG), which functions as a decoy receptor by competing for binding to RANK. Denosumab mimics the effect of OPG on RANKL (Kearns *et al*, 2008).

The optimal dose of denosumab, one subcutaneous injection of 60 mg every 6 months, is associated with a continuous increase of BMD over the years, with some disparities versus bisphosphonate effects (Lewiecki et al, 2007; Miller et al, 2008; Brown et al, 2009):

- A decrease in serum CTX (C-telopeptide of type 1 collagen) levels, a bone resorption marker, occurs rapidly, as early as 3 days after the injection. After treatment discontinuation, bone turnover transiently rebounds above baseline values and most of the BMD gains are lost after 12 months.
- Denosumab demonstrated significantly greater gains in BMD (3.5% vs 2.6% at total hip at 12 months), and greater reduction in bone turnover markers compared with alendronate. In the denosumab extension study (up to 10 years of treatment with denosumab), BMD continuously increase.
- In contrast to bisphosphonates, denosumab has no residual effect.

The results of a phase III fracture trial using a dose of 60 mg subcutaneously every 6 months was published in 2009. In 7808 women with osteoporosis followed for 3 years, denosumab reduced the risk of new vertebral fractures by 68% (2.3% denosumab vs 7.2% placebo; $p < 0.001$), the risk of hip fractures by 40% (0.7% denosumab vs 1.2% placebo; $p = 0.036$), and the risk of non-vertebral fractures by 20% (6.5% denosumab vs 8% placebo; $p = 0.011$) (Cummings et al, 2009).

Regarding potential adverse events, concerns about possible adverse immune effects of denosumab are still debated. This is biologically plausible since RANKL is expressed on activated T and B lymphocytes, which, in the lymph nodes, are responsible for recognition of foreign antigens. Nevertheless, there is no evidence of impaired immunity in humans treated with denosumab. Skin infections (cellulitis erysipelas) and other skin-related conditions (eczema) were reported in denosumab-treated patients. Clinicians should provide adequate calcium and vitamin D supplementation to limit the risk of hypocalcaemia following denosumab administration, which appears to be higher than with bisphosphonates. ONJ and atypical fractures of the femur have also been described with denosumab, associated with its effects on bone resorption. The efficacy and safety of association of biological agents targeting cytokines such as TNF or interleukin 6 (IL-6), and denosumab, will need to be specifically investigated in the treatment of rheumatoid arthritis and other inflammatory diseases. Reassuring data have been recently published showing that the rate of hospitalized infections among patients with rheumatoid arthritis receiving denosumab concurrently with biologic agents was not increased compared to those receiving zoledronate (Curtis et al, 2015).

Discontinuation of denosumab is associated with a transient increase in bone resorption and decline in BMD, to check. Some cases of multiple vertebral fractures have been reported in this context (Lamy et al, 2016), although it remains unclear whether these fractures are related to the rebound of bone turnover or to the fact that the patients in which they occur are at particularly high risk of fracture (Brown et al, 2013). Thus, CTX levels should be regularly monitored after denosumab discontinuation. Recent data indicate that prior

exposure to bisphosphonates may prevent the rebound of bone turnover markers after denosumab discontinuation (Uebelhart et al, 2016). In case of bone resorption rebound, oral bisphosphonates for a few months or one zoledronic acid injection should be added. This attitude is indirectly supported by the data of the DAPS (Denosumab Adherence Preference Satisfaction) study, in which no BMD loss was observed after denosumab discontinuation in the group of postmenopausal women, with no prior bisphosphonate use, who received denosumab then alendronate over successive 12-month periods (Freemantle et al, 2012).

4.2.4 PTH family

The continuous endogenous production of PTH, as seen in primary or secondary hyperparathyroidism, can lead to harmful consequences for the skeleton, particularly on cortical bone. However, intermittent administration of PTH (eg, with daily subcutaneous injections) results in an increase in the number and activity of osteoblasts, leading to an increase in bone mass and an improvement in skeletal architecture at both cancellous and cortical skeletal sites (Black et al, 2003; Hodsman et al, 2005). At present, PTH is the only available anabolic agent, with two available peptides: teriparatide or recombinant PTH 1-34, and the intact recombinant hormone PTH 1-84.

The most common reported adverse events in patients treated with PTH or teriparatide are nausea, pain in the limbs, headache and dizziness. In normo-calcaemic patients, slight and transient elevations of serum calcium concentrations have been observed following the injection of PTH or teriparatide, which are usually dealt with by discontinuation of calcium supplements.

The use of peptides of the PTH family is contraindicated in conditions characterised by abnormally increased bone turnover (eg, pre-existing hypercalcaemia, metabolic bone diseases other than primary osteoporosis, including primary hyperparathyroidism and Paget's disease of the bone, unexplained elevation of alkaline phosphatase, prior external beam or implant radiation therapy to the skeleton, or in patients with skeletal malignancies or bone metastases).

The duration of treatment is limited in Europe to no more than 24 months (the median duration of the pivotal trials was 19 months). The safety data indicate that the expected incidence in the exposed population adjusted for age is identical to that of the general population. Teriparatide has demonstrated its efficacy for preventing both vertebral and non-vertebral fracture, whereas PTH 1-84 has demonstrated its efficacy for preventing vertebral fractures only. There is an initial brisk increase in markers of bone formation (P1NP) within days or weeks of initiating teriparatide. Bone formation marker levels usually peak within 1 year (varying for the specific marker measured) and begin to decline thereafter towards baseline, despite continued treatment. Increases in markers of bone resorption are delayed until after 1 month, but also peak and decline towards baseline during the second year of teriparatide. The increase in spine BMD after teriparatide is also most rapid within the first 6 months, consistent with the biochemistry (Cosman et al 2015).

Due to their elevated cost, teriparatide and PTH 1-84 are used in most countries only in patients with severe osteoporosis.

4.2.5 Hormone replacement therapy

For several decades, hormone replacement therapy (HRT) was widely used for the treatment or prevention of osteoporosis on the basis of surrogate endpoints. The Women's Health Initiative study provided the first solid evidence of its efficacy to reduce the risk of both clinical vertebral fracture and non-vertebral fracture (including hip). However, the results of the same study also indicated that HRT is associated with an increased risk of breast cancer, cardiovascular diseases and stroke. It appeared that the long-term risks of HRT outweigh the benefits and for this reason the indication for HRT for osteoporosis treatment was cancelled by the EMA (Rossouw et al, 2002).

4.3 Combination and sequential treatments

The combination of two antiresorbers (eg, HRT with a bisphosphonate) is associated with greater decreases in bone resorption and greater increases in BMD than either agent alone. These combinations might be used in limited cases—for example, in women with low oestrogen doses with persistent high turnover.

Patients pre-treated with inhibitors of bone resorption, who have not achieved a full therapeutic response, are good candidates for treatment with anabolic agents. However, the combination of an antiresorptive agent and either PTH or teriparatide is associated with bone mass changes generally lower than those obtained with PTH alone. There are data suggesting that the administration of an inhibitor of resorption (bisphosphonate or SERM) after treatment with PTH prevents the rapid bone loss observed after treatment discontinuation (Black et al, 2005). Therefore, the administration of inhibitors of bone resorption is strongly recommended after a treatment course with PTH or teriparatide. More recently, it has been shown that combination of teriparatide and denosumab was associated with higher BMD gain than each one of these treatment alone, suggesting that this combination may be of potential interest in postmenopausal women with a very high risk of both vertebral and non-vertebral fractures.

4.4 First choice treatment

In the absence of head-to-head studies that directly compare the drugs for antifracture efficacy, there is no evidence to allow conclusions on differences among drugs. Surrogate markers (i.e., effects on BMD or biochemical markers) cannot help in this matter in clinical practice.

Anti-osteoporotic agents include drugs that can increase bone formation (such as teriparatide and PTH) or decrease bone resorption (such as bisphosphonates, raloxifene and denosumab). One could expect that the choice between these agents may be driven by bone remodelling (i.e., a bone-forming agent in the case of low

turnover and an antiresorptive drug in the case of high turnover). However, current data do not support this concept. There are no convincing data to suggest that serum CTX or PINP (procollagen type I N propeptide), currently the most relevant markers of bone resorption and formation, respectively, may help in choosing the first anti-osteoporotic drug.

In early postmenopausal subjects, considering that the risk of vertebral fractures is higher than the risk of hip fractures, and that sequential therapies will probably be necessary, drugs with demonstrated effectiveness at all sites should not necessarily be preferred to one without demonstration at the hip, for example. It has to be kept in mind that demonstration of a fracture risk reduction at a specific site (i.e., vertebral versus non-vertebral fractures) can be achieved statistically in populations with high risk of fractures at this site in particular. Studies evaluating as the primary outcome the effect of drugs on vertebral fracture risk were not necessarily designed to demonstrate a decrease in non-vertebral fracture risk in the same population during the same length of follow-up.

Thus, the decision is based on (table 8) (Geusens et al, 2008*; Rizzoli et al, 2011):

- the characteristics of patients (age, climacteric symptoms, gastrointestinal intolerance)
- the characteristics of the disease (main risk at the spine, the hip or both)
- the characteristics of the drug (similarity between the real-life patients and the patients enrolled in the pivotal studies of the drug)
- the patient preference that influences long-term patient adherence to treatment. The prescribers must be aware that one determinant of effectiveness is adherence to treatment, so the information given to the patient must be optimal, and low persistence and compliance must be anticipated. The cost of the drug is also an important determinant of treatment adherence in some countries.

Table 8 Main factors influencing treatment choice in addition to evidence of efficacy (see table 6)

Most relevant individual concern	Drug of first choice
Gastrointestinal intolerance	Intravenous ibandronate or zoledronate, raloxifene, denosumab
Convenience	Monthly ibandronate, intravenous zoledronate, denosumab
Cost of treatment	Generic alendronate, generic risendronate, generic zoledronate
High risk of breast cancer	Raloxifene
Postmenopausal symptoms in patients <60 years old	Hormone replacement
Severe osteoporosis	Teriparatide, PTH 1-84

4.5 Duration of treatment and drug holidays

Osteoporosis requires long-term treatment to prevent fracture and its damaging consequences in the elderly, but efficacy against fracture should be balanced against the risk of adverse events. The drug and duration of treatment will depend on individual patient characteristics and the severity of osteoporosis (new incident fracture, levels of BMD) (Cooper *et al*, 2012). Data are available from study extensions over periods of 10 years for alendronate and denosumab, 7 years for risedronate, 8 years for raloxifene, and 6 years for zoledronic acid. It appears appropriate to evaluate treatment (clinical risk factors, BMD variation, incident fractures, including vertebral fractures assessed by back pain and/or height loss of 2 cm or more during follow-up, radiographs of the spine or vertebral fracture assessment) after 5 years of treatment, and after 3 years for zoledronic acid (Adler *et al*, 2016). Long-term treatment often consists of the sequential use of several osteoporosis drugs. There is no scientific evidence supporting a specific treatment sequence, the only exception being teriparatide followed by a bone resorption inhibitor. Several factors guide the clinician in selecting drugs in an individual patient (health insurance reimbursement restrictions, severity of the osteoporosis, predominant risk of peripheral fractures, comorbidities, contra-indications to specific drugs, and patient adherence to prescriptions).

With regards specifically to long-term bisphosphonate use, questions are often raised about optimal duration of therapy. As alluded to above, there is no evidence base beyond 10 years to guide treatment. Pivotal clinical trials have mainly been limited to duration of 3 years with recommendations for drug holidays and longer term treatment based on limited evidence from extension studies in post-menopausal women. Withdrawal of treatment is associated with decreases in BMD and increased bone turnover after 2–3 years for alendronate and 1–2 years for ibandronate and risedronate (Compston *et al*, 2017). In the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly (HORIZON) study extension, withdrawal of zoledronic acid after 3 years' treatment was associated with only a very small decrease in BMD and bone markers after a further 3 years without treatment. Moreover, a post hoc analysis of subgroups of subjects from the HORIZON-PFT and HORIZON-RFT studies who received only one infusion of zoledronic acid, assessed fracture incidence in these patients. There was a 32% reduction in clinical fracture with zoledronic acid given once versus placebo over 3 years of follow-up, which is comparable with the fracture reduction seen in those who had three or more annual infusions (Reid *et al*, 2013). These data indicate that the effects of a single dose of zoledronic acid on BMD and bone turnover last for much more than 1 year. Drug holidays have therefore been defined as being between 1-3 years, varying by drug, on the above basis.

Nevertheless, it was also seen that the risk of morphometric vertebral fractures was significantly lower in women continuing on zoledronic acid for 3 years after 3 years therapy when compared with those switched to placebo, but the risk of non-vertebral fractures was similar in the treatment and placebo groups. (Black *et al*, 2012). In the Fracture Intervention Trial Long-term Extension study of alendronate (FLEX), there were

significantly fewer clinical vertebral fractures in women previously treated with alendronate for 5 years who continued with alendronate for five more years than in those assigned to placebo after 5 years of alendronate (Black et al, 2006). Post hoc analyses from the alendronate and zoledronic acid extension studies suggest that women most likely to benefit from long-term bisphosphonate therapy are those with low hip BMD (T-score < -2.0 in FLEX and \leq -2.5 in HORIZON), those with a prevalent vertebral fracture and those who sustained one or more incident fractures during the initial 3 or 5 years of treatment. Older age was also associated with increased fracture risk after discontinuation of alendronate therapy (Compston et al, 2017).

The UK National Osteoporosis Guideline Group (NOGG) has generally advised continuation of bisphosphonate treatment beyond 3–5 years (3 years for zoledronic acid and 5 years for alendronate, ibandronate and risedronate) for the following situations:

- Age 75 years or more
- Previous history of a hip or vertebral fracture
- Occurrence of one or more low trauma fractures during treatment, after exclusion of poor adherence to treatment (for example less than 80% of treatment has been taken) and after causes of secondary osteoporosis have been excluded
- Current treatment with oral glucocorticoids \geq 7.5 mg prednisolone/day or equivalent

If treatment is discontinued after a course of treatment on the basis of FRAX below intervention threshold and hip BMD T-Score > -2.5, fracture risk should be reassessed:

- After a new fracture regardless of when this occurs
- If no new fracture occurs, after 18 months to 3 years

Although not in widespread clinical use, the residual effect of bisphosphonates in bone can be monitored using beta-crosslaps levels (CTX), a bone resorption marker, to guide treatment efficacy or retreatment, the objective being to maintain CTX levels in the lower limit of the normal premenopausal range.

We make a note here that strontium ranelate will no longer be manufactured in Europe beyond August 2017 and has not previously been approved for use in the USA by the FDA. The manufacturer chose to do this because use was declining with the restrictions in place limiting its use to patients unable to take other medications for osteoporosis and who did not have a history of heart disease or a history or high risk of venous thromboembolism (Reginster et al, 2015) due to increases in cardiovascular risk and venous thromboembolism with the drug. Patients currently on strontium will need their treatment regimen reviewed.

4.6 Treatment efficacy and failure

Failure of treatment can be inferred when:

- two or more incident fractures have occurred during treatment
- serial measurements of bone remodelling markers are not suppressed by antiresorptive therapy
- BMD continues to decrease.

It has to be noted that treatment failure can be considered only after checking for adequate calcium and vitamin D intakes, and greater than 80% treatment adherence (Diez-Perez *et al*, 2012).

5 Glucocorticoid-induced osteoporosis

5.1 General management

Osteoporosis is the most debilitating complication of glucocorticoid therapy. Thus, glucocorticoids should be prescribed at the lowest possible dose and for the shortest possible duration, as the fracture risk increases with increasing daily dose, cumulative doses, and treatment duration.

The non-pharmacological measures to prevent fractures for glucocorticoid-induced osteoporosis (GIOP) are similar to those recommended for other causes of osteoporosis.

As intestinal calcium absorption is impaired by glucocorticoid therapy, a diet rich in calcium or calcium supplements is recommended, even though evidence of efficacy is lacking and calcium alone is definitely not sufficient to prevent rapid bone loss in patients starting high-dose glucocorticoids.

Cholecalciferol plus calcium or vitamin D metabolites are somewhat more efficacious in preserving BMD than no therapy, but the overall effect is modest. Nowadays, it is highly recommended that all patients on chronic glucocorticoid treatment have an adequate calcium intake (eg, >1000 mg/day) and 25(OH) vitamin D levels well within the normal range (eg, >30 ng/mL or 75 nmol/L). Weight-bearing exercise is recommended if the underlying condition allows this in order to maintain muscle mass, which could be potentially endangered by glucocorticoid therapy.

5.2 Threshold for a pharmacological intervention

The risk of fracture in patients taking pharmacological doses of glucocorticoid is related to daily dose and only in part to cumulative dose, and it is mostly independent of BMD. An analysis of the placebo groups of randomised clinical trials found that glucocorticoid users had considerably higher risks of vertebral fracture at the same levels of BMD than controls.

Thus, glucocorticoid therapy influences fracture risk by a mechanism independent of BMD, which amplifies the risk of fracture associated with low BMD and other typical risk factors for osteoporotic fractures (Rizzoli *et al*, 2012b).

Treatment thresholds for pharmacological interventions are nowadays set in terms of fracture risk over a limited lag time, assessed by FRAX. Specific considerations regarding fracture risk assessment in patients taking glucocorticoids are as follows:

- There is a dose relationship between glucocorticoid use for more than 3 months and fracture risk. The average dose exposure captured within FRAX is likely to be a prednisone dose of 2.5–7.5 mg/day or its equivalent. Fracture probability is under-estimated when prednisone dose is greater than 7.5 mg/day and is over-estimated when the prednisone dose is less than 2.5 mg/day. The proposed adjustments are: ($\times 0.8$) if glucocorticoids ≤ 2.5 mg/day, and ($\times 1.15$) if glucocorticoids ≥ 7.5 mg/day for major fracture probability; and ($\times 0.65$) if glucocorticoids ≤ 2.5 mg/day, and ($\times 1.20$) if glucocorticoids ≥ 7.5 mg/day for hip fracture probability (Kanis *et al*, 2011).
- Frequent intermittent use of higher doses of glucocorticoids increases fracture risk. Because of the variability in dose and dosing schedule, quantification of this risk is not possible.
- High-dose inhaled glucocorticoids may be a risk factor for fracture. FRAX may underestimate fracture probability in users of high-dose inhaled glucocorticoids.
- Appropriate glucocorticoid replacement in individuals with adrenal insufficiency has not been found to increase fracture risk. In such patients, use of glucocorticoids should not be included in FRAX calculations.

As the incidence of fracture increases rapidly after the initiation of glucocorticoid therapy, a therapeutic intervention is generally strongly recommended as soon as glucocorticoids are started (particularly for postmenopausal women), thus making the distinction between primary prevention (initiation of bone protective therapy at the time glucocorticoids are initiated) and secondary prevention (that bone protection is started later in the course of glucocorticoid therapy) not really relevant.

The most recent recommendations are reported in table 8. IOF-ECTS GIOP guidelines recommend a pharmacological intervention in men and women over the age of 50 years committed or exposed to ≥ 3 months of oral glucocorticoids, in individuals with a history of previous fractures, or older than 70 or receiving prednisolone ≥ 7.5 mg/day. In other situations, fracture risk assessment using FRAX with or without BMD should help to determine if the patient's risk has reached the intervention threshold adapted to the particular country. In younger people, the evidence base is limited: a previous fracture should be considered, but otherwise, treatment decisions are based on clinical judgment (Lekamwasam *et al*, 2012).

Country-specific restrictions for drug reimbursements often include a minimum daily dose and treatment duration for glucocorticoid.

Table 8 Intervention threshold for glucocorticoid-induced osteoporosis in postmenopausal women and men >50 yrs in recent recommendations

	ACR 2010	IOF/ECTS 2012	SFR 2014	NOF 2014
Glucocorticoids	≥ 7.5 mg/day ≥ 3 months if low risk; any dose ≥ 3 months if medium risk; no dose threshold if high risk	≥ 7.5 mg/d ≥ 3 months	≥ 7.5 mg/d ≥ 3 months	
Age		OR ≥ 70 yrs	OR ≥ 70 yrs	
Prior fracture		OR Fragility fracture	OR Fragility fracture	Fragility fracture
DXA T-score			OR T-score ≤ -2.5	OR T-score ≤ -2.5
FRAX	AND FRAX MOF: ≤ 10 % : low risk 10-20 % : medium risk >20 % : high risk	OR FRAX* > intervention threshold of general population	OR FRAX* > intervention threshold of general population	AND FRAX >20% MOF or >3% hip fracture

*Adjusted for GC dose

ACR, American College of Rheumatology; IOF/ECTS, International Osteoporosis Foundation/European Calcified Tissue Society; SFR, French Society for Rheumatology; NOF, National Osteoporosis Foundation

5.3 Pharmacological intervention

Fracture reduction has not been a primary endpoint in any of the intervention studies in GIOP. Thus, evidence for antifracture efficacy has to be derived from post hoc analyses, meta-analyses or safety data, invariably limited to vertebral fractures (Rizzoli and Biver, 2014).

Vitamin D metabolites, calcitonin, etidronate, pamidronate and clodronate have been tested in the past for the treatment of GIOP, but the trials never provided sufficiently robust results.

The bisphosphonates alendronate, risedronate and zoledronic acid are licensed in both Europe and North America for GIOP therapy. A Cochrane Review of the effects of bisphosphonates in the prevention and treatment of GIOP concluded that there were significant treatment benefits for lumbar spine and proximal femur BMD, which were generally somewhat lower than those observed in postmenopausal women. However, the 24% reduction in the odds of spinal fractures did not reach statistical significance.

A randomised clinical trial compared the effect on BMD (primary endpoint) and fracture risk (secondary endpoint) of subcutaneous teriparatide (20 µg/day) and oral alendronate (10 mg/day) therapy for 36 months in patients with GIOP. Teriparatide resulted in significantly greater increases in lumbar spine and hip BMD compared with alendronate, and was associated with significantly fewer patients with new vertebral fractures in the teriparatide group (Saag *et al*, 2009).

The results of this study are not surprising. GIOP is primarily a disorder characterised by reduced bone formation, which is expected to benefit from an anabolic approach rather than antiresorbers. Based on these data and its high cost, teriparatide treatment may be considered a therapeutic strategy for GIOP patients at high fracture risk.

6 Osteoporosis in men

6.1 General management

Male osteoporosis remains under-diagnosed, probably because of the common perception that osteoporosis is a disease of women, and the existence of an underlying cause in 50% of men with osteoporosis. Male osteoporosis is also clearly undertreated, since 15% of men older than 50 years will experience at least one osteoporotic fracture at some point, an event associated with higher morbidity and mortality rates than in women (Liu *et al*, 2008). Ensuring adequate calcium and vitamin D intake, and appropriate physical activity, is essential. Lifestyle factors known to be associated with bone loss should be avoided (eg, alcohol, tobacco).

6.2 Pharmacological intervention

Several drug classes are now available for treating male osteoporosis. For drugs allowed for the treatment of postmenopausal osteoporosis in women at high risk of fracture, bridging studies using the same formulation, dose and route of administration in male osteoporotic patients were considered as sufficient by the EMA for granting these drugs a marketing authorisation with the indication 'treatment of osteoporosis in men at increased risk of fracture', provided that:

- the duration of the study is at least 1 year
- the dosage is justified
- the applicant justifies that the cut-off of BMD, age and any other risk factor chosen for the inclusion of men in the pivotal study will generate a fracture risk of a similar magnitude compared with postmenopausal women who were recruited in the studies used to obtain the indication 'treatment of postmenopausal osteoporosis in women at increased risk of fracture'

- the magnitude of the changes in BMD versus placebo is similar to that observed in postmenopausal osteoporotic women treated with the same compound and is proportional to the decreased incidence of fractures in treated women.

Compared to studies in postmenopausal osteoporotic women, studies evaluating these drugs in male osteoporosis are characterised by considerably lower sample sizes (about 100 versus 1000 patients per group), shorter follow-up durations (2 years at most), and very few data on the occurrence of fractures. A recent report with new morphometric vertebral fractures as the primary endpoint indicates an antifracture efficacy of intravenous zoledronic acid in osteoporotic men, with the same trend as observed in women (Boonen *et al*, 2012).

Thus, alendronate, risedronate, zoledronic acid, and teriparatide are effective in male osteoporosis and have been validated in this indication by the EMA (Orwoll *et al*, 2000; Orwoll *et al*, 2003; Finkelstein *et al*, 2003; Boonen *et al*, 2009; Orwoll *et al*, 2010). They improve BMD in men, regardless of age and gonadal function. Indications for using these drugs should be based on absolute fracture risk.

6.3 Secondary osteoporosis in men

Secondary causes of osteoporosis should be identified and treated.

Data on the effect and safety of testosterone replacement therapy on bone density and fracture risk in men are lacking. Testosterone replacement therapy is appropriate for the management of hypogonadal syndrome, but the treatment of osteoporosis in a man with low testosterone levels is most likely undertaken with a bisphosphonate or PTH (Martin, 2011).

Androgen-deprivation therapy (ADT) for the treatment of prostate cancer is now a major secondary cause of osteoporosis. Bisphosphonate therapy prevents the bone loss associated with such therapy. Denosumab significantly reduces vertebral fracture risk in men on ADT (Smith *et al*, 2009).

GIOP is also a frequent cause of male osteoporosis.

7 Potential new drugs for osteoporosis

7.1 Novel antiresorptive agents

The development of odanacatib, a cathepsin K inhibitor, has recently been stopped because of a higher incidence of stroke in the treatment arm of the studies testing the effect of odanacatib in postmenopausal osteoporosis. Cathepsin K is a cysteine protease enzyme selectively expressed by osteoclasts, which is required to resorb bone matrix proteins including collagen.

7.2 Novel anabolic agents

Romosozumab, a monoclonal anti-sclerostin antibody, targets Wnt signalling, a pathway that regulates gene transcription of proteins important for osteoblast function such as β -catenin (Baron and Kneissel, 2013). Inhibitors of Wnt signalling, such as sclerostin or DKK1, decrease bone formation, while deficiencies in the inhibitors or antibodies to them result in increased Wnt signalling and bone formation. Sclerostin is an osteocyte-derived inhibitor of osteoblast activity. Romosozumab binds to sclerostin and increases bone formation. In a phase II trial in postmenopausal women, romosozumab (210 mg subcutaneous monthly) increases BMD at the lumbar spine more than placebo, alendronate or teriparatide. This positive effect on BMD was associated with a transitory increase (greatest at 1 month) in P1NP, a bone-formation marker, and a sustained decrease in CTX, a bone-resorption marker (McClung et al, 2014). The phase 3 Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) (n=7180) has been reported in 2016, showing that romosozumab lowers the risk of vertebral fractures compared to placebo at 12 months, then from months 12-24 both groups received 6 monthly 60mg S/C denosumab and the romosozumab group continued to have a lower risk of vertebral fracture 0.6% vs 2.5% (Cosman et al, 2016). Perhaps surprisingly, one atypical femoral fracture and two cases of osteonecrosis of the jaw were observed in the romosozumab group.

A press release from the manufacturer in May 2017 from a different phase 3 study has indicated in a primary analysis that treatment with romosozumab for 12 months followed by alendronate significantly reduced the incidence of new vertebral fractures through 24 months, clinical fractures (primary endpoints) and non-vertebral fractures (key secondary endpoint) in postmenopausal women with osteoporosis at high risk for fracture, compared to alendronate alone. However, an imbalance in positively adjudicated cardiovascular serious adverse events was observed as a new safety signal (2.5 percent romosozumab versus 1.9 percent alendronate at 12 months).

Abaloparatide, a selective activator of the parathyroid hormone type 1 receptor, is another bone anabolic agent which reduces the incidence of new vertebral fractures and nonvertebral fractures compared with placebo when studied over 18 months. Hypercalcemia may be less frequent with abaloparatide than with teriparatide (Miller, 2016). This study was extended to then offer both groups alendronate straight after the 18 months and a published interim analysis at a further 6 months shows a relative risk reduction of new morphometric vertebral fractures by 87% and lower estimated rates of non-vertebral fractures (risk reduction 52%) in the abaloparatide/alendronate group versus placebo/alendronate group (Cosman et al, 2017). In April 2017, subcutaneous abaloparatide received its first global approval, in the USA, for the treatment of postmenopausal women with osteoporosis at high risk for fracture (defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy).

The calcium sensing receptor (CaSR) is a G protein-coupled, seven-pass transmembrane molecule present in the parathyroid gland and kidney which monitors and controls calcium homeostasis by releasing PTH (Brown, 2007). Manipulation of the receptor by small molecule allosteric modulators can either decrease or increase PTH secretion (calcilytic agents). One of these agents (ronacaleret) has shown a robust PTH response associated with increases in both cortical and trabecular bone formation, but its development has been terminated because of insufficient efficacy in clinical trials.

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SUMMARY POINTS

- Any pharmacological intervention for postmenopausal osteoporosis and osteoporosis of the elderly should be preceded and accompanied by the elimination of risk factors: inadequate intake of calcium and vitamin D, smoking, low physical activity, excess alcohol intake.
- Among elderly people, vitamin D deficiency is extremely common and may severely jeopardise the outcomes from pharmacological interventions.
- Preventive measures should be recommended to all elderly subjects and in women after the menopause with risk factors.
- All pharmacological agents registered for the treatment of postmenopausal osteoporosis have evidence of efficacy on vertebral fracture risk. The same evidence for non-vertebral fracture is rather inconsistent.
- Antiresorbers (bisphosphonates, denosumab, raloxifene) are the most commonly used drugs for the treatment of osteoporosis. Most of the beneficial effects on bone mineral density (BMD) are achieved during the first year, provided that calcium and vitamin D deficiency is corrected.
- A pharmacological treatment is recommended when fracture risk is considered unacceptable, and this threshold may vary individually. Clinical risk factors and FRAX can help to assess fracture risk, although there is no universal threshold intervention associated with the FRAX tool.
- In patients with a history of major osteoporotic fracture, treatment should be recommended independently of the bone densitometry assessment.
- Chronic use of glucocorticoids is associated with a dramatic increase in fracture risk. The risk rises soon after treatment initiation and it is considerably higher than that expected from the actual value of BMD or its changes.
- Alendronate, risedronate and zoledronic acid have been the only agents registered for the treatment of glucocorticoid-induced osteoporosis until the registration for the same condition of teriparatide, which has shown superior antifracture efficacy over alendronate. Teriparatide is likely to become the treatment of choice for patients with severe glucocorticoid-induced osteoporosis.

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EULAR on-line course on Rheumatic Diseases

Osteoporosis: Treatment

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A previous version was coauthored by Christian Roux, Silvano Adami, Emmanuel Biver, Bernard Cortet



IN-DEPTH DISCUSSION I

**Vitamin D deficiency and response to treatment in
postmenopausal osteoporosis**

The registration of all available drugs for osteoporosis was obtained from the results of large randomized clinical trials (RCTs) demonstrating their ability to reduce fracture risk (Sambrook et al, 2006). All these clinical trials were conducted for patients with baseline 25-hydroxy-vitamin D (25OHD) within the normal range (with or without previous vitamin D supplements) and vitamin D supplements were provided all throughout the clinical trials to both active and control group. This implies that the reported benefits in terms of both increases in bone mineral density (BMD) and mainly reduced fracture risk can be expected only in vitamin D and calcium replete individuals.

In routine clinical settings this is not consistently achieved particularly for patients who do not get a qualified medical follow-up. A number of reasons may explain this. Vitamin D deficiency is extremely common among the elderly affecting proportions ranging from 40 to 100% (Holick et al, 2007). It is quite likely that both the prevalence and the severity of vitamin D deficiency are considerably greater among people requiring an osteoporosis treatment. Severe osteoporosis is very common among the elderly living in nursing homes and these patients are at high risk of vitamin D deficiency. Both the risk of vitamin D deficiency and the risk of osteoporosis rise with aging and the level of 25OHD are related to bone mineral density, fracture incidence and frailty (Isaia et al, 2003). Thus, people requiring pharmacological treatment for osteoporosis are likely to be at the highest risk of vitamin D deficiency for their osteoporosis (Bischoff-Ferrari et al, 2008). The patients participating on clinical trials for osteoporosis are generally younger and less frail than people on treatment for osteoporosis in a routine setting. More than 50% of postmenopausal women taking medications for osteoporosis were found to have suboptimal levels of 25OHD (below 30 ng/ml or 75 nmol/l) in the USA (Holick et al, 2005). In Italy, 35 % of the patients on pharmacological treatment for severe osteoporosis and followed by qualified osteoporosis centres had vitamin D deficiency (Adami et al, 2009). These findings are somewhat surprising since all guidelines recommend that any pharmacological intervention should be associated with calcium and vitamin D supplements. However, the implementation of these guidelines is hampered by a number of factors.

The definition of vitamin D insufficiency and deficiency has been changed only recently (Rizzoli et al, 2013) (table 1). From a number of different studies, it appears that 25OHD > 75 nmol/l are required in order to consistently prevent secondary hyperparathyroidism (Thomas et al, 1998; Holick et al, 2005), to achieve the genetically determined optimal bone mass and to optimize muscle strength (Bischoff-Ferrari et al, 2010). Intestinal calcium absorption is also dependant of 25OHD levels (Heaney et al, 2003). Many laboratories still report as normal levels of 25OHD > 10 ng/ml (25nmol/l), which are now considered totally inadequate for bone health.

Meta-analyses of vitamin D supplementation have provided evidence that a dose of 800UI/day vitamin D is required to achieve the correct daily allowance of vitamin D (Bischoff-Ferrari et al, 2012). This approach may be inadequate if the patient is vitamin D deficient and therefore deprived of appropriate vitamin D reserves.

However, the use of high loading doses of vitamin D at the outset of repletion has been reconsidered by recent data indicating that women receiving once annual high dose of oral cholecalciferol (500,000 IU) experienced more falls and fractures than the placebo group (Sanders et al., 2010). The causes of these effects remain speculative and need further studies. Similar observations on falls were found with lower loading doses (60 000 IU of vitamin D per month) versus 24 000 IU vitamin D per month in community-dwelling men and women 70 years and older (Bischoff-Ferrari et al, 2016). The specific vitamin D dosing regimen to correct vitamin D deficiency or insufficiency should use more frequent but low dose regimens for which there is no evidence of adverse effects (for example if the patient is vitamin D deficient, 1500-2000 IU vitamin D per day for one to three months followed by 800 IU vitamin D per day).

The impact of vitamin D deficiency on the response to treatment in postmenopausal osteoporosis has been occasionally underestimated. For example, from a post-hoc analysis of the MORE trial, it was concluded that vitamin D insufficiency does not affect the BMD response to raloxifene (Antoniucci et al, 2005). Regarding patients treated with bisphosphonates, it has been shown that patients with a mean 25(OH)D ≥ 33 ng/ml (82nmol/l) have a substantially greater likelihood of maintaining bisphosphonate favourable response (no T-score < -3 that persists between DEXA scans, no decrease in BMD higher than 3%, and no incident fracture on bisphosphonate therapy) (Carmel et al., 2012). The BMD changes were analysed according to individual 25OHD levels as measured at the time of randomization and they were found somewhat greater among vitamin D insufficient patients. Patients with vitamin D insufficiency are expected to exhibit greater changes in BMD from the vitamin D supplementation provided during clinical trials than people with normal 25OHD levels.

An additional problem may come from the way the problem of calcium and vitamin D supplementation is discussed with the patient. Typically, most osteoporotic patients are advised to take pharmacological formulations combining calcium salts to vitamin D. The treatment adherence to these formulations is modest due to the poor tolerability of calcium salts (Rossini et al, 2006). The general attitude is the recommendation of taking as much as possible of the prescription but the consequence may be that many patients, for the intolerance of calcium, get neither calcium nor vitamin D.

Providing adequate calcium intake is a puzzling problem for the many patients who are intolerant to both dairy products and calcium supplements. Calcium intake and 25OHD levels are both important determinants of PTH secretion (Steingrimsdottir et al, 2005; Adami et al, 2008).

The consequences of vitamin D deficiency on the treatment outcome of pharmacological treatment of osteoporosis are poorly understood since ad hoc prospective studies are ethically unconceivable. The only information comes from case reports or retrospective studies.

A study looking at the prevalence of inadequate response to anti-resorptive agents (alendronate, risedronate and raloxifene) in patients with severe osteoporosis showed that the inadequate supplementation with calcium and vitamin D was associated with 98% higher occurrence of clinical fracture (Adami et al., 2006). In a study evaluating retrospectively the treatment outcomes of at least one year therapy with anti-resorptive agents (Adami et al, 2009), it was reported that one third of the patients were vitamin D deficient. In those patients, BMD slightly decreased during the one year of observation while it raised by 2% in women replete with vitamin D. It was also observed that the proportion of patients with incident clinical fracture was almost double in vitamin D deficient as compared to vitamin D-replete women.

In conclusions undiagnosed vitamin D deficiency is frequent even among patients on pharmacological treatment for osteoporosis. Vitamin D deficiency is associated with the complete abolition of the benefits expected from osteoporosis therapy and is also likely to be associated with an increased risk for a number of severe conditions such as falls, cancer, cardiovascular diseases and cognitive impairment (Holick et al, 2007). It is highly recommended that all patients are checked for vitamin D deficiency before commencing any pharmacological treatment for osteoporosis. If the 25OHD levels are low, a personalized and continuous dose should be considered, avoiding the loading doses.

Table 1.

Definition	25 OH vitamin D	Manifestations - Comments
Vitamin D deficiency	< 10 ng/ml (25 nmol/l)	Osteomalacia (mineralization defect), muscle weakness
Vitamin D insufficiency	< 20 (50 nmol/l)	Secondary hyperparathyroidism, osteoporosis, increased morbidity
Vitamin D adequacy	20-30 ng/ml (50 to 75 nmol/l)	Bone turnover and PTH normalized
	≥ 30 ng/ml (75 nmol/l)	Desirable target in the fragile elderly due to optimal benefits on fracture, falls and mortality
Upper limit of adequacy	> 80 ng/ml (200 nmol/l)	Possible adverse effects above this level (Hypercalcaemia, hypercalciuria)
Maximum safe dose	2000 IU/day	Higher toxicity in patients with granulomatosis
Increases per 100 IU/day of vitamin D	1,2 ng/ml	Greater changes in vitamin D repleted subjects

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IN-DEPTH DISCUSSION II

Atypical femoral fractures in patients on antiresorptive therapy

Bisphosphonates and denosumab decrease the risk of fracture in postmenopausal osteoporosis. Nevertheless, reports of femoral shaft fractures in primarily postmenopausal women treated for long periods of time with alendronate generated the definition of “atypical femoral fractures” (AFFs). These were suggested as a possible clinical manifestation of the old and unproven “frozen bone” concept, in which treatment-induced suppression of bone turnover would lead to decrease bone strength.

The first nine reported cases of spontaneous non-vertebral fractures in alendronate-treated patients, including 3 diaphyseal femoral fractures, were characterized by delayed or absent healing and bone turnover inhibition with no double labelling on histomorphometry, suggesting a treatment effect that was either too strong or too long lasting (Odvina et al, 2005). A systematic analysis of 141 published cases (Giusti et al, 2010) showed that the link between bisphosphonate exposure, bone turnover suppression and atypical femoral fractures occurrence was not as clear as suggested initially. First, the histomorphometry findings do not clearly support treatment-induced bone turnover inhibition as the only mechanism underlying atypical femoral fractures. A decrease in bone formation was not found in all cases. This decrease was marked in some patients but was not accompanied with mineralization disorders, and increased resorption was observed occasionally (Somford et al, 2009; Giusti et al, 2010; Shane et al, 2014). In addition, atypical femoral fractures occurred after less than 3 years of bisphosphonate exposure in 25% of cases (median of 60 months, range of 3 to 192 months) (Giusti et al, 2010), which does not support a role for excessively prolonged bone turnover inhibition. However, recent retrospective data indicate that longer duration of treatment with bisphosphonates results in augmented risk of atypical fractures (Meier et al, 2012). Moreover, atypical femoral fractures are also observed in patients treated with denosumab, and in bisphosphonate and denosumab-naïve patients (Meier et al, 2012), adding further complexity to the understanding of the pathogenesis.

The reported cases have allowed the identification of several distinctive features of atypical femoral fractures (Lenart et al, 2005). A task force of the American Society for Bone and Mineral Research (ASBMR) defined diagnostic criteria, revised in 2013, to improve the recognition and incidence assessment of atypical femoral fractures (Table 1) (Shane et al, 2014). AFFs are characterized by unique radiographic and clinical features (prodromal pain, bilaterality) that resemble stress fractures or reactions (figure 1 and 2).

Epidemiological data support a relationship between bisphosphonates use and atypical subtrochanteric and femoral shaft fractures (Abrahamsen et al, 2009; Abrahamsen et al, 2010; Schilcher et al, 2011). AFFs appear to be more common in patients who have been exposed to long-term bisphosphonates, usually for more than 3 years, even if AFFs have been reported in patients treated by denosumab, or patients who have never been treated with antiresorptive drugs. The risk for AFFs may decline after bisphosphonates are stopped (Schilcher et al, 2011). The majority of studies have found a significant association with glucocorticoids or proton pump inhibitors use or duration. Although the relative risks of AFFs are very high in patients on BPs, ranging from 2.1 to 128, their absolute risk is extremely low, ranging from 3.2 to 50 cases per 100,000 person-years.

Table 1: Diagnostic criteria for atypical femoral fractures (ASBMR Task Force 2013 Revised Case Definition of AFFs) (Shane et al, 2014).

To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least four of five Major Features must be present. None of the Minor Features is required but have sometimes been associated with these fractures.

Major features

- The fracture is associated with minimal or no trauma, as in a fall from a standing height or less
- The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
- The fracture is non-comminuted or minimally comminuted
- Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”)

Minor features

- Generalized increase in cortical thickness of the femoral diaphyses
- Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral incomplete or complete femoral diaphysis fractures
- Delayed fracture healing

Exclusion criteria

- fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumours and miscellaneous bone diseases (e.g., Paget’s disease, fibrous dysplasia).

These fractures are now considered as stress or insufficiency fractures which do not normally heal. The suppression by anti-resorptive therapy of intracortical remodelling at the site of the stress fracture would impair the processes by which stress fractures normally heal, potentially including microdamage accumulation and changes to bone mineralisation and collagen crosslinking, which can progress to full fracture. The location of AFFs at the subtrochanteric and femoral shaft regions is probably related to mechanical forces on the lower limb, which may be influenced by the geometry of the hip and proximal femur. Hip geometry determines in part the stresses that are experienced on the lateral aspect of the femoral cortex. The lateral cortex of the femur is known to sustain high levels of tensile stress due to bending which may precipitate the damage in this location especially in those people with lower limb geometry that could exacerbate that effect (e.g., a bowed femur, Asian race).

Regarding clinical prodromal symptoms, a complaint of thigh pain from a patient at risk for osteoporosis should suggest this possibility, particularly if the patient has a history of bisphosphonate exposure. The time

interval from the onset of prodromic pain and the diagnosis of an atypical femoral fracture varies widely, from 1 week to 2 years (Giusti et al, 2010). Any thigh pain in a BP-treated patient should lead to the immediate interruption of the treatment and appropriate diagnosis procedure. Incomplete AFF may be observed on X-ray in this context before the complete fracture occurs (Figure 2). The index of suspicion should be particularly high in patients with rheumatoid arthritis, chronic obstructive pulmonary disease, asthma, or diabetes; and in those with a history of exposure to systemic glucocorticoid therapy or proton pump inhibitors. Recurrences have been reported in patients who had several of these risk factors (Giusti et al, 2010).

Bone scintigraphy combined with single photon emission CT (SPECT) or MRI can assist in the early diagnosis of bone fragility heralding a fracture, consistent with a stress fracture (Somford et al, 2009), which should be considered if clinical suspicion for AFF remains high despite normal plain radiographs. In contrast, it seems that neither bone marker levels (Shane et al, 2014) nor bone mineral density values (Giusti et al, 2010) are of diagnostic assistance.

Where an atypical femoral fracture is diagnosed, the ASBMR recommend discontinuing the bisphosphonate, optimising calcium and vitamin D status, and to consider teriparatide. It is still unclear if teriparatide may advance healing of AFFs with no available randomised studies, but there are an increasing number of case reports of its beneficial impact on healing as an adjuvant. Its use has been considered due to improved bone turnover and microarchitecture in patients on long term alendronate - with enhanced fracture healing by increased callus formation and mechanical strength – together with two clinical trials showing shortened healing time in patients with osteoporotic fractures (Kharwadkar et al 2017). Intramedullary nailing should be considered for complete AFF or painful incomplete AFF. If asymptomatic incomplete AFF, then minimal weightbearing until MRI shows no bone oedema with MRI surveillance is suggested. The UK MHRA recommends imaging the contralateral side if an AFF is found as they can occur bilaterally.

Although both the existence of atypical femoral fractures and the major role for bisphosphonate therapy as a risk factor have been firmly established, these fractures account for only a small proportion of subtrochanteric and diaphyseal femoral fractures. Therefore, the risk of atypical femoral fractures does not call into question the favourable risk/benefit ratio of antiresorptive drugs in patients with osteoporosis at high risk of fracture. Together with recent data on the effect of bisphosphonate duration on fracture risk reduction, these AFFs contribute, in clinical practice, to limit currently bisphosphonate duration to 3 to 5 continuous years.

Figure 1: Subtrochanteric atypical femoral fracture



Figure 2: Diaphyseal complete right atypical femoral fracture, with incomplete left atypical femoral fracture at the same diaphyseal level.



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module

EULAR on-line course on Rheumatic Diseases

Other bone diseases

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1 PAGET'S DISEASE OF BONE

LEARNING OBJECTIVES

- Determine the epidemiology and main genetic factors involved in Paget's disease
- Make the diagnosis of Paget's disease based on clinical evaluation, imaging and biology testing
- Manage and monitor treatment

1.1 Introduction

Paget's disease of bone (PDB) is a chronic benign condition characterised by focal areas of increased and disorganised bone remodelling affecting various sites throughout the skeleton. The disease mostly involves the axial skeleton, and bones that are commonly affected include the pelvis, femur, tibia, lumbar spine, skull and scapula. The condition can be monostotic (i.e., affecting one bone only) or polyostotic (i.e., involving several bones).

1.2 Epidemiology

Paget's disease is seldom diagnosed before the age of 40 but gradually increases in incidence thereafter to affect up to 10% of the UK population by the age of 85. PDB affects both genders, with apparently a small male predominance. Incident disease activity decreases with age and no impact on survival has been observed in a US population (Wermers et al, 2008). The disease is common in Caucasian populations from north-west and southern Europe but is rare in Scandinavian, Asian, Chinese and Japanese populations. This ethnic susceptibility persists after migration in particular in Caucasians, illustrating the importance of genetic factors in aetiology. According to a recent meta-analysis, the incidence of PDB has also been found to have decreased in some countries over the past 25 years (Corral-Gudino et al, 2013), suggesting that environmental factors also play a role. This decrease in the prevalence of PDB has not been observed in Spain and Italy, nor in Asian descents living in New Zealand (Sankaran et al, 2012). It should be recalled that part of the appearing decrease in prevalence could be attributed to the evolution in radiological techniques. Indeed, plain abdomen X rays, intravenous pyelography or barium colonic enema that were used in initial epidemiologic studies to determine the PDB frequency, are nowadays much less utilized than ultrasonography and endoscopic examinations which are unable to study the skeleton. What seems to have been observed more recently is a decrease in the severity of PDB and changes in the mode of presentation of PDB (Tan et al, 2014).

1.3 Pathogenesis

Pagetic bone lesions show evidence of focal increased osteoclastic bone resorption which is accompanied by other abnormalities such as marrow fibrosis, increased vascularity of bone and increased bone formation (Galson et al, 2014*). The rapid rate of bone turnover in PDB leads to the production of woven bone which has reduced mechanical strength, leaving patients at increased risk of developing deformities and pathological fractures. Osteoclasts are increased in number and size and contain nuclear inclusion bodies, which are micro-cylindrical structures that resemble virus particles. These inclusion bodies are not specific for PDB, however, and their true identity has not yet been established. The discovery of these particles led to the suggestion that PDB may be due to a persistent measles viral infection of bone cells, although data on this are conflicting. Interestingly, osteoblasts are also abnormal in PDB. They are produced in greater numbers, and they form more bone for a longer time than normal osteoblasts. Also, they overexpress cytokines such as IL-6 and Dickkopf-1, an antagonist of the Wnt/ β -catenin signalling pathway.

The cause of PDB is incompletely understood, but genetic factors clearly play an important role (Galson et al, 2014*). Approximately 15% of PDB patients have a positive family history and the risk of developing PDB is increased seven- to tenfold in the first degree relatives. In several families, classic PDB is inherited as an autosomal dominant trait with high penetrance. In the recent years, several genetic variations have been identified in genes associated with PDB and related syndromes. The most important gene linked to classic PDB is sequestosome 1 (SQSTM1) which encodes p62, a scaffold protein that is involved in NF- κ B signalling (Hocking et al, 2012). Missense and stop mutations of SQSTM1, almost all located in the region coding the ubiquitin binding domain of the SQSTM1/p62 protein, have been reported to account for 20–50% of cases of familial PDB and 8–20% of cases of sporadic PDB. Some evidence suggests that loss of ubiquitin binding is one mechanism by which SQSTM1 mutations causes PDB, although autophagy may also be involved (Hocking et al, 2012). Patients with SQSTM1 mutations have severe PDB and penetrance is between 80% and 100% by the seventh decade. It is likely that environmental factors interact with SQSTM1 mutations to affect disease severity since a recent study showed that children of SQSTM1 mutation carriers resident in New Zealand had a 5–10-year delay in onset of the disease compared with their parents. In approximately 60% of patients with classic PDB, the gene is unknown but candidate loci for susceptibility genes have been discovered on chromosomes 5q31 and 10p13. Recent genome-wide association studies have identified polymorphisms that are associated with the disease: TNFRSF11A, which encodes the receptor activator of NF- κ B, colony stimulating factor-1 and optineurin (Albagha et al, 2010), as well as TM7SF4, encoding DC-STAMP, RIN3, NUP205, and PML (Albagha et al, 2011).

The pathogenetic role of environmental factors, classically associated with PDB according to the literature, such as deficiencies in calcium or vitamin D during childhood, biomechanical stress from repetitive use of affected bones, environmental exposure to combustion products, rural lifestyle, domestic animal exposure,

and chronic infection with the paramyxoviruses such as measles virus, canine distemper virus, and respiratory syncytial virus (Galson et al, 2014*) still remains unclear.

1.4 Clinical features

The most common presentation of PDB nowadays is through incidental finding of elevated serum alkaline phosphatase (ALP) or an abnormal X-ray that is performed for another clinical indication. Occasionally, PDB presents with specific features such as bone pain and deformity. Bone pain due to PDB is typically present at rest and at night as well as upon using an affected limb. In clinical practice, however, it is often difficult to distinguish pain secondary to the increased metabolic activity of PDB from pain due to secondary osteoarthritis or unrelated conditions such as degenerative disc disease. Bone deformity is a feature of advanced PDB (figure 1). Patients with metabolically active disease may exhibit an increase in the skin temperature over affected bones, explained by hypervascularity. This sign is usually most apparent in patients with PDB of the tibia or the patella. Paget's disease can be associated with several complications including deafness, pathological fracture, secondary osteoarthritis, cranial nerve compression syndromes and spinal stenosis (box 1) and the disease has a significant negative impact on quality of life (Langston et al, 2007). Although these conditions are common in elderly patients without PDB, epidemiological studies have shown that Paget's patients are three times more likely to need a hip replacement for osteoarthritis compared with age-matched controls and nearly twice as likely to need a knee replacement (van Staa et al, 2002). Other complications that are significantly more common in Paget's disease when compared with controls include hearing loss, tinnitus, dizziness, back pain, osteoarthritis and fracture. Partial fissure fractures can be observed perpendicular to the outer cortex of bowed bones. They can prolong to complete transverse atypical fractures. Paraplegia is a rare complication. This can occur as the result of spinal cord compression to bony expansion of affected vertebrae but can also occur as the result of a vascular steal phenomenon due to increased blood flow in affected vertebrae. Osteosarcoma is a rare complication of PDB, occurring in about 0.1% of patients, but most osteosarcomas that occur in adulthood are associated with PDB (van Staa et al, 2002). Patients with PDB who are immobilised can develop hypercalciuria and hypercalcaemia. The most common scenario is the result of dehydration when an affected patient is confined to bed because of an intercurrent illness or following surgery. High output cardiac failure has been described due to increased blood flow through affected bone but is extremely rare.

Figure 1. Bone deformity of the tibia in Paget's disease



Box 1. Complications of Paget's disease of bone.

Common
• Bone pain
• Bone deformity
• Pathological fracture
• Osteoarthritis
• Deafness
Less Common
• Spinal stenosis
• Nerve compression syndromes
Rare
• Hypercalcaemia (with immobilisation)
• Hydrocephalus
• Paraplegia
• Cardiac failure
• Osteosarcoma

1.5 Diagnosis

The diagnosis of PDB is usually made on the basis of X-ray, biochemical screening and radionuclide bone scans. The typical biochemical abnormality in active PDB is an elevated ALP level in the presence of otherwise normal biochemistry, including Gamma-glutamyl transferase. Levels of ALP are elevated in over 90% of cases but can be normal when only a single bone is affected. Other specialised biochemical markers such as the urine deoxypyridinoline/creatinine ratio, bone specific ALP and the amino-terminal propeptide of type I collagen

(P1NP) are also elevated in active PDB, but in routine practice their evaluation does not seem to offer much advantage over ALP in the assessment of patients. A radionuclide bone scan is a useful way of screening for the presence of PDB and documenting its extent (figure 2). If the bone scan is positive, radiographs should be performed on all affected bones to confirm the diagnosis. Typical features on X-ray are osteosclerosis, alternating with osteolysis, bone expansion and bone deformity (figures 3–7). Bone biopsy is not usually required to make the diagnosis of PDB, but it can be helpful when the diagnosis is not clear and specifically to differentiate PDB from osteosclerotic metastases, particularly in prostate cancer bone metastases that can co-exist with PDB in the same patient. In rare cases, giant cell tumours can develop, particularly in very extensive PDB (figure 8A–C) (Rendina *et al*, 2015). Increase in pain intensity, pain at night, occurrence of a biological inflammatory syndrome and/or hypercalcemia without a context of immobilization can be considered as red flags for malignant degeneration of pagetic bone (figure 9).

Figure 2. Bone scan in Paget's disease

a. Radionuclide scan showing increased tracer uptake in the pelvis, both femurs, lumbar spine, scapula, sternum and base of the skull, typical of PDB at these sites.



b. Other patient with uptake in the left tibia and both femurs. Personal collection of Prof P Orcel, Rheumatology, Lariboisière Hospital, Paris, France.

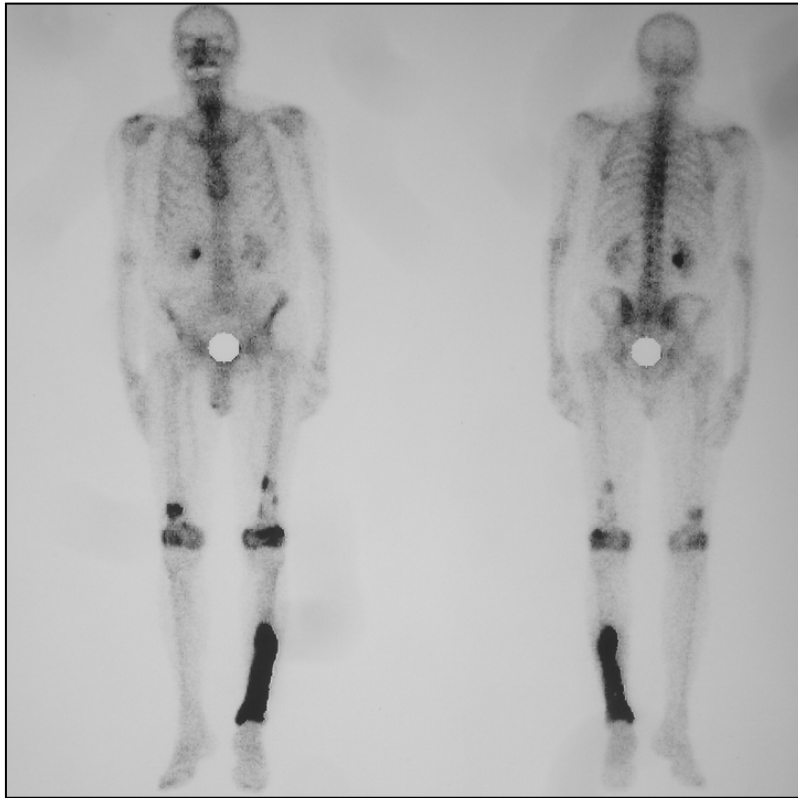


Figure 3. X-ray appearances in Paget's disease. X-rays of the tibias (lateral view) show alternating areas of osteosclerosis and osteolysis and expansion of the bone. (Same patient as in Figure 2b). Personal collection of Prof P Orcel, Rheumatology, Lariboisière Hospital, Paris, France.



Figure 4. Involvement of the skull. X-ray of the skull from a patient with PDB showing circumscribed osteolytic skull lesion. Personal collection of Prof P Orcel, Rheumatology, Lariboisière Hospital, Paris, France.

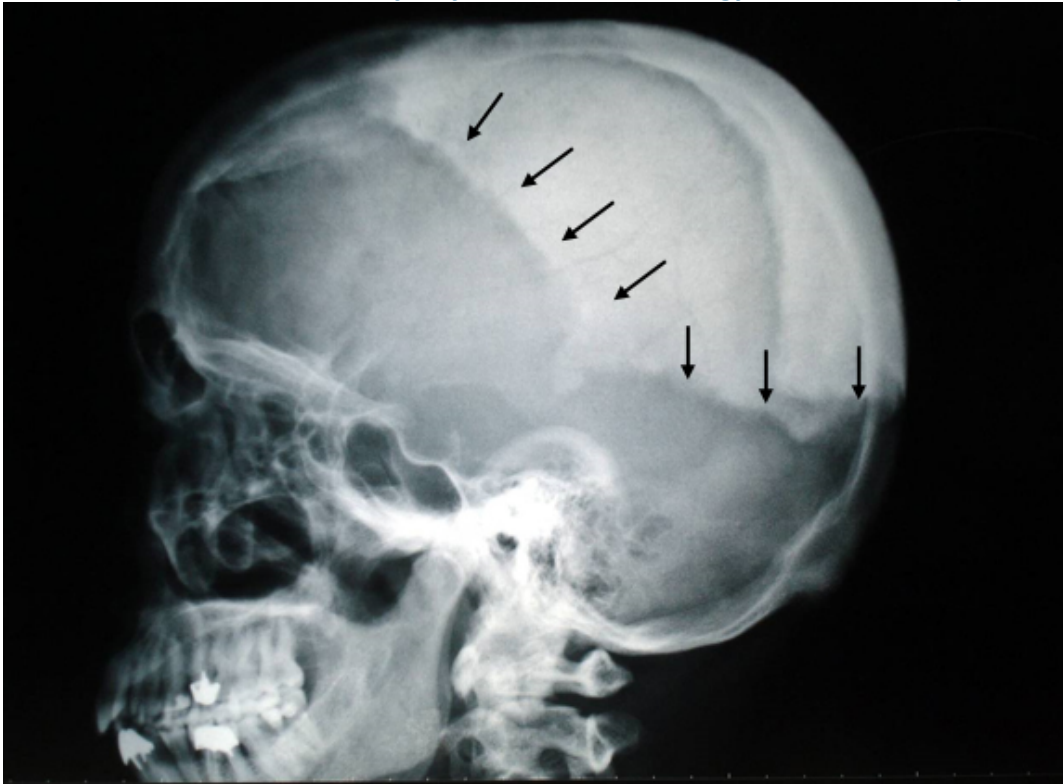


Figure 5. Secondary osteoarthritis in PDB. Typical PDB radiographic signs with bilateral secondary osteoarthritis of the hips. Personal collection of Prof P Orcel, Rheumatology, Lariboisière Hospital, Paris, France.



Figure 6 a, b and c. Monostotic vertebral Paget's disease in the lumbar vertebra L4 with secondary spinal stenosis, in a female patient aged 82 years (CT-scan, sagittal views). Diagnosis was made at 58 years. Patient was treated with IV bisphosphonates. Personal collection of Prof JP Devogelaer, Rheumatology, Cliniques Universitaires Saint - Luc, Brussels, Belgium.



Figure 7 a and b. Spinal stenosis secondary to PDB of the lumbar vertebra L2 (MRI sagittal and axial views) in a 74 years old man.

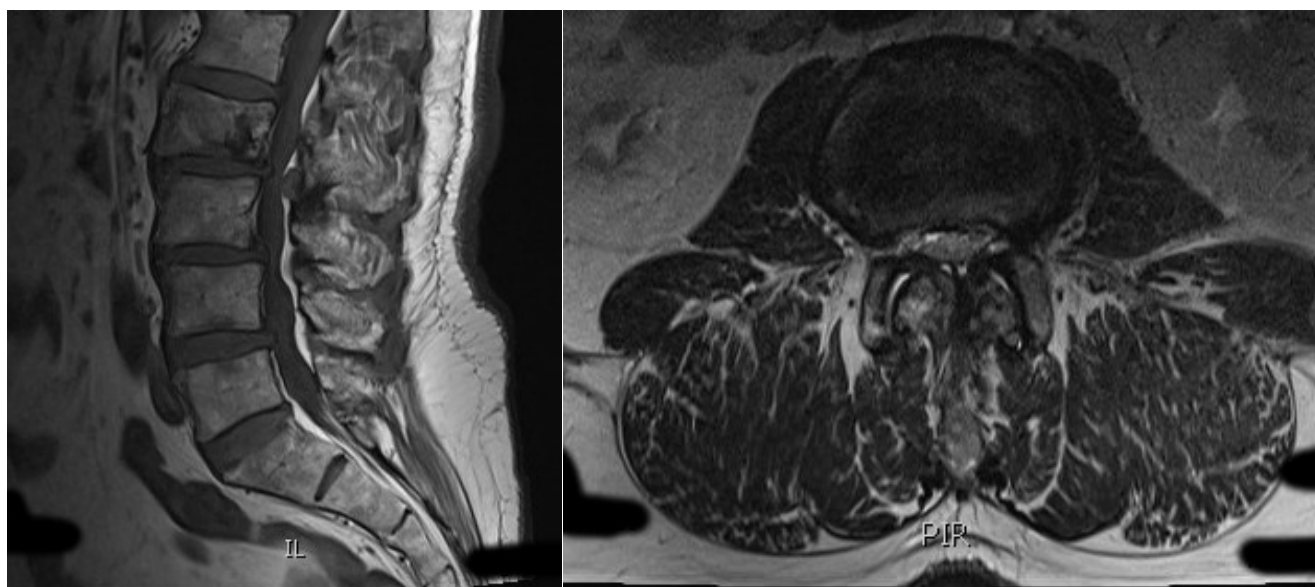


Figure 8. Giant cell tumour in a Pagetic site at the humerus, in a polyostotic Paget disease in a male patient aged 31. Personal collection of Prof JP Devogelaer, Rheumatology, Cliniques Universitaires Saint - Luc, Brussels, Belgium.

a. Radionuclide scan showing increased tracer uptake at several sites in polyostotic PDB



b, c. Giant cell tumour in a Pagetic site at the humerus in the same patient (X-ray, MRI t1 weighted coronal image)

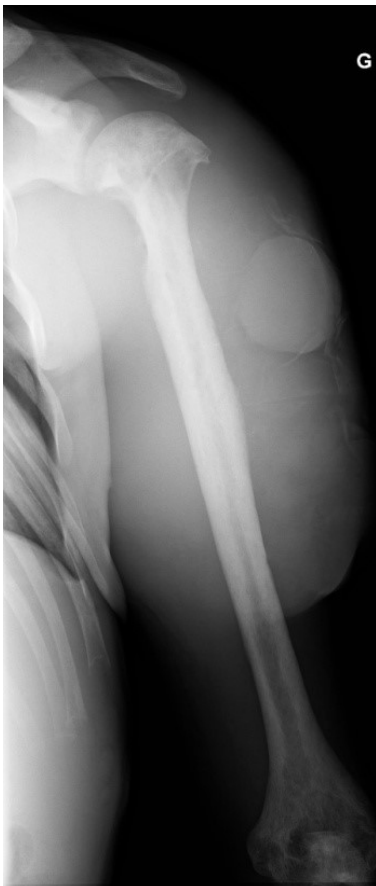
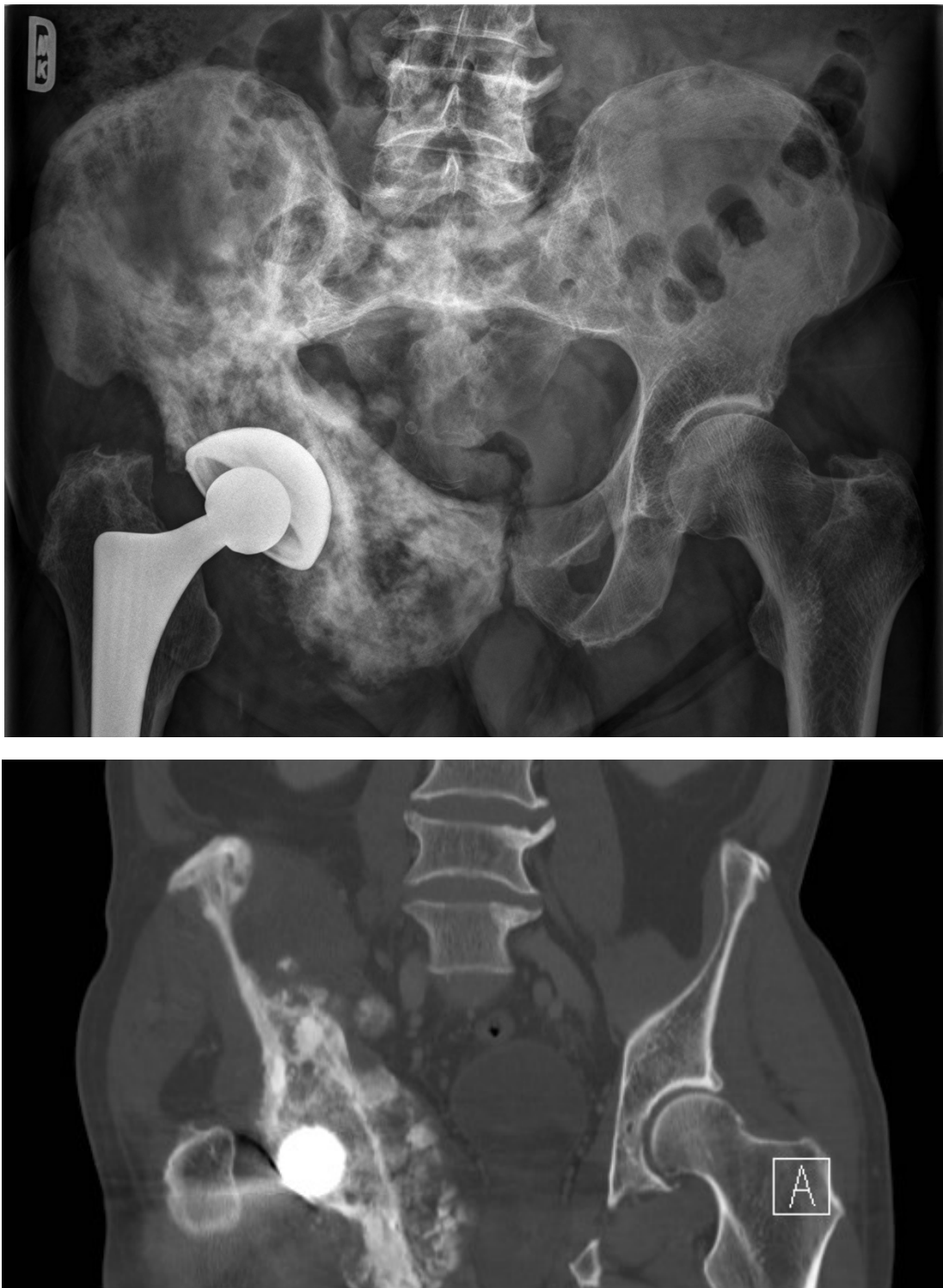
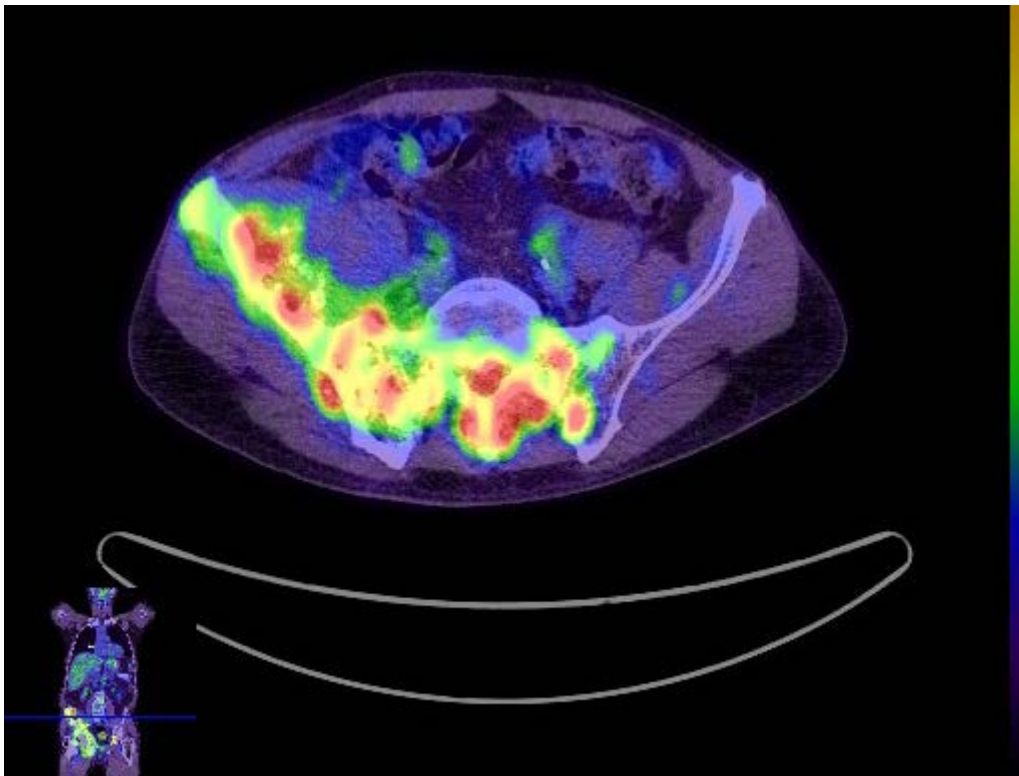


Figure 9 a, b and c. Osteosarcoma complicating Paget's disease of the right pelvis and sacrum in a 75 years old patient with PDB and persistent bone pain at night, even after right hip replacement. Typical aspects of heterogeneous bone lesion with severe osteolysis and blastic lesions on radiographs, CT-scan and heterogeneous hypermetabolism on FDG-PET scan.





1.6 Medical Management

The main indication for treatment of PDB is pain, which may arise from an increase in metabolic activity, from bone deformity, from nerve compression syndromes, from secondary osteoarthritis or from co-existing diseases. In many cases, pain can be adequately controlled by administration of painkillers such as paracetamol or non-steroidal anti-inflammatory drugs, but if these measures are ineffective, then bisphosphonates should be given (table 1). Bisphosphonates are generally effective at controlling pain from the increased metabolic activity of PDB, but are generally less effective at treating pain which occurs as the result of complications such as deformity, nerve compression syndromes or secondary osteoarthritis. Aminobisphosphonates such as pamidronate, risedronate, alendronate and zoledronic acid are more effective than older bisphosphonates such as etidronate and tiludronate at suppressing biochemical markers of bone turnover in PDB. However, randomised comparative studies of different bisphosphonates have generally shown no significant difference between therapies in terms of pain control (Langston and Ralston, 2004*) except from recent comparative study of risedronate versus zoledronic acid where zoledronic acid was shown to be slightly superior to risedronate in treating bone pain (Reid et al, 2005). The advantages of zoledronic acid are mainly its easy mode of administration and its long-lasting efficacy (Devogelaer et al, 2014), a single infusion being able to induce a disease suppression in two-third of patients (Cundy et al, 2017). Calcitonin can be used as an alternative to bisphosphonate therapy in PDB, but is less convenient to administer and

significantly more expensive. It should be reserved for the rare cases of intolerance to bisphosphonates. There is no longer any indication for etidronate in PDB therapy.

Table 2. Bisphosphonates used in the treatment of Paget's disease

Drug	Trade Name	Dose
Clodronate	Loron, Bonefos	400–1600 mg/day orally for 3–6 months or 300 mg/day intravenously for 5 days
Pamidronate	Aredia	60 mg/day intravenously for 3 days
Alendronate	Fosamax	40 mg/day for 6 months
Tiludronate	Skelid	400 mg/day for 3 months
Risedronate	Actonel	30 mg/day for 2 months
Zoledronic acid	Aclasta/Reclast	5 mg intravenously by a single injection

The long term effects of anti-resorptive therapy with bisphosphonates and calcitonin on complications of PDB such as deafness, bone deformity and fracture are unknown since most studies were on short term follow-up and have focused on biochemical markers as the primary endpoint.

1.7 Surgical Management

Surgery is frequently required for the management of complications. The most common indication for surgical treatment is arthroplasty for osteoarthritis, but surgery may also be required for fracture fixation, osteotomy to correct bone deformity, and surgery to correct spinal stenosis. Surgery in patients with PDB can be technically challenging because of bony enlargement, deformity and increased vascularity, although in general, the results of surgery in PDB are favourable and significantly improve the quality of life for patients with the condition, particularly those with advanced osteoarthritis. Bisphosphonate therapy is frequently given before elective orthopaedic surgery in the hope that this might reduce operative blood loss. The effects of bisphosphonate therapy on blood loss have never been studied in a controlled trial but this approach is widely recommended by experts (Singer et al, 2014). Orthopaedic surgery may also be required for the treatment of osteosarcoma, but the prognosis is poor even with aggressive operative treatment.

1.8 Monitoring disease activity

Serum alkaline phosphatase (total ALP) levels are generally used to assess the activity of PDB and to monitor the effects of anti-resorptive treatment. Other specialised markers of bone turnover are marginally more sensitive, but costs are greater and there is no evidence that, beyond the context of monostotic PDB, they offer any clinical benefit over ALP. Some clinicians give anti-resorptive therapy routinely when ALP levels are raised (by $\geq 25\%$ compared to the lowest total ALP level) and aim to maintain levels within the lower half of the normal range by repeated courses of anti-resorptive therapy (Singer et al, 2014). After a first successful course

of therapy, ALP should be measured every 6–12 months in order to identify any recurrence of the condition. Other clinicians provide treatment when patients experience symptoms related to Paget's disease. These strategies seem to provide equivalent results in established PDB; in a recent study, no clinical benefit was observed in patients who received repeated courses of bisphosphonate with the aim of maintaining normal levels of ALP as compared with those given symptomatic treatment for bone pain. This randomised trial showed no significant differences between groups in quality of life, bodily pain, Pagetic bone pain, clinical fractures or orthopaedic surgery (Langston *et al*, 2010). Currently, there is no evidence to show that prophylactic therapy with bisphosphonates is effective at preventing complications of Paget's disease. Experts recommend the repeat of x-rays in the follow-up of osteolytic lesions after one year, in case of persistent elevation of bone markers and persistence of bone pain (Singer *et al*, 2014).

2 OSTEOMALACIA

LEARNING OBJECTIVES

- ➔ List the main causes of osteomalacia

2.1 Definition

Osteomalacia is the term used to describe a syndrome of defective bone mineralisation, bone pain, increased bone fragility and fractures that occurs in adults. Osteomalacia is considerably less common nowadays due to improved nutrition and sunlight exposure. However, the disease remains prevalent in elderly and housebound patients who have a poor diet, limited sunlight exposure and in Moslem women who live in northern latitudes. The most common cause of osteomalacia is vitamin D deficiency, but many pathological states can lead to osteomalacia including tumours and drugs.

2.2 Vitamin D deficiency and osteomalacia

The most common cause of osteomalacia is reduced sunlight exposure since ultraviolet light stimulates conversion of 7-dehydrocholesterol in the skin to cholecalciferol. Cholecalciferol then undergoes 25-hydroxylation in the liver to produce $25(\text{OH})\text{D}_3$ which is converted into the active metabolite $1,25(\text{OH})_2\text{D}_3$ by the kidney. Osteomalacia can also occur as the result of reduced dietary intake, as vitamin D concentration is usually low in most foods, except in oily fish, so the amount present in the average diet is generally insufficient to meet requirements.

In the presence of vitamin D deficiency, production of $1,25(\text{OH})_2\text{D}_3$ is therefore reduced. This results in impairment of intestinal calcium absorption with reduced influx of calcium from the gut into the blood. This tends to lower serum ionised calcium which is detected by the parathyroid gland, causing increased secretion of parathyroid hormone (PTH). This secondary hyperparathyroidism leads to renal phosphate wasting and increased bone turnover. While the elevation in PTH is usually sufficient to maintain serum calcium levels within the normal range, in the early phase of the disease, this is at the expense of progressive demineralisation of bone and increased fracture risk. Low vitamin D, calcium and high PTH thus contribute to the bone defects.

2. 3 Other causes of osteomalacia

Aluminium intoxication can cause osteomalacia in patients with chronic renal failure due to direct inhibition of mineralisation (Boyce et al, 1982). The condition is now rare due to a reduction in the use of aluminium-containing phosphate binders and removal of aluminium from water supplies used in dialysis. The diagnosis can be confirmed by demonstration of aluminium accumulation in an iliac crest biopsy specimen.

Bisphosphonates can cause osteomalacia due to direct inhibition of mineralisation. This has mostly been described in patients with Paget's disease receiving etidronate and high dose pamidronate (Boyce et al, 1984; Boyce et al, 1994). In most cases the osteomalacia is asymptomatic and healing occurs when treatment is stopped. Excessive intake of fluoride also causes osteomalacia due to direct inhibition of mineralisation and is common in region where there is a high fluoride content in drinking water. The condition is reversible when fluoride intake is reduced. A rare cause of osteomalacia is tumour-induced osteomalacia (mesenchymal tumours). The presentation resembles vitamin D-deficient osteomalacia, but serum phosphate levels are low due to increased urinary phosphate excretion. The syndrome is caused by over-production of FGF23 by the tumour. FGF23 acts directly on the proximal tubule to inhibit renal phosphate reabsorption (Shimada et al, 2001; Quarles, 2012). The mesenchymal tumour producing FGF23 can be localized by octreotide scan (figure 4). Treatments include supplementation with active vitamin D and phosphate but definitive cure is only possible by removal of the tumour.

Finally, drugs used in the treatment of AIDS can provoke hypophosphatemic osteomalacia, notably the association tenofovir/emtricitabine. Serum phosphate level should always be measured in AIDS patients before initiation of therapy as well as every 6 months during treatment.

The main causes of osteomalacia are summarised in box 1.

Box 1. Non-exhaustive causes of osteomalacia**Shortage in vitamin D or vitamin D action**

- Dietary deficiency
- Malabsorption (small intestinal diseases, gastrectomy, hepatobiliary disease, pancreatic insufficiency)
- Deficient endogenous synthesis
 - Acquired: hepatic or renal insufficiency, hypoparathyroidism
 - Hereditary: Pseudo vitamin D deficiency type I (autosomic recessive transmission), due to a mutation in the gene coding for the P450 cytochrome in the 25(OH)D-1 α -hydroxylase enzymatic complex, implicated in 1,25-dihydroxy-vitamin D production in the kidney
- Renal loss (nephrotic syndrome)
- Excessive catabolism (chronic intake of anticonvulsants)
- Deficient action due to vitamin D receptor mutation
 - Pseudo vitamin D deficiency type II (autosomic recessive transmission)

Shortage in calcium

- Dietary deficiency (daily intake < 200 mg/d, parenteral nutrition)
- Malabsorption (small intestinal diseases, vitamin D shortage)

Shortage in Phosphate

- Dietary deficiency (i.e. parenteral nutrition)
- Malabsorption (low phosphate intake associated with ingestion of non-absorbable antacids)
- Renal loss due to impaired renal phosphate reabsorption:
 - Proximal tubulopathy (complete or incomplete Fanconi's syndromes)
 - primary renal (phosphate diabetes)
 - intoxications (i.e. cadmium, lead, iphosphamide, tetracycline, HIV treatment)
 - metabolic abnormalities (i.e. cystinose, glycogenose, tyrosinose, Wilson's disease, fructose intolerance...)
 - multiple myeloma, nephrotic syndrome, transplanted kidney
 - neurofibromatosis, fibrous dysplasia
- Excess of phosphatonines: excess of FGF-23 (i.e. tumour-induced osteomalacia)

Defect in bone mineralization

- Enzymatic deficiency (hypophosphatasia)
- Intoxications (Aluminium, Fluoride, first generation bisphosphonates, i.e. etidronate, high dose of pamidronate)

2.4 Clinical features

Clinical presentation of steomalacia is usually insidious. Mild osteomalacia can be asymptomatic or presents with fractures and mimic osteoporosis. More severe osteomalacia presents with muscle and bone pain, general malaise and fragility fractures. Proximal muscle weakness is prominent and the patient may walk with a waddling gait and experience difficulty in climbing stairs or getting out of a chair. There is bone and muscle tenderness on pressure. Focal bone pain may occur in association with fractures of the feet, ribs and pelvis.

Osteomalacia due to phosphate diabetes can be complicated by spinal stenosis due to ossification of intervertebral ligaments, which is the posterior longitudinal ligament, the ligamenta flava (figures 1 and 2) (Velan *et al*, 2001).

2.5 Investigations

In most cases the diagnosis can be made or strongly suspected on the basis of a routine biochemical screen with measurement of serum 25(OH)D, calcium, phosphate, and PTH. Typically, serum alkaline phosphatase levels are increased, 25(OH)D levels are low or undetectable and PTH is raised. Serum calcium and phosphate levels may also be low, but normal values do not exclude the diagnosis. The bone remodelling is increased, and parameters of bone turnover such as alkaline phosphatase activity (total and bone-specific), C-telopeptide (CTx) and PINP are elevated. In tumour-induced osteomalacia, phosphatonins such as FGF23 levels are high. A careful review of the patients' medications (that can cause osteomalacia) should be performed.

Radiographic examination is not generally helpful and is normal until advanced disease where focal radiolucent areas (pseudo-fractures or Looser's zones) may be seen in the ribs, pelvis and long bones (figure 3). Radiographic osteopenia is common and the presence of vertebral crush fractures may cause confusion with osteoporosis. In children, there is thickening and widening of the epiphyseal plate. Radio-nuclide bone scans can show multiple hot spots in the ribs and pelvis at the site of fractures and sometimes the appearance is mistaken for metastatic disease. In cases where there is any doubt, the diagnosis can be confirmed or excluded by iliac crest biopsy, which shows the pathognomonic features of increased thickness and extent of osteoid seams (non-mineralized bone).

2.6 Management and treatment

Osteomalacia responds rapidly and fully to treatment with ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) (250 µg or 10 000 IU daily). This results in normalization of 25(OH)D and a reduction in PTH levels. Serum alkaline phosphatase levels sometimes rise initially as mineralisation of bone increases, but eventually returns to normal values as the bone disease heals. After 3 to 4 months of treatment, the dose of vitamin D is reduced to a maintenance level of 20 µg or 800 IU cholecalciferol daily, except in patients with underlying disease such as malabsorption, where higher doses may be required.. In tumour-induced osteomalacia, removal of the tumour (if possible) should be performed.

Figure 1. Spinal stenosis provoked by ossification of the posterior longitudinal ligament at C2, C3 levels, as seen on X-ray films and on MRI, in the same male patient aged 49 years. Personal collection of Prof JP Devogelaer, Rheumatology, Cliniques Universitaires Saint - Luc, Brussels, Belgium.

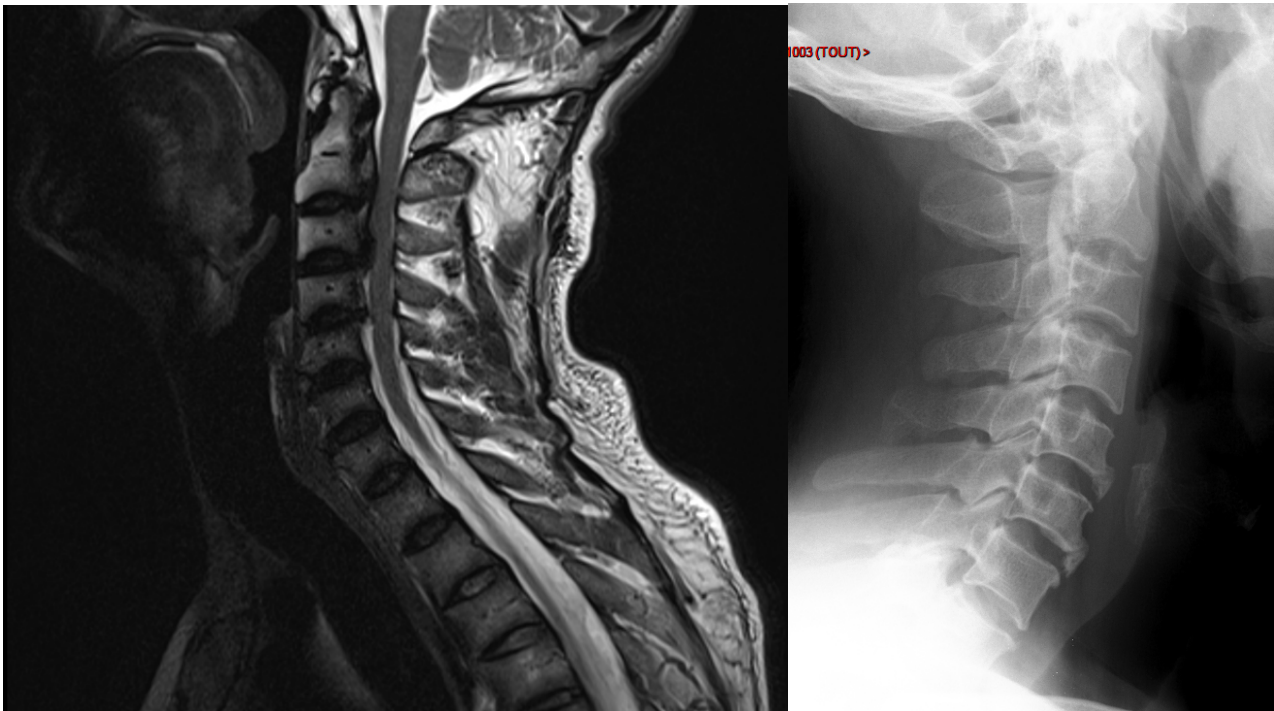


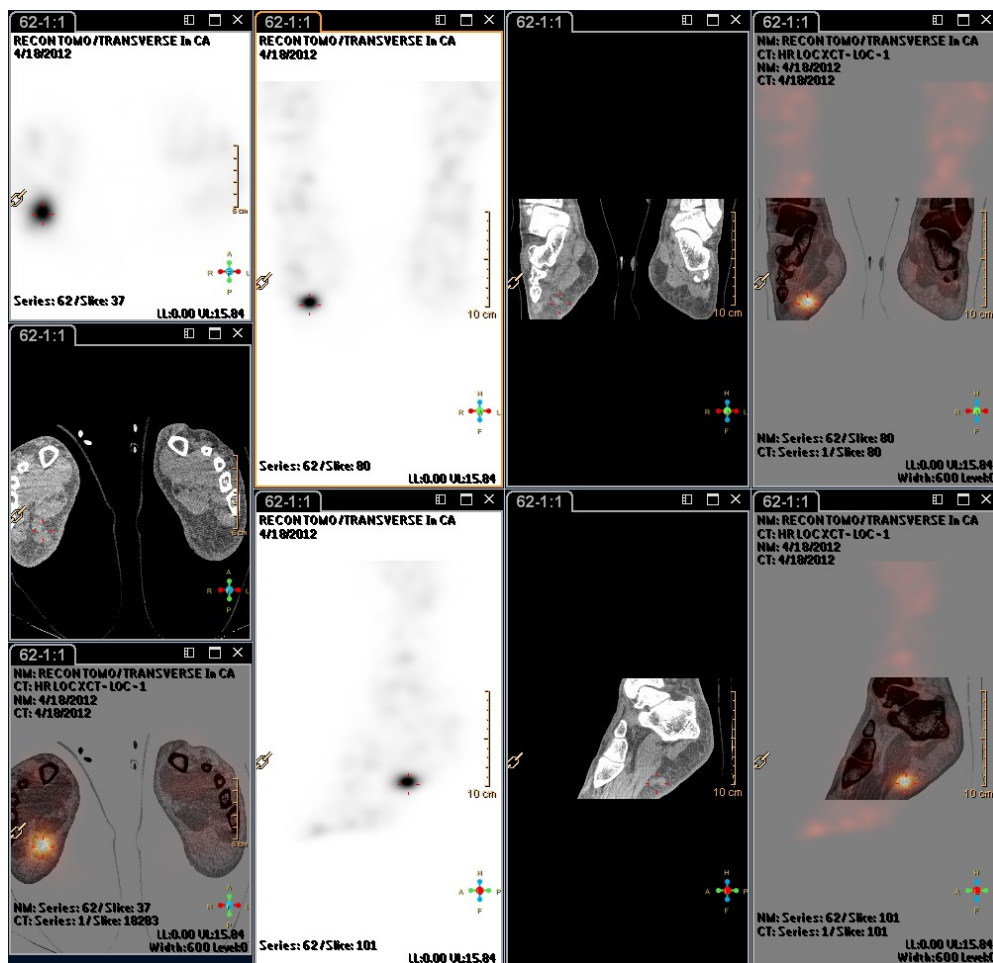
Figure 2. Severe spinal stenosis provoked by ossification of the ligamenta flava at dorsal level, in a female patient aged 56 years. Personal collection of Prof JP Devogelaer, Rheumatology, Cliniques Universitaires Saint - Luc, Brussels, Belgium.



Figure 3. Looser's zones of both femoral necks in a 56 years old man with tumour-induced osteomalacia.



Figure 4. Tumour-induced osteomalacia. Localization of the tumour at the right sole by octreotide scan (same patient than in figure 3).



SUMMARY POINTS

- ➡ Osteomalacia due to vitamin D deficiency can induce muscle weakness, bone pain and fracture.
- ➡ Biological diagnosis relies on a low level of 25(OH)D and increased serum alkaline phosphatase.
- ➡ Treatment is based on ergocalciferol or cholecalciferol.
- ➡ Osteomalacia can also be caused by aluminium intoxication, excess fluoride or overproduction of FGF23.

3 RENAL OSTEODYSTROPHY**LEARNING OBJECTIVES**

- ➡ Explain the pathophysiology of renal osteodystrophy
- ➡ Classify the different forms of renal osteodystrophy

3.1 Introduction and pathophysiology

Renal osteodystrophy (ROD) is defined by the bone anomalies that occur in patients with chronic kidney (CKD) disease. It is a part of a syndrome called CKD-MBD (chronic kidney disease-mineral and bone disorders) that also includes biochemical anomalies and vascular calcification (Mac-Wee et al, 2012). In CKD, there is inability of the failing kidneys to hydroxylate 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 (the active form of vitamin D) and to excrete phosphate. Reduced production of 1,25-dihydroxyvitamin D3 causes reduced intestinal calcium absorption leading to mild hypocalcaemia while hyperphosphatemia contributes to the increased prevalence of vascular and soft tissue calcifications in CKD patients to compensate for these changes, secondary hyperparathyroidism develops with hyperplasia of the parathyroid glands and increased FGF23 from the bone. The progressive lowering of 1,25-dihydroxyvitamin D3 furthermore changes the 'set point' of the parathyroid glands, leading to a higher level of serum parathyroid hormone (PTH) than expected for a given serum concentration of calcium. In addition, there is evidence at the tissue level of downregulation of vitamin D receptor and resistance to the action of PTH. Unfortunately, kidney fails to respond adequately to PTH and FGF23, which normally promote phosphaturia and calcium reabsorption so that PTH and FGF23 are chronically elevated and deleterious for the bone. Recently, anomalies of osteocytes (bone cells), through sclerostin secretion, have been suggested to be involved in the pathophysiology of ROD. Therefore, anomalies of calcium, phosphate, vitamin D, PTH and FGF23 all contribute to the anomalies of bone in CKD patients.

Further contributors to bone disease are age, immobilisation, glucocorticoid treatment, diabetes mellitus, postmenopausal osteoporosis and aluminium intoxication. The latter problem was common two decades ago, but control of the concentration of aluminium in dialysis water and cessation of the use of aluminium-containing phosphate binders have dramatically reduced the prevalence of the condition.

The mineral and biochemical anomalies that occur in CKD are defined according to the patient's glomerular filtration rate (GFR) in order to highlight mineral and bone disorders (table 1).

Table 1. Stages of chronic kidney disease

Stage	Description	GFR (ml/min/1.73 cm ²)
1	Slight kidney damage with normal or increased filtration	≥ 90
2	Mild decrease in kidney function	60-89
3	Moderate decrease in kidney function	30-59
4	Severe decrease in kidney function	15-29
5	Kidney failure	< 15 or dialysis

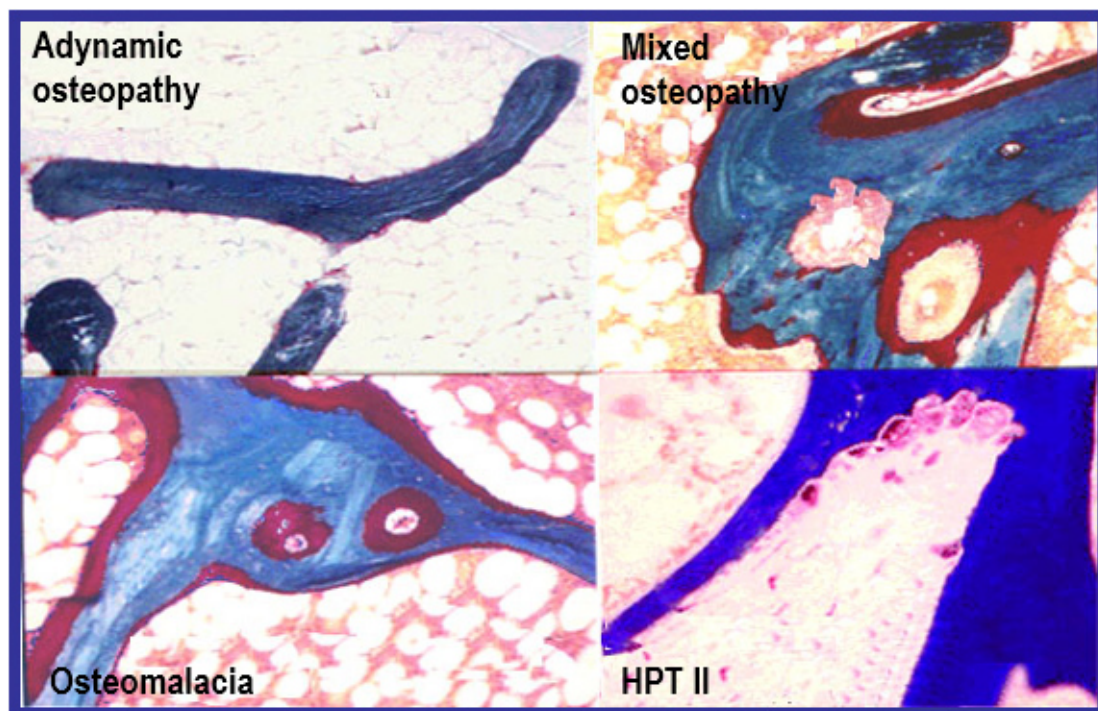
If there are no biochemical anomalies (in PTH, calcium, phosphate, FGF23) suggesting ROD, osteoporosis can be diagnosed by dual energy X-ray absorptiometry if the T score is ≤−2.5 and/or if the patient has already experienced a fragility fracture (Miller, 2005). In patients where serum mineral metabolism is already abnormal or if GFR is <15 or under dialysis, a biochemical profile cannot easily distinguish between the various types of bone disease seen in CKD (see below). An iliac crest bone biopsy is thus needed to differentiate ROD from osteoporosis and in order to propose adapted treatment.

3.2 Different forms of ROD

The gold standard for the classification of ROD is bone histomorphometry with double tetracycline labelling from iliac crest biopsy. According to the extent of osteoid (unmineralised bone) and bone turnover (the bone formation rate evaluated by the double tetracycline labelling), four different types have been described: osteitis fibrosa (secondary hyperparathyroidism), mixed form (secondary hyperparathyroidism + mineralisation defect), osteomalacia (classical mineralisation defect) and adynamic bone disease (ABD, figure 1). The distribution of these histological types differs between studies, which may not reflect reality and might be due to the fact that only symptomatic patients have bone biopsies. Osteomalacia is actually extremely rare and was previously mainly the consequence of aluminium overload. Most patients with CKD have some degree of mineralisation defect corresponding to the mixed form. They present with evidence of high bone turnover as a consequence of secondary hyperparathyroidism. ABD has a histomorphometric definition (low bone formation rate without mineralisation defect). Its pathogenesis is multi-factorial, but excessive suppression of

parathyroid hormone, that may be secondary to excessive treatment with calcium and active vitamin D supplements, is the main determinant of adynamic bone disease. Recent studies suggest that sclerostin, which is an inhibitor of bone formation, may be implicated in the development of ABD. Adynamic bone disease may affect 30% of patients with ROD. It can present with high serum calcium and extraskeletal calcifications because of the inability of the adynamic bone to incorporate calcium.

Figure 1 Different histomorphometric forms of renal osteodystrophy: iliac crest bone biopsy, undecalcified, stained with Masson Trichrome (×50). Mineralised bone is blue and osteoid is red. (A) Adynamic osteopathy: absence of thick osteoid and few bone cells along the bone surfaces. (B) Mixed form: eroded bone surfaces are associated with thick osteoid on some trabecular surfaces. (C) Osteomalacia: thick osteoid on most of the trabecular surfaces. (D) HPT II (osteitis fibrosa): trabecular surfaces are eroded by many osteoclasts, marrow fibrosis and absence of thick osteoid. This figure is from the personal collection of Professor MC de Vernejoul.



3.3 Clinical features and investigations

ROD can be asymptomatic, but bone pain, periarticular pain, arthralgia, skeletal deformities and muscle weakness occur in patients with severe forms of the disease. Recently, it has also been observed that fractures are two to four times more frequent among patients on dialysis than in an age- and sex-matched population with normal renal function (Alem *et al*, 2000). Finally, there has been increasing concern regarding extraskeletal (vascular, periarticular or subcutaneous) calcifications that may result from the deranged mineral and bone metabolism of chronic renal failure and from the therapies used to correct these abnormalities. Several cohorts have shown an association between disorders of mineral metabolism and fractures, cardiovascular disease and mortality. These studies have broadened the focus of ROD to include cardiovascular disease, which is the leading cause of death in patients with CKD.

Because bone biopsy is not easily available, patients are classified according to biochemical measurement of serum PTH and total or bone alkaline phosphatase levels that reflect bone turnover (Mac-Wee *et al*, 2012 *et* Urena *et al*, 1996). In the recent KDIGO recommendations, the PTH level should be kept between 2 to 9 times the upper level of the normal PTH range in patients on dialysis. A sustained lower level of PTH could reflect adynamic bone disease and a higher level secondary hyperparathyroidism. The target levels of PTH in stage 3 and 4 are unknown but progressive elevation should probably be corrected. Serum calcium should be kept within normal values. An increase in serum calcium suggests tertiary hyperparathyroidism (autonomous production of PTH). In addition, serum phosphorus should be monitored and controlled tightly as prolonged hyperphosphatemia will induce extraskeletal calcifications and is associated with increased mortality. Low levels of 25-hydroxy-vitamin D3 (25(OH)D) should be corrected in most patients on dialysis as it has been associated with increased mortality by an unknown mechanism. Finally, FGF23 increase has been extensively shown to be associated with cardiovascular mortality and renal outcomes in CKD so that every effort should be made to avoid its elevation (Kanaan *et al*, 2010; Isakova, 2012; Isakova, 2013).

3.4 Management of patients with ROD

Guidelines for patients with CKD and mineral metabolism anomalies have been reviewed recently (Kidney Disease: Improving Global Outcomes, 2017*). In order to maintain normal serum phosphorus and prevent secondary hyperparathyroidism, phosphate binders (lanthanum carbonate or sevelamer chloride) should be used in addition to phosphate diet restriction. If there is hypocalcaemia, calcium supplements can be an option. Since calcium supplements may be associated with vascular calcification, recent KDIGO recommended to limit the calcium intake in CKD patients.

Vitamin D supplementation with cholecalciferol may be required in CKD patients in order to obtain a 25(OH)D serum level >30 ng/mL.

In case of secondary hyperparathyroidism, 1 α vitamin D derivatives can be used to reduce the PTH level. However, they will also induce an increase in both serum calcium and phosphate levels and could therefore contribute to extraskeletal calcifications if the serum phosphate level is not controlled. If PTH levels remain elevated (> 9 times the upper level of normal range), parathyroidectomy or cinacalcet, a calcimimetic binding the calcium sensing receptor in the parathyroid glands should be proposed. Cinacalcet will induce a decrease in parathyroid hormone levels and consequently also a decrease in serum calcium and phosphorus levels, and therefore has the potential to decrease extraskeletal calcifications. Patients with severe hyperparathyroidism who fail to respond to this cinacalcet will require subtotal parathyroidectomy.

There is no medical treatment for adynamic bone disease. Excessive suppression of PTH by calcium and 1 α vitamin D derivatives should be avoided.

Finally, management of CKD patients with fracture are challenging. CKD patients without mineral anomalies should be treated as osteoporosis patients (Moe S, 2017). Otherwise, a CKD patient with high risk of fracture or with established fracture should be evaluated for an iliac crest biopsy in order to determine the level of bone turnover (KDIGO 2016). If this is not available, PTH and alkaline phosphatase should help. In patients with high bone turnover, anti-resorptive treatments such as bisphosphonate or denosumab can be used (Block *et al*, 2012). It is however important to control the biochemical anomalies that are typically seen in CKD before considering anti-resorptive. CKD patients with ABD may be treated with teriparatide but a bone biopsy is recommended in order to confirm the diagnosis.

SUMMARY POINTS

- ➔ Renal osteodystrophy defines the bone anomalies in CKD and is a reflect of calcium, phosphate, PTH, FGF23 and vitamin D abnormalities.
- ➔ A low level of PTH can induce adynamic bone disease.
- ➔ Vitamin D, phosphate binders and calcimimetics are used to treat patients with secondary hyperparathyroidism.
- ➔ High FGF23 levels are strongly associated with cardiovascular mortality and renal outcomes in CKD

4 OSTEONECROSIS

LEARNING OBJECTIVES

- ➔ Determine risk factors for osteonecrosis
- ➔ Describe and explain the X-ray and imaging features of the different stages of osteonecrosis
- ➔ Manage patients according to clinical and imaging staging

Osteonecrosis defines the death of bone and bone marrow due to impaired blood supply. This condition may occur in any bone, but mostly in subchondral weight-bearing bone such as in the femoral condyles and in the femoral head. If the damage is sufficiently important, it may lead to trabecular fractures or collapse of the articular cartilage (with subsequent osteoarthritis) and in severe cases, total collapse of the femoral head (figures 1 and 2), Osteonecrosis can involve any other epiphyseal extremity such as the humeral head, the tibial plateau and the talus. Involvement of the lunate and scaphoid bones of the hand is also possible.

4.1 Pathogenesis

The physiopathology mechanisms are incompletely understood. Osteonecrosis is caused by a compromised blood supply leading to ischaemia. The causes are obvious in traumatic osteonecrosis, for instance after a femoral neck fracture. However, in cases of atraumatic osteonecrosis, the aetiology has not been fully elucidated and could be related to intraluminal obliteration (vasculopathy) or extraluminal obliteration in the bone marrow. Risk factors associated with atraumatic osteonecrosis are shown in Table 1. Most risk factors are related to conditions, diseases and treatments which may have an impact on bone vascular flow. Glucocorticoid treatment is a major risk factor (Mankin, 1992), especially prolonged high doses of glucocorticoids (oral prednisone > 20 mg/d or high intravenous doses) where this complication typically occurs. 2–6 months after the onset of glucocorticoid therapy. Otherwise, patients with systemic lupus erythematosus or with positive anti-phospholipid antibody are also at risk (Houssiau et al, 1998).

Table 1. Risk factors for atraumatic osteonecrosis.

Biochemical factors
Anti-thrombin III deficiency
Protein C deficiency
Protein S deficiency
Resistance to activated protein C
Plasminogen activator deficiency
High plasminogen activator inhibitor
Secondary conditions of hyper coagulation
Intake of steroids
Alcoholism
Myelodysplastic syndromes
Pregnancy
Contraceptive use
Hyperlipidaemia
Collagen diseases
Ehlers–Danlos syndrome
Raynaud’s disease
Diabetes mellitus
Anti-phospholipidaemic antibodies (APLA)
Hematologic diseases
Haemophilia
Haemoglobinopathies
Polycythaemia
Metabolic diseases
Hyperparathyroidism
Cushing’s disease
Gaucher’s disease
Alimentary system diseases

Pancreatitis
Ulcerative colitis
Crohn's disease
Other risk factors
Smoking
Decompression disease
Radiation
Haemodialysis
HIV infection

4.2 Clinical symptoms

Patients often present with complaints of acute pain. For osteonecrosis of the femoral head, the pain is typically located in the groin and may radiate down the thigh to the knee. The pain is exacerbated by weight bearing. Movement of the hip joint may be normal or restricted. Shortening of the extremity may occur as a consequence of the collapse of the femoral head.

4.3 Imaging

Imaging is crucial for diagnosis and correlates with the natural history of the disease. The Steinberg classification is often used to stage osteonecrosis of the femoral head (Table 2) (Steinberg et al, 1995). The surface area and volume of the femoral head osteonecrosis can be assessed by CT scan or by MRI imaging.

Table 2. Steinberg classification (Steinberg ME, 1995)

Stage 0	Theoretical stage: Asymptomatic. All diagnostic tests are normal
Stage 1	X-Rays and CT-scan are normal. MRI and Tc99 are abnormal. Symptoms may or may not be present.
Stage 2	X-Rays are abnormal - With linear sclerosis or cysts. There is no Subchondral lucency Head of the femur is still spherical.
Stage 3	The femoral head starts to fail mechanically - with trabecular collapse. The radiolucent crescent sign is visible at the Subchondral endplate. The femoral head itself is still spherical.
	- Stage 3a. Crescent < 15%. Surgery still possible.
	- Stage 3b Crescent 15-30%
	- Stage 3c Crescent >30%
Stage 4	Flattening of the femoral head is now seen
	- Stage 4a <15% of the surface is collapsed depression <2mm
	- Stage 4b 15-30% collapse or 2-4mm depression
	- Stage 4c >30% collapse or >4mm depression
Stage 5	Any or all X-ray features may be present There is a decrease in joint space. Secondary Osteoarthritis is present with: Sclerosis / Cysts / Osteophytes
Stage 6	Extensive destruction

In early stages of the disease, conventional X-rays are normal (stage 0 and 1). MRI is more sensitive in these early stages and shows a circumscribed subchondral 'band-like' lesion with low signal intensity on T1-weighted images, corresponding to a sclerotic response of the bone surrounding the necrosis. This image sign is considered pathognomonic. MRI can also show bone marrow oedema and early subchondral necrotic lesions. If MRI is not available, bone scintigraphy with 99m-Technetium may be of help in the early stages. When the lesion progresses, this sclerotic zone becomes visible on X-ray (stage 2). A crescent lucent subchondral line resulting from a subchondral fracture characterises stage 3 (figures 3 and 4). The 'double-line' sign is seen on T2-weighted spin echo or turbo spin echo sequences and consists of a low signal intensity outer rim and a high signal intensity inner rim (figures 5 and 6). Flattening of the femoral head (stage 4) followed by joint space narrowing (stage 5) leads to extensive joint destruction (stage 6). Technetium-99m bone scanning is less sensitive than MRI, especially in early-stage lesions. Hence, it is not used for the diagnosis of or screening for osteonecrosis. In later stages, Technetium-99m bone scanning might show the so called "doughnut sign": increased uptake surrounding a cold area corresponding with increased bone turnover at the junction of dead and reactive bone (Figure 3). In case of multiple osteonecrosis, several sites may be visible on the scan.

Pain can be related to joint effusion, bone marrow oedema, subchondral bone fracture and collapse of the femoral head.

In case of hip pain with normal X-rays, other diagnoses are possible. Lumbar radiculopathy is easily differentiated by clinical examination. In hip algodystrophy, radiographs are often normal, and bone scans show non-specific increased tracer uptake. Bone oedema and joint effusion are visible on MRI, with no other signs of osteonecrosis. The diagnosis of stress fractures may be difficult, especially if located in the femoral head as well.

4.4 Treatment

Here we shall limit the discussion to osteonecrosis of the femoral head since this location is by far the most frequent and since this condition may be extremely disabling. Patients with limited osteonecrosis of the femoral head may have only modest symptoms. Many, however, develop osteoarthritis due to incongruity of the femoral joint surface. The treatment approach here is analogous to that for hip osteoarthritis; that is, medication against pain, physiotherapy and aids. If symptoms worsen with a severe reduction in the patient's daily living activities, hip joint replacement therapy is indicated. In contrast, hip arthroplasty early in the disease course is necessary with femoral head collapse and severe impairment. Several more or less validated treatment approaches are in use. These include surgical femoral neck-saving procedures, core decompression, vascularised or non-vascularised bone grafting, and rotational osteotomy.

Figure 1. Advanced osteonecrosis of the hip. X-ray of the left hip (anteroposterior and lateral view) showing advanced osteonecrosis with segmental flattening of the femoral head, fracture of the subchondral bone. Personal collection of Prof JD Laredo, Radiology, Lariboisière Hospital, Paris, France.



Figure 2. MRI showing osteonecrosis of the hip. The T1-weighted image shows a normal aspect of the right hip. However, on the left hip, segmental flattening of the femoral head, a band-like lesion with low signal and joint effusion can be seen. Personal collection of Prof JD Laredo, Radiology, Lariboisière Hospital, Paris, France.

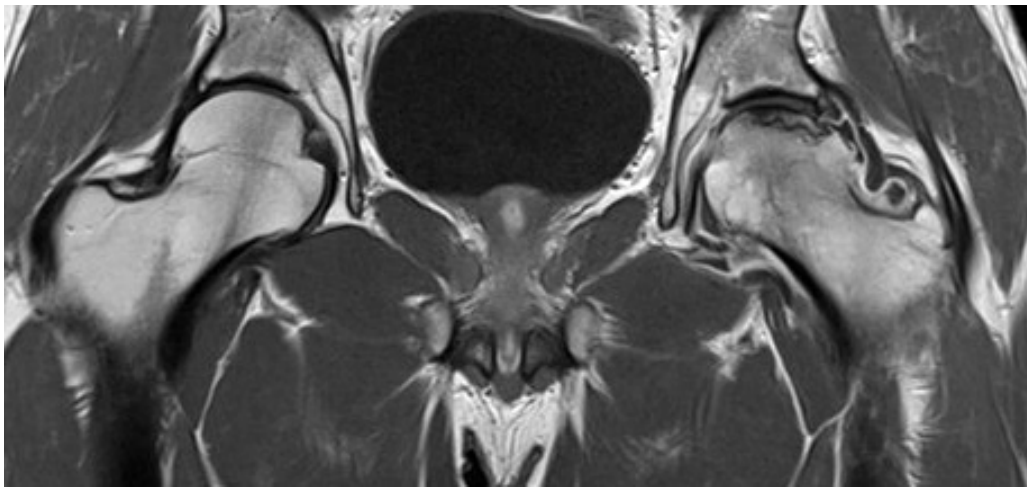


Figure 2 (a to e). Bilateral osteonecrosis of the humeral head, in a 38 year old male patient known with juvenile type 1 diabetes, 4 years after combined kidney and pancreas transplantation. Six months later, osteonecrosis of the femoral heads.

Personal collection of Prof JP Devogelaer, Rheumatology, Cliniques Universitaires Saint - Luc, Brussels, Belgium.

Figure 2 a, b : Osteonecrosis of the right humeral head, MRI coronal view T1 (a), T2 weighted (b). Osteonecrosis of the upper portion of the humeral head with deformation of the head contour.

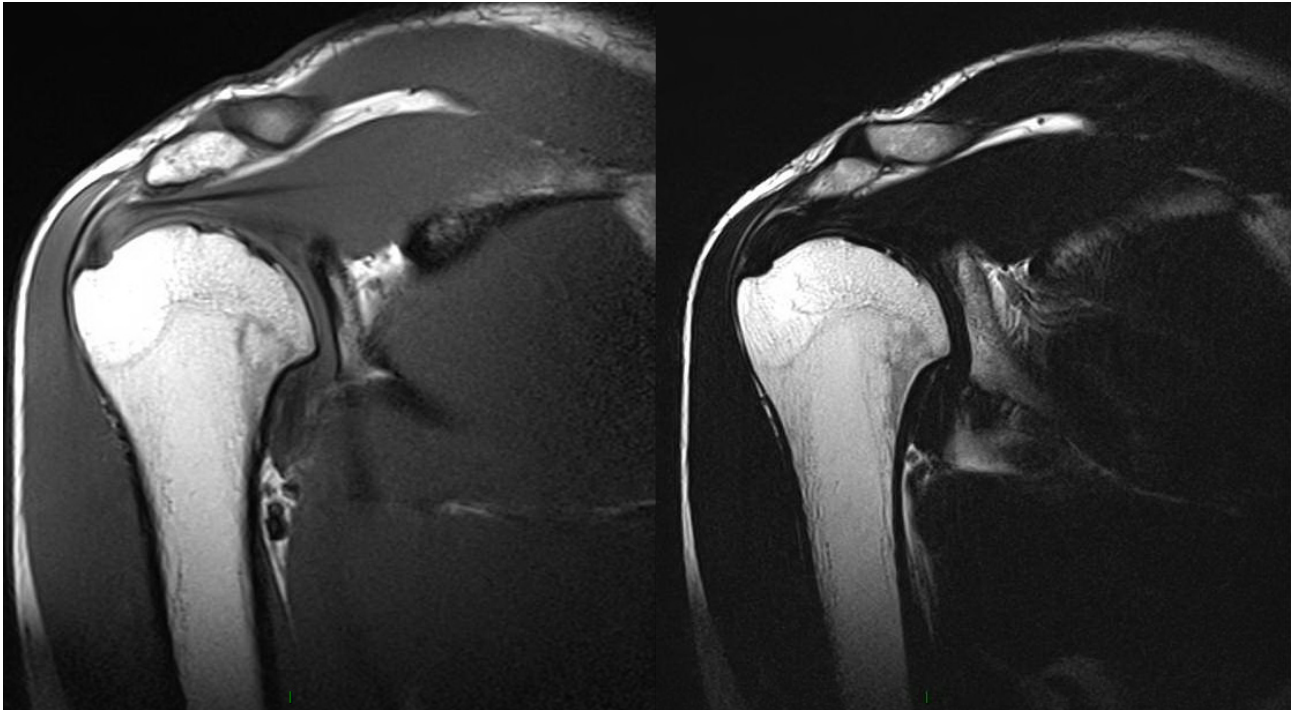


Figure 2 c, d, e: Osteonecrosis of the femoral heads without deformation of the head contour, MRI coronal view T2 (c), coronal view T1 (d), sagittal view T2 weighted image (e).



Figure 2 f, g, h: Osteonecrosis of the femoral heads. X-ray films, 4 years later in the same patient, showing irregularities of the epiphyseal contour.

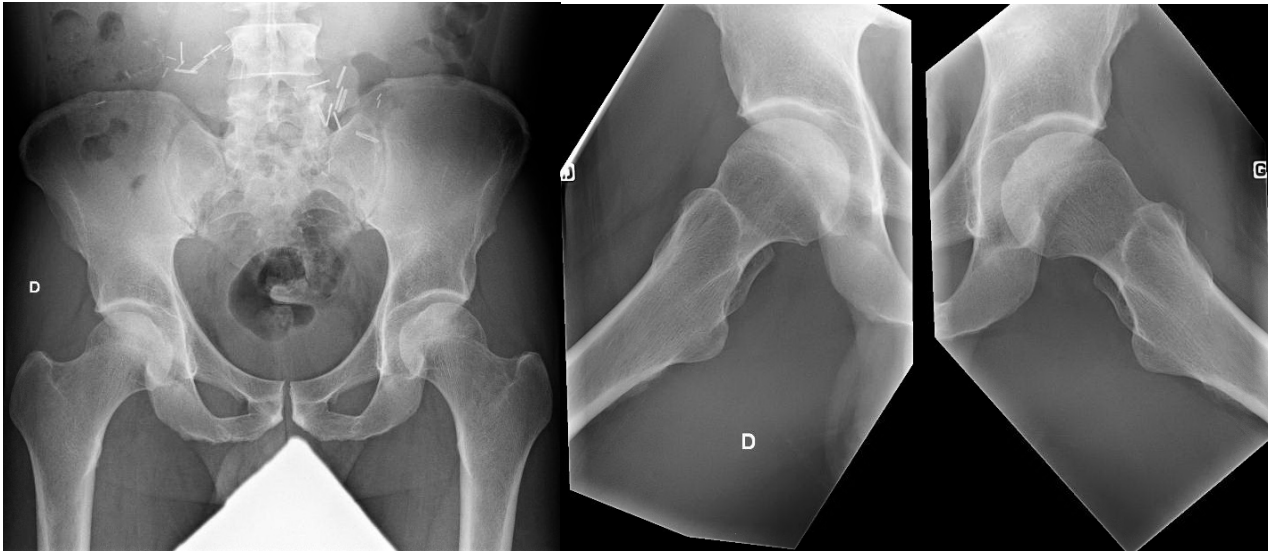
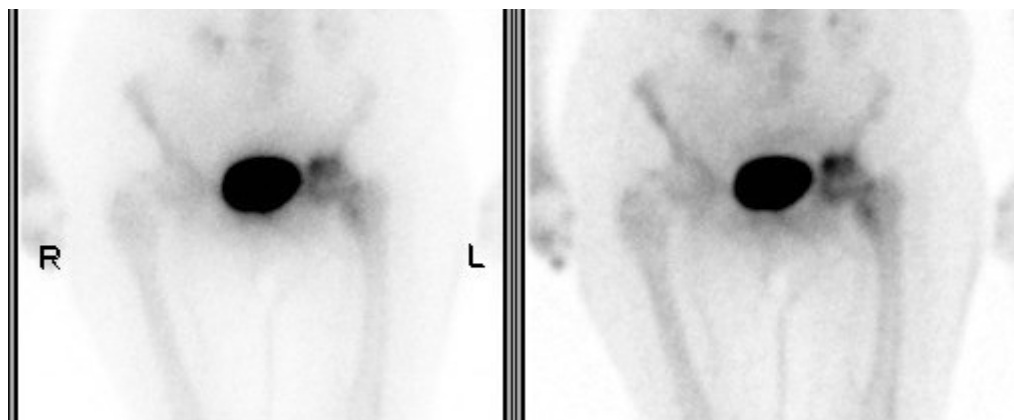


Figure 2 i, j, k: Osteonecrosis of the humeral heads. X-ray films, again 4 years later in the same patient.



Figure 3. Bone scan in an 82 year old woman with late stage of avascular necrosis of the left hip.



SUMMARY POINTS

- The main cause of osteonecrosis is glucocorticoid treatment.
- MRI is the most sensitive imaging technique to diagnose osteonecrosis.
- More severe osteonecrosis can lead to osteoarthritis.

5 SCLEROSING BONE DYSPLASIAS**LEARNING OBJECTIVES**

- Classify the different forms of osteopetrosis and their related genes
- To recognize typical aspect of osteopoikilosis and melorheostosis on radiographs

Sclerosing bone dysplasias represent a large group of rare diseases with a hereditary component or not. These disorders are characterized by failure to resorb the primary spongiosa during embryogenesis, resulting in the accumulation of calcified cartilage matrix within the medullar cavity (like in osteopetrosis) or of focal densities into the medullary cavity such as in osteopoikilosis (Boulet et al, 2015). Osteopetrosis is the name given to a rare group of inherited diseases caused by failure of osteoclast function (Balemans et al, 2005). The presentation is highly variable, ranging from a lethal disorder that presents with bone marrow failure in infancy to a milder and sometimes asymptomatic form that presents in adulthood. Severe osteopetrosis is inherited in an autosomal recessive manner and presents with failure to thrive, delayed dentition, cranial nerve palsies (due to absent cranial foramina), blindness, anaemia and recurrent infections due to bone marrow failure. The adult-onset type (Albers-Schönberg disease) shows autosomal dominant inheritance and presents mainly with fractures, rarely with osteomyelitis, osteoarthritis (OA), vision impairment and sometimes as an incidental radiographic finding ('sandwich vertebrae') (figures 1 and 2). In many cases the genetic mutations responsible for osteopetrosis have been identified and affect the molecular machinery that the osteoclast uses to resorb bone matrix (table 1) (Michou and Brown, 2011). Thus, recessive osteopetrosis is caused mainly by mutations in *TCIRG1*, which encodes a component of the osteoclast proton pump, whereas mutations in the *CLCN7* gene, which encodes the osteoclast chloride pump, are responsible for a few cases of recessive and most cases of autosomal dominant osteopetrosis. Mutations in the carbonic anhydrase II gene are responsible for a syndrome of osteopetrosis and renal tubular acidosis due to failure of acid production within the osteoclast and renal tubules. Another recessive type of osteopetrosis, termed pycnodysostosis, is caused by mutations in cathepsin K, which is essential for degradation of bone matrix. Mutations in the *RANK* gene and *RANKL* gene cause osteoclast-poor osteopetrosis in which there is failure of osteoclast formation,

rather than function. Management of recessive osteopetrosis is difficult. Interferon γ treatment can improve blood counts and reduce the frequency of infections but in severe cases bone marrow transplantation is required to provide a source of normal osteoclasts that resorb bone normally. There is currently no treatment available for other rare sclerosing bone dysplasias, such as osteopoikilosis and melorheostosis (figures 3 and 4).

Figure 1. X-ray of the pelvis of a patient with Albers-Schönberg disease (Autosomal Dominant Osteopetrosis II). Note the “bone within a bone” appearance of the iliac wings, thick femoral cortices and osteosynthesis of a femoral neck fracture. Personal collection of Prof MC de Vernejoul.



Figure 2. X-ray of the lumbar spine of a patient with Albers-Schönberg disease (Autosomal Dominant Osteopetrosis II). Note the accentuation of the vertebral end-plate realizing a “rugger jersey” or “sandwich” appearance. Personal collection of Prof MC de Vernejoul.

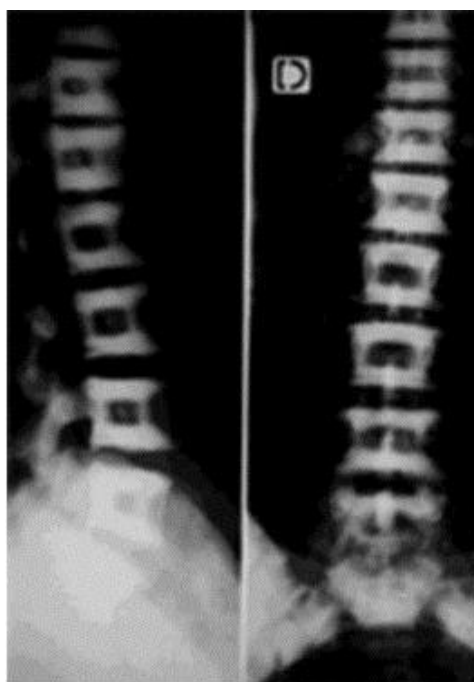


Table 1. Classification of the main forms of human osteopetrosis

Type	Phenotype	Gene ^b
<i>Autosomal recessive osteopetrosis</i>		
1	Malignant neonatal or infantile form, bone sclerosis, fractures, pancytopenia, infections, hepatosplenomegaly, neurological abnormalities	TCIRG1
2	Intermediate form, low osteoclast numbers, short stature, fractures	RANKL
3	Intermediate form associated with renal tubular acidosis, short stature, mental retardation	CAII
4	Malignant infantile form, fractures, bone marrow involvement; or intermediate form	CLCN7
5	Malignant infantile form, fractures, bone marrow involvement	OSTM1
6	Variable severity, often intermediate	PLEKHM1
7	Severe form with low osteoclast numbers associated with hypogammaglobulinaemia	RANK
<i>Autosomal dominant osteopetrosis</i>		
1 ^a	Diffuse bone sclerosis predominating at the cranial vault, often asymptomatic, no fractures	LRP5
2	Sandwich vertebrae, bone-within-bone images, fractures, dental abscesses	CLCN7

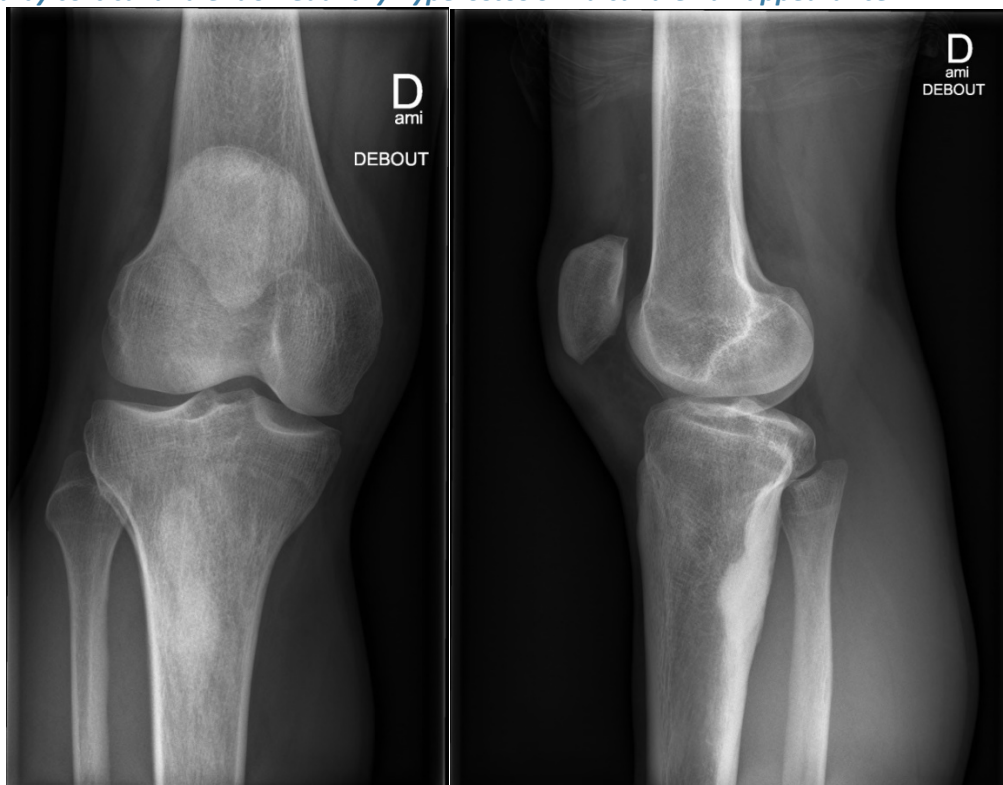
a. This type is no longer classified as a form of osteopetrosis, because it is due to increased bone formation and not to decreased bone resorption.

TCIRG1 gene encoding the 1, ATPase, H⁺ transporting, lysosomal V0 subunit A3; RANKL or TNFSF11, tumour necrosis factor (ligand) superfamily, member 11; CAII, carbonic anhydrase II; CLCN7, chloride channel 7; OSTM1, osteopetrosis-associated transmembrane protein 1; PLEKHM1, pleckstrin homology domain containing, family M (with RUN domain) member 1; RANK or TNFRSF11A, tumour necrosis factor receptor superfamily, member 11a, NFκB activator; LRP5, low-density lipoprotein receptor-related protein

Figure 3. Incidental finding of an osteopoikilosis in a 22 years old man, characterized by multiple rounded blastic lesions. This disorder is inherited in an autosomal dominant mode of inheritance and cause by mutation in the LEMD3 gene.



Figure 4. Melorheostosis of the right tibia in a 26 years old man. This non-hereditary disorder is characterized by cortical and endomedullary hyperostosis in a candlewax appearance.



SUMMARY POINTS

- ➡ Most osteopetrosis is caused by mutations in genes important for osteoclast function.
- ➡ Recessive osteopetrosis occurring in children is severe and may require marrow transplantation.
- ➡ Other rare sclerosing bone diseases should be recognized on X-rays by rheumatologists

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EULAR on-line course on Rheumatic Diseases

Other bone diseases

Fabrice Mac-Way, Laëtitia Michou, Jean-Pierre Devogelaer

A previous version was coauthored by Anne Durnez, Marie-Christine de Vernejoul, Thomas Funck-Brentano, Stuart H Ralston, Anna Daroszewska, Jan Pødenphant

IN-DEPTH DISCUSSION I

Osteomyelitis

Osteomyelitis is an infectious disease of the bone and bone marrow. This common disease is often a challenge requiring input from rheumatologists, radiologists and orthopaedics. The main mechanisms for osteomyelitis are haematogenous spread to long bones metaphyses or vertebrae, contiguous spread due to local tissue infection, or infection associated with a periprosthetic joint. The disease is also commonly classified in acute, sub-acute and chronic osteomyelitis. Antibiotic therapy depends on the microorganism involved and treatment may require orthopaedic surgery. In the present section we shall limit the topic to atraumatic osteomyelitis and will not cover bone infection associated with traumatism.

Pathogenesis

In children, osteomyelitis preferentially affects the metaphyses of long bones, due to haematogenous spread, or contiguous spread from soft tissue infection. In adults, the most frequent site for haematogenous spread is the vertebrae. Osteomyelitis may also occur in long bones, by spread from a contiguous soft tissue infection or by reactivation of a former episode during childhood. Bone is relatively resistant to infections and infection requires large inocula from trauma or the presence of foreign bodies. Furthermore, *Staphylococcus aureus*, a common cause of osteomyelitis has the ability to survive intracellularly in osteoblasts, which protects him from humoral immunity and several classes of antibiotics. Finally, the spread of pus into vascular canals raises the intraosseus pressure and impairs blood flow. This may lead to ischemic necrosis and generation of sequestrae – devascularised bone fragments. The consequences of these conditions are the need for long-term antibiotic treatments and often surgical intervention.

Risk factors and type of microorganisms

As in a number of other infectious diseases patients with existing co-morbidities such as diabetes are at increased risk. In cases of bacterial spread from contiguous soft tissue, local factors have an influence (see Table 1). In this setting, attention should be drawn to rheumatology patients. Indeed, they already have chronic articular or bone diseases and have increased risk of infection due to immunosuppressive medicine including steroids and biologic agents. Sickle cell disease is another recognized risk factor.

The microorganisms causing osteomyelitis are shown in Table 2. They differ with age and depend on the underlying comorbidities. The most common etiologic agent is *Staphylococcus aureus*. Furthermore, attention should be drawn to the less common tuberculous osteomyelitis. In a Swedish study, *Mycobacterium tuberculosis* was identified in 27% of cases of vertebral osteomyelitis. Increased travelling and immigration have led to an increase in the incidence of tuberculosis in many European countries.

By haematogenous seeding, identification of the primary source is important.

This is obvious in the majority of cases (from skin, lung, urinary or postoperative wound infections). The possibility of a hidden abdominal infection, endocarditis or tuberculosis should be investigated if the source is not easily diagnosed.

Clinical symptoms

Symptoms, especially in vertebral osteomyelitis, may be vague and consist of low-grade fever, non-specific pain, tiredness, weight-loss and night sweats. This may lead to a considerable delay in diagnosis, in some cases to several months. In other cases, there is a severe back pain and eventually symptoms of nerve root compression or in late cases spinal cord compression. For long bone osteomyelitis patients in the acute phase may present with pain and impairment of motion in the affected extremity.

Osteomyelitis occurs with an increased frequency in patients with rheumatoid arthritis. In these cases, clinical signs and symptoms sometimes may mimic an exacerbation in the patient's inflammatory joint disease.

Biochemistry

Patients with osteomyelitis typically display an elevated white blood count with predominance of neutrophilic granulocytes as well as elevated ESR and CRP. Blood cultures will often be positive.

Imaging (Figures 1 to 3)

Plain x-rays are useful, but often insufficient in the initial disease stage. CT and MR scans are more sensitive. MR-scans have the advantage to identify and delineate surrounding soft tissue involvement. Bone scintigraphy with technetium 99m-labelled diphosphonate will show activity in the affected area. The investigation, however, is not able to distinguish infection from other disease causes.

Scintigraphy with labelled white cells or positron emission tomography (PET) scanning is also alternative modalities that can be used to make the diagnosis.

Diagnosis

A clinical diagnosis is made from anamnesis and clinical findings. The diagnosis is supported by laboratory tests, imaging preferably CT or MR scan and blood culture. In blood culture negative patients, invasive procedures with biopsy or aspiration of pus from the suspected area is necessary. It is suggested to repeat blood culture immediately after the biopsy. The search of a primary source is of particular importance.

Positive blood cultures without an obvious source should encourage the search for an endocarditis.

Treatment

Antibiotic treatment is started as soon as material for microbiologic investigation is secured. A frequent suspicion is infection with *Staphylococcus aureus* requiring treatment with oxacillin (cloxacillin) and gentamycin. Choice of antibiotics is subsequently adjusted to the established microbiology. In case of resistance to oxacillin, glycopeptides (vancomycin) should be proposed.

The properties of bone as mentioned earlier yields poor drug penetration and long term treatments with high doses are necessary. A typical regimen is 3 weeks of intravenous treatment followed by at least 5 weeks of oral therapy. In chronic osteomyelitis a much longer duration of treatment is necessary. In vertebral osteomyelitis stabilisation of the spine with a corset or body brace may be needed. Besides medical treatment consultation with orthopaedic surgeon is necessary in many cases. Abscess drainage, debridement surgery and surgical stabilisation are often needed. Response to treatment is followed by clinical parameters and inflammatory markers. Radiologic healing is typically not seen before weeks to months after cessation of antibiotics.

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Table 1 Risk factors for osteomyelitis. After: Cierny G et al. Clin Orthop and Rel Res 2003, 414, 7-24

Systemic	Local
Malnutrition	Chronic Lymphedema
Renal or liver failure	Venous Stasis
Alcohol abuse	Major vessel compromise
Immune deficiency	Arteritis
Chronic hypoxia	Extensive scarring
Malignancy	Radiation fibrosis
Diabetes mellitus	
Extremes of age	
Steroid therapy	
Tobacco abuse	
I.v. drug abuse	

Table 2 Microbiology of osteomyelitis. After: Sia IG, Osteomyelitis in Clinical Rheumatology (Woolf A D ed.) Elsevier 2006 1065-81

Common
Staphylococcus aureus
Coagulase-negative staphylococci
Streptococci
Enterococci
Pseudomonas sp.
Enterobacter sp.
Proteus sp.
Escherichia coli
Serratia sp.
Anaerobes (Peptostreptococcus sp. Clostridium sp. Bacteroides fragilis group)
Less common
Mycobacterium tuberculosis
Mycobacterium avium complex
Rapidly growing mycobacteria.
Dimorphic fungi
Candida sp.
Aspergillus sp.
Mycoplasma sp.
Tropheryma whippelii
Brucella sp.
Salmonella sp.
Actinomyces

Figure 1 : Acute osteomyelitis of the proximal humeral metaphyso-diaphysis with *Staphylococcus Aureus*, in a 5-day-old infant.

Left. Radiograph showing osteolysis and periosteal apposition.

Middle. Sonography showing cortical rupture and abscess under the deltoid muscle.

Right. After 22 months of evolution: complete healing.

These pictures are from the personal collection of Prof. PL Docquier, Orthopedic surgery, Cliniques Universitaires Saint-Luc, Brussels, Belgium.

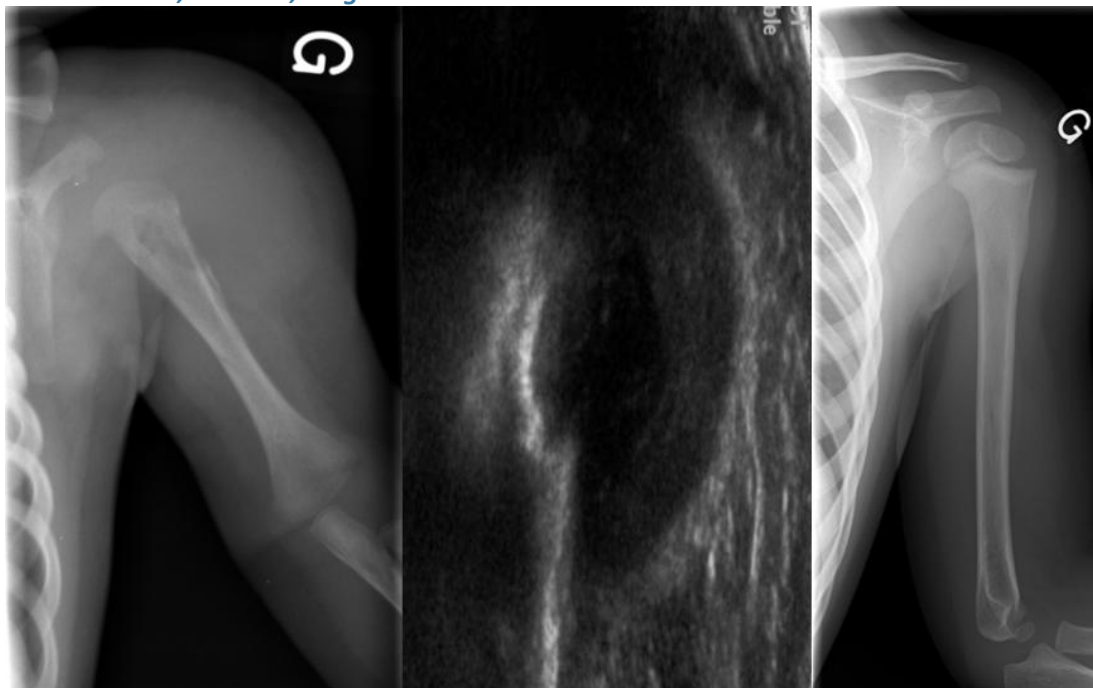
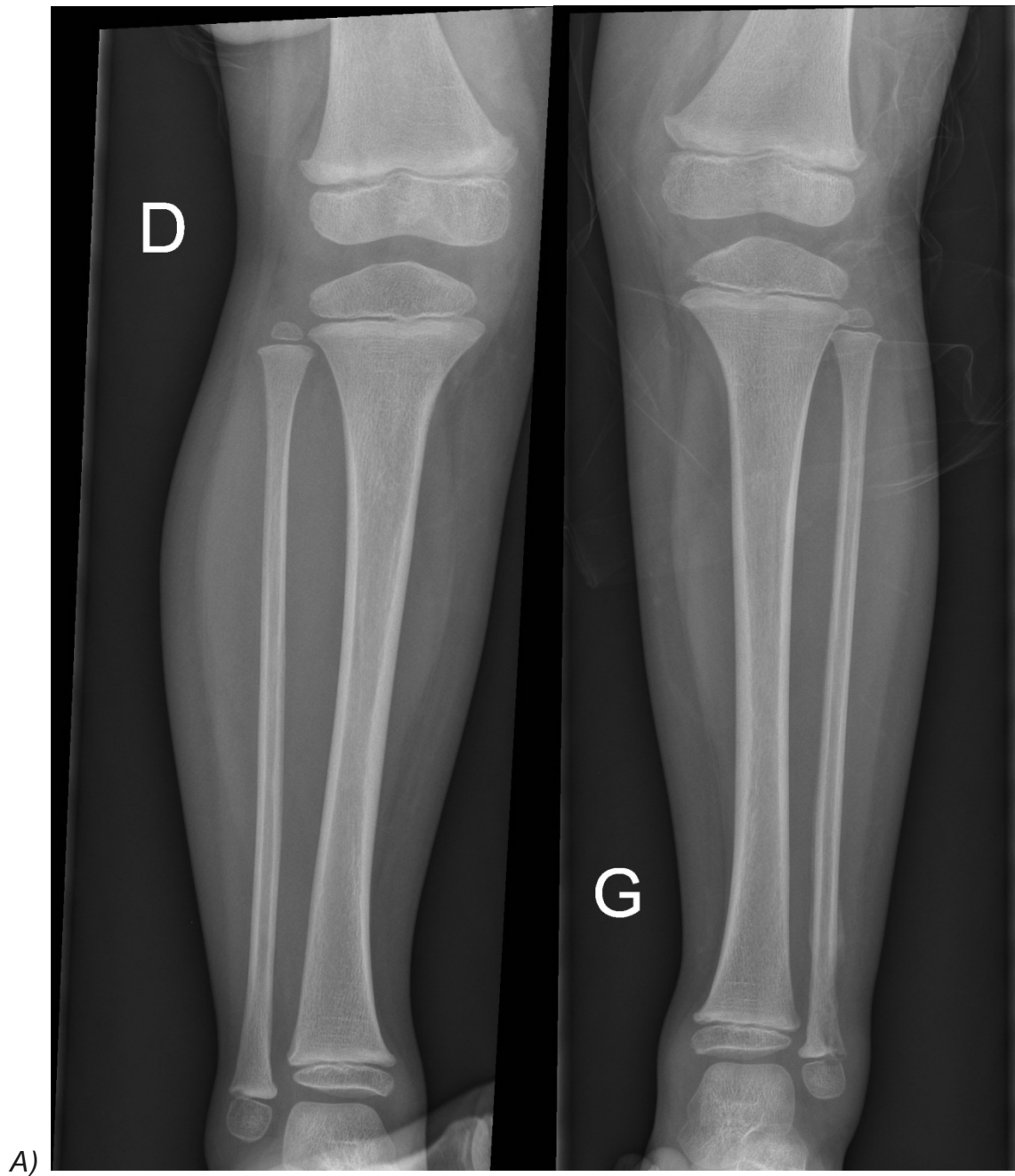


Figure 2 : T1-weighted-MRI, sagittal view of an acute osteomyelitis of the distal tibial metaphysis with fistulisation to the skin through the epiphysis and the joint (secondary septic arthritis) with *Staphylococcus Aureus*, in a 10-year-old girl.

These pictures are from the personal collection of Prof. PL Docquier, Orthopedic surgery, Cliniques Universitaires Saint-Luc, Brussels, Belgium.



Figure 3. Subacute osteomyelitis of the distal part of the left fibula in a three and a half year old girl. A) Radiograph showing a lytic lesion of the distal metaphysis of the left fibula associated with proximal unilamellar periosteal reaction. B) Bone scan: early and late abnormal bone reaction of the left distal fibula. C) Different views and sequences of MRI: abnormal signal intensity of the epiphyseal and metaphyseal-diaphyseal part of the distal fibula with subperiosteal abscess.







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Other bone diseases

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IN-DEPTH DISCUSSION II

Osteogenesis imperfecta in adult patients

Osteogenesis imperfecta (OI) is a genetic disorder of increased bone fragility and decreased bone mass. The clinical range of this condition is extremely broad, from cases that are lethal in the perinatal period to cases that present as primary osteoporosis. Classical OI is an autosomal dominant condition caused by a defect in type I collagen, the major component of bone extracellular matrix. Recent exciting developments have identified the genetic causes of severe recessive OI. These are rare conditions where the clinical presentation is extremely severe and will not often come to the rheumatologist's attention. However, it is possible that patients with monoallelic mutations that cause recessive OI will present clinically like primary osteoporosis.

Diagnosis of osteogenesis imperfecta in an adult patient

The diagnosis is straightforward in patients with familial history of fractures in whom typical extra-skeletal features are present. They include blue sclera and dentinogenesis imperfecta which are more usual in primary than in permanent teeth. Hearing loss starts in the 20s and progresses with age: half of patients older than 50 report hearing loss. Increased ligamentous laxity is frequent.

The skeletal phenotype is variable according to the type of OI and its mutation. All of them are listed in table I. In the mildest form of the disease (Type I of Sillence classification) fractures occur after ambulation. Fractures can also begin later in early mid-life where it presents as early onset osteoporosis. Fracture incidence then decreases markedly after puberty but can resume during pregnancy or lactation and with ageing (menopause in women). Vertebral fractures are common. Usually the height is normal and there is no scoliosis.

In Type III the number of fractures can be dramatically high during the patient's lifetime. The long bones are soft and deform/fracture easily due to normal muscle tension. Patients have extreme height deficiency and they develop scoliosis. They require intensive rehabilitation and often require a wheelchair for mobility.

In type V the phenotype is moderate to severe. The patients present with three typical findings: radiodense metaphyseal bands at the growth plate of long bones, hypertrophic callus and calcification of the forearm interosseous membrane.

The diagnosis can be difficult in the absence of familial history and in the absence of extra-skeletal signs. There is no minimum agreed common criterion to establish a clinical diagnosis.

Classification and genetic defect

Table I shows the different forms that have been described to date. Sillence proposed four types based on clinical and radiological criteria. Although this classification is still useful new types based on clinical and radiological or histological findings and on gene defects are now described.

All these new types are recessive, severe to lethal, and rarely come to the rheumatologist's attention. However, interestingly, it was shown that biallelic mutations of WNT10 are responsible for the extremely severe skeletal phenotypes, but patients with monoallelic mutations present like primary osteoporosis. Osteogenesis imperfecta should therefore be ruled-out in young subjects where a diagnosis of osteoporosis is made.

Table 1. Mutations and phenotype associated with the different types of OI

OI Type	Phenotype	Inheritance	Gene defect
I	mild	AD	COL1A1
II	lethal	AD or AR	COL1A1/COL1A2
III	progressive deforming	AD	COL1A1/COL1A2
IV	moderate	AD	COL1A1/COL1A2
V	moderate (hypertrophic callus)	AD	IFITM5
VI	Mineralization defect	AR	SERPINF1
<u>Defects in 3-hydroxylation of collagen I</u>			
VII	severe	AR	CRTAP
VIII	severe	AR	LEPRE1
IX	severe	AR	PPIB
<u>chaperone defect</u>			
X	severe	AR	SERPINH1
XI	severe	AR	FKBP10
C pro peptide cleavage defect			
XII	moderate	AR	SP7
XIII	mild to moderate	AR	BMP1
XIV	moderate to severe	AR	TMEM38B
XV	moderate to severe	AR	WNT1
XVI	lethal	AR	Homozygous deletion on chromosome 11?
XVII	mild to moderate	AR	SPARC
Legend AD: autosomal dominant, AR: autosomal recessive			

Adapted from Marini and Blisset (reference2) and updated by assessing OMIM website on June 19, 2017.

X-ray and laboratory findings

X-rays show generalized osteopenia with thin cortices. Vertebrae often have central compression. Vertebral collapses may be difficult to assess in patients with scoliosis. The skull of a patient with OI often has wormian bones. In patients that have not received pamidronate, the dense metaphyseal bands are typical of OI type V.

Bone densitometry is useful in the mildest form and facilitates the follow-up. There is a general correlation between the Z-score and the severity of OI but discrepancy is not uncommon. Mineral metabolism is generally normal. 25 hydroxy-vitamin D should always be measured in order to treat possible insufficiency.

Figure 1 a : Vertebral compression fractures in a patient with OI type 1 (personal collection Pr de vernejoul)



Figure 1 b : dense metaphyseal bands in a patient with OI type V (personal collection Pr laredo)



Management

The management of OI is multidisciplinary and includes pain management, rehabilitation, and orthopaedic surgery in the most severe forms. Regular monitoring of hearing is important in adults.

In children bisphosphonate increases bone density, decreases pain and reduces fractures. In adults the benefit of bisphosphonate is less well proven but improvement in bone density has been shown with oral bisphosphonate. It is however difficult to prove that the treatment induces a reduction in fracture incidence due to the small number of patients involved in trials. Bisphosphonate should be prescribed only in patients with recent fractures. The period of treatment should not be too long as atypical fracture of the femur has been reported in adult OI patients on long term bisphosphonate treatment.

Anabolic treatment could be more appropriate and beneficial. Antisclerostin antibodies have been used successfully in murine models of OI. Recently, treatment with teriparatide has been tested in OI adult patients and was able to increase bone density and markers of bone formation in patients with less severe forms (type I). Larger trials are required to assess the benefits in the other forms of OI.

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Autoinflammatory syndromes

EULAR on-line course on Rheumatic Diseases

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LEARNING OBJECTIVES

This chapter gives an overview of:

- ➔ the pathogenesis of autoinflammatory diseases.
- ➔ the genetic and molecular defects that cause the most well-known autoinflammatory diseases.
- ➔ clinical features of autoinflammatory diseases and the typical clinical features of the best described autoinflammatory diseases.
- ➔ the diagnostic workup for suspected autoinflammation.
- ➔ treatment of autoinflammatory diseases.
- ➔ complications of autoinflammatory diseases.
- ➔ Follow up of autoinflammatory diseases.

1. Introduction

Autoinflammatory diseases are characterized by fever or other signs and symptoms of inflammation, such as elevation of acute phase proteins, without an infectious or autoimmune cause. Rather, unregulated activation of the innate immune system is mainly to blame.(Kastner et al, 2010)* In contrast to autoimmune diseases there are no high-titer autoantibodies or autoantigen-specific T cells, because the acquired immune system is not affected.

Many diseases, including more common diseases such as atherosclerosis, Crohn's disease or gout are at least partly explained by autoinflammation. One might see it as a immunological disease continuum with on one side the monogenetic autoinflammatory diseases, on the other side the monogenetic autoimmune diseases, and in the middle the mixed patterns and polygenetic diseases like Crohn's disease.(McGonagle 2009)

Systemic Juvenile Idiopathic Arthritis (SJIA) and its adult counterpart Adult Onset Still's Disease (AOSD) are examples of acquired autoinflammatory diseases. The genetic autoinflammatory diseases are rare.(Masters et al, 2009)* These are monogenic diseases with a distinct phenotype characterized by recurrent fever, accompanied by other inflammatory symptoms, such as skin rash, mucosal ulceration, arthritis, and serositis. Examples of these diseases are familial Mediterranean fever (FMF), cryopyrin associated periodic syndrome (CAPS), tumour necrosis factor (TNF)-receptor associated periodic syndrome (TRAPS), and mevalonate kinase deficiency (MKD, formerly known as the hyperimmunoglobulin D and periodic fever syndrome, HIDS). These classical autoinflammatory diseases usually have childhood onset and are inherited either in an autosomal dominant (TRAPS, CAPS) or recessive (FMF, MKD) fashion. Besides these well described diseases, many other autoinflammatory diseases have been identified since the introduction of the term autoinflammation almost 20 years ago. Some of these diseases have a known genetic defect, while in others no cause has been found so far. As the spectrum of autoinflammatory diseases keeps expanding, it is impossible to give a complete account of all these ultra-rare diseases here. Therefore, this chapter will give an overview of the pathogenesis, clinical picture, and treatment of the most common or best-described autoinflammatory diseases. We will also describe Schnitzler syndrome and adult onset Still's disease; two diseases with an interesting clinical picture for which patients may consult a rheumatologist. At the end of this chapter we summarize few other interesting autoinflammatory syndromes.

2. Pathogenesis

The common final pathway in many of the autoinflammatory diseases is overproduction of the pro-inflammatory cytokine interleukin-1 beta (IL-1 β). This cytokine is produced by large cytoplasmic protein complexes, called inflammasomes. Multiple inflammasomes have been identified, the best known of which is the NLRP3-inflammasome, named after the nucleotide binding and leucine-rich repeat containing protein 3 (NLRP3) at its core. (Figure 1) The NLRP3-inflammasome consists of three different proteins:

1. NLRP3. This protein consists of a leucine-rich repeat (LRR)-domain, a nucleotide binding and oligomerization (NACHT) domain and a pyrin (PYD) domain.(Hoffman et al, 2001) The LRR-domain is able to detect a variety of danger signals derived from damaged cells or micro-organisms. This in turn results in a conformational change that activates the NACHT domain and allows (figure 1A and B), NLRP3 to bind
2. The adaptor protein apoptosis-associated speck-like protein (ASC)(Agostini et al, 2004), which in turn recruits
3. The effector protein pro-caspase 1, which becomes autocleaved to active caspase-1.(Cerretti et al, 1992, Thornberry et al, 1992, Kuida et al, 1995) After this, caspase-1 is able to cleave the inactive procytokine pro-IL-1 β to its mature and active form IL-1 β .(Figure 1C). Likewise, caspase-1 can activate pro-IL-18 to mature IL-18.

Cryopyrin-associated periodic syndrome (CAPS) is the best-studied example of what happens when the NLRP3-inflammasome dysfunctions. CAPS is caused by gain-of-function mutations in the *NLRP3*-gene (Hoffman et al, 2001, Aksentijevich et al, 2002, Feldmann et al, 2002). The NLRP3 protein had also been referred to as cryopyrin in the past, hence the name Cryopyrin-associated periodic syndrome. The majority of CAPS-associated mutations are located in exon 3 of this gene, which encodes its NACHT-domain.

Although the cryopyrin-associated periodic syndrome is an autosomal dominant disorder, many patients don't have the pathogenic mutation in all of their cells. A low percentage (<5%) of mutant cells may be sufficient to give rise to the full inflammatory phenotype (Tanaka et al 2011). This phenomenon, known as somatic mosaicism shows how powerful the pro-inflammatory effect of these mutations can be.

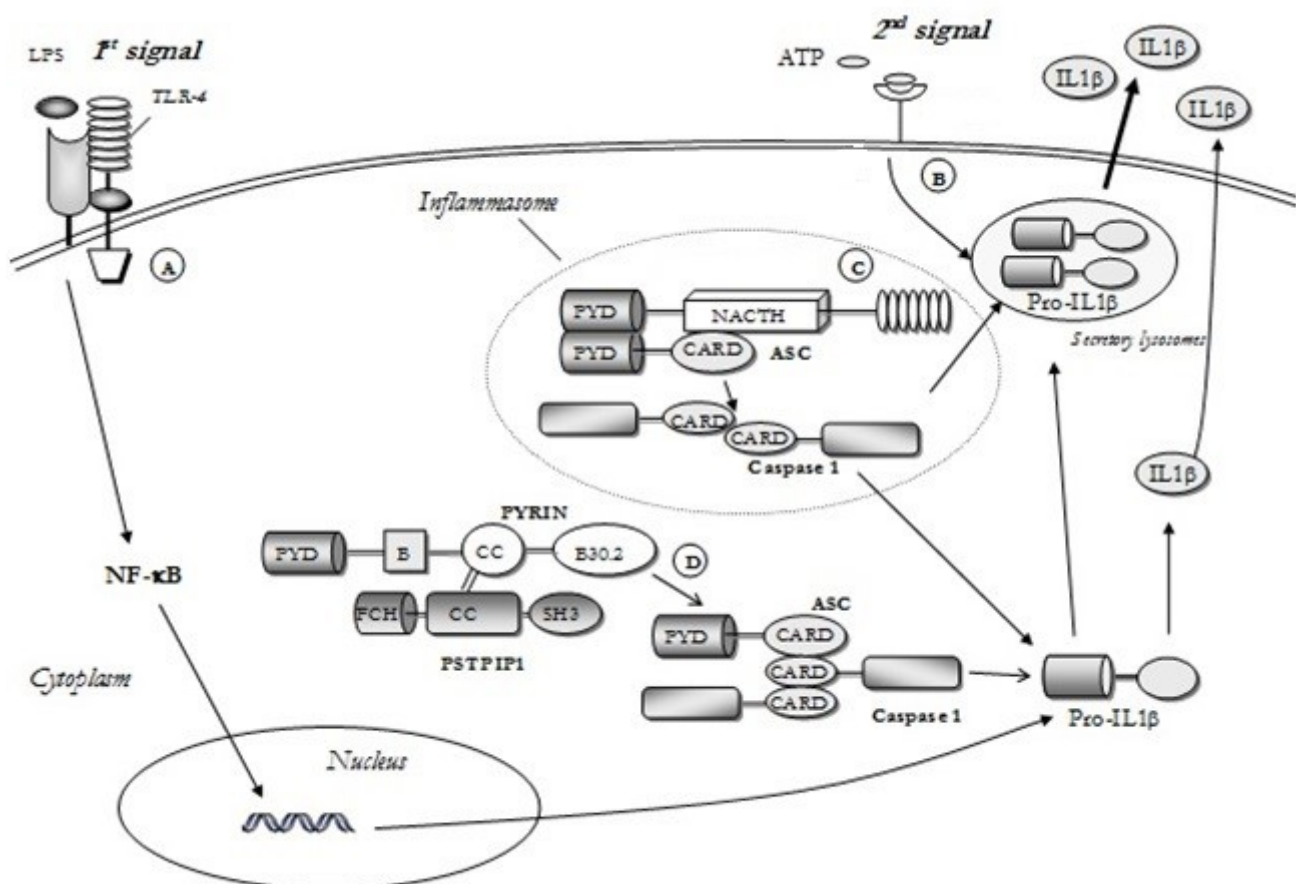
Familial Mediterranean fever (FMF) is caused by mutations in the Mediterranean fever (*MEFV*) gene, which encodes a protein, commonly called pyrin. This name is derived from the Latin word for fever. Pyrin is structurally related to NLRP3 and likewise can form inflammasomes. The natural signal to activate pyrin is reduced activity of RhoA protein in phagocytes (Xu et al, 2014). Some pathogens interfere with RhoA to impair host defence, but pyrin senses this alteration and therefore indirectly responds to the bacterial presence. Pyrin is then able to form its own inflammasome by combining with ASC and caspase-1 without involvement of NLRP3.(Manukyan et al, 2016). The FMF-associated *MEFV* alleles contain highly conserved founder mutations originating from around the Mediterranean basin. There are strong indications that heterozygote carriers of these mutations have had an evolutionary advantage during the great plague, because they allow for a strong inflammatory response to *Yersinia pestis*.(Chung et al. 2016) Besides FMF, pyrin may also be involved in several other autoinflammatory syndromes. Mutations at specific serine residues that abolish pyrin's ability to be inhibited by RhoA that give rise to a severe autosomal dominant autoinflammatory syndrome: pyrin-associated autoinflammation with neutrophilic dermatosis, PAAND (Masters et al 2016), while other mutations give rise to a distinct autosomal dominant hereditary autoinflammatory syndrome. (Stoffels et al, 2014). The

inflammation in mevalonate kinase deficiency (see below) is largely mediated via activation of the pyrin-inflammasome (Park 2016).

Pyrin is able to bind proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1) (Shoham et al, 2003), a protein that is mutated in the autoinflammatory disease pyoderma gangrenosum, pyogenic arthritis and acne (PAPA) syndrome.

Figure 1. The NLRP3-inflammasome and the production of IL-1 beta.

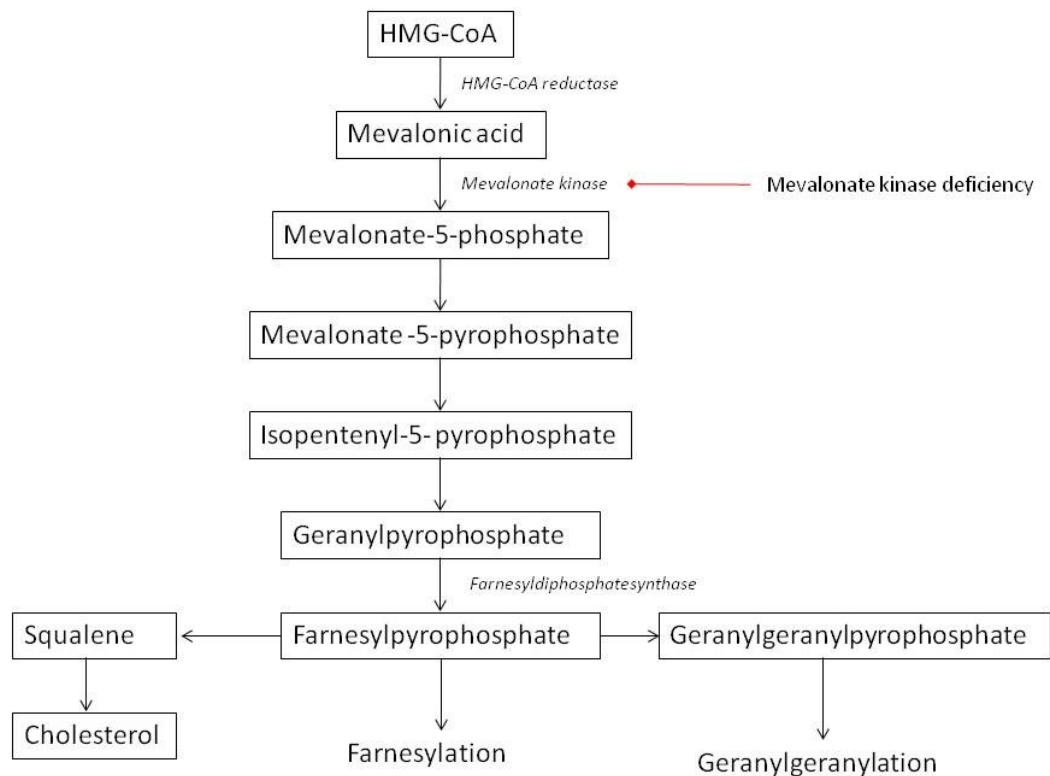
A: a first signal (in this case lipopolysaccharide (LPS) triggers the Toll-like receptor 4 (TLR-4), inducing the production of nuclear factor kappa-B (NF- κ B), which in turn induces the transcription of pro-interleukin-1 beta (pro-IL-1 β). B: a second signal (adenosine tri-phosphate (ATP) triggers the conversion of pro-IL-1 β to active IL-1 β . IL-1 β is then secreted. C: the nucleotide binding and leucine-rich repeat containing protein 3 (NLRP3)-inflammasome, containing the proteins NLRP3 (upper part, including a pyrin- (PYD) domain and a nucleotide binding and oligomerization (NACHT) domain); apoptosis-associated speck-like protein (ASC) (middle part), including a PYD and a caspase activation and recruitment domain (CARD); and two caspase-1 molecules, that also contain a CARD domain. D: interaction between pyrin and ASC. Shown is pyrin (upper part) and its PYD, B, CC and B30.2 domains and its association with proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1).



In mevalonate kinase deficiency (MKD) the genetic defect lies in the mevalonate kinase gene (*MVK*). (Houten et al 1999; Drenth et al, 1999) Mutations in this gene lead to decreased production of the protein mevalonate

kinase. End-products of the mevalonate kinase pathway are cholesterol and non-sterol isoprenoids. (Figure 2) Decreased production of the latter forms the link between this pathway and the secretion of IL-1 β . Non-sterol isoprenoids are involved in protein prenylation, a process in which small non-sterol isoprenoids are coupled to larger proteins, influencing their activity or cellular localization. Deficiency of the non-sterol isoprenoid geranylgeranyl pyrophosphate (GGPP) leads to increased production of IL-1 β in patients with MKD (Mandey et al, 2006, Kuijk et al, 2008, Liao et al, 2013) via defective prenylation of the protein Ras homolog gene family, member A (RhoA). RhoA is an important inhibitor of the *MEFV*-gene product, pyrin. Hence impaired prenylation of RhoA in mevalonate kinase deficiency can lead to over-activation of pyrin and the excess production IL-1 β . (Park et al 2016)

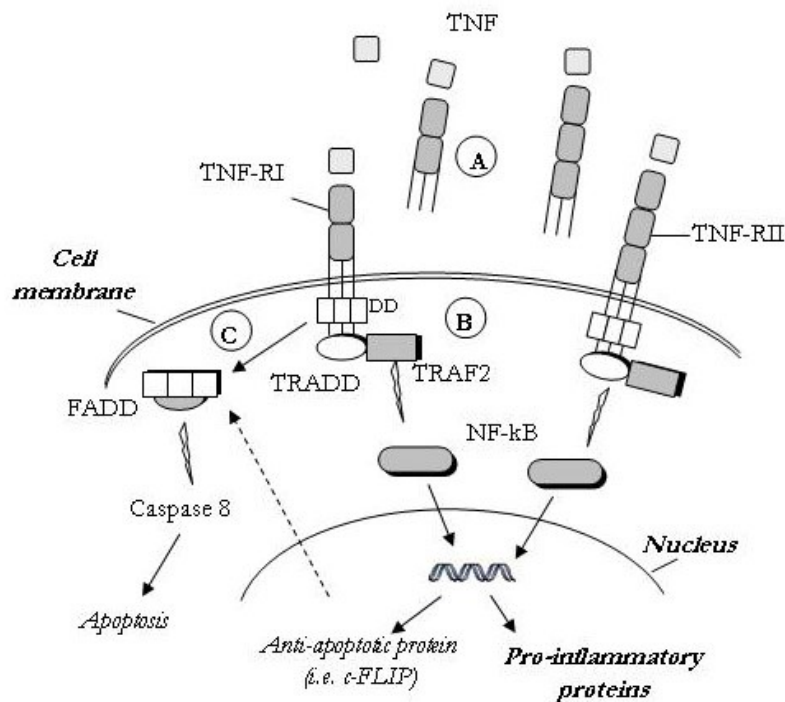
Figure 2. The mevalonate kinase pathway



TRAPS is caused by mutations in the tumour necrosis factor (TNF) receptor superfamily 1A (*TNFRSF1A*)-gene, encoding the TNF-receptor type 1. (McDermott et al, 1999) At first, it was thought that these autosomal dominant mutations would lead to defective receptor shedding from the cell membrane, resulting in a decreased extracellular pool of soluble TNF-receptors to mitigate the inflammatory response. (McDermott et al, 1999, Huggins et al, 2004, D'Oswaldo et al, 2006, Lobito et al, 2006) However, defective shedding is not present in all TRAPS patient (Aksentijevich et al, 2001, D'Oswaldo et al, 2006, Lobito et al, 2006, Churchman et al, 2008) and TRAPS-associated mutations were found to influence protein folding, resulting in altered receptor trafficking and secretion. Mutated TNF-receptors accumulate intracellularly. (Todd et al, 2004, Lobito

et al, 2006, Todd et al, 2007)(figure 3) Ligand-independent signalling of these mutated receptors (Todd et al, 2004), induction of a stress response in the endoplasmatic reticulum with consequent production of reactive oxygen species (Bulua et al, 2011), or defects in TNF-mediated apoptosis (D'Ousualdo et al, 2006, Lobito et al, 2006) may lead to the inflammatory phenotype in TRAPS. Of all mutations found in TNFRSF1A, the R92Q- and P46L-variants (these are traditional names; official designations in the current nomenclature are R121Q and P75L) are somewhat unusual. These mutations do not lead to receptor misfolding and are present in low frequency in the healthy population. Nevertheless, they have also been associated with mild inflammatory phenotypes. As a consequence, the finding of one of these two mutations does not per se confirm a diagnosis of TRAPS.

Figure 3. Pathophysiologic mechanism of tumour-necrosis factor associated periodic syndrome. A shows the shedding hypothesis: decreased shedding would lead to a decreased pool of circulating soluble TNF-receptors that normally mitigate the immune response. B shows the trapping hypothesis, in which mutated receptors are accumulated in the endoplasmatic reticulum. Ligand-independent signalling leads to inflammation.



The pathogenesis of both Schnitzler syndrome and adult onset Still's disease (AOSSD) remains unknown. The beneficial effects of anti-IL-1 therapy indicate an important role for this cytokine in their pathogenesis.(de Koning et al, 2007, de Koning et al, 2011, Kadavath et al, 2015) For both diseases, no underlying genetic defect has been found. In a few patients with Schnitzler syndrome, somatic mosaicism of NLRP3 in myeloid cells has been found recently.(de Koning et al, 2015)* Somatic mosaicism may explain the late onset of Schnitzler syndrome. Other genetic defects have been described in limited numbers of patients, but their role remains unclear.

3. Clinical picture

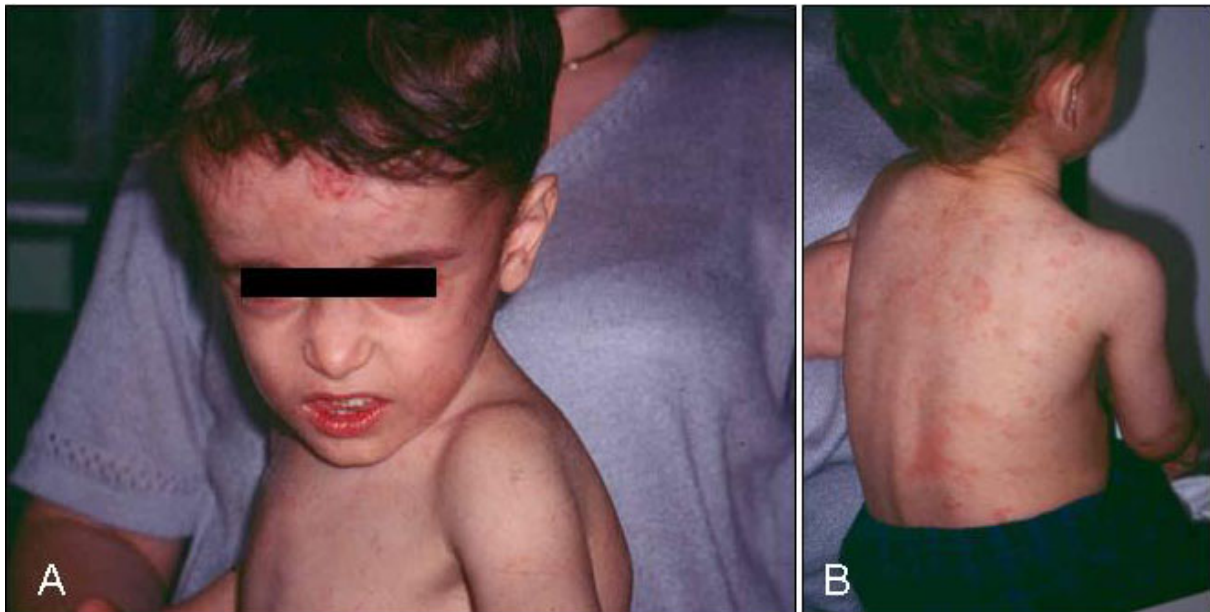
The clinical picture of autoinflammatory diseases is highly variable between diseases, within the same disease, and even between episodes in the same patient. Autoinflammatory diseases are characterized by systemic inflammation. Common symptoms are:

- Fever, which may be accompanied by rigors or chills. Malaise, and anorexia
- Abdominal pain due to peritonitis, colitis or hepatosplenomegaly. It can be accompanied by diarrhoea, constipation, nausea or vomiting.
- Chest pain caused by pleuritis, pericarditis or of musculoskeletal origin.
- Lymphadenopathy: enlarged cervical, axillar, inguinal or abdominal lymph nodes may be present and can be painful.
- Arthralgia or arthritis, sometimes with persisting joint destruction.
- Myalgia affecting limbs and/or trunk.
- Neurological abnormalities, such as headache, aseptic meningitis, papilledema, ataxia, loss of vision, or hearing loss.
- Skin rash.
- Mucosal aphthous ulcers
- Ocular symptoms, such as conjunctivitis, iritis or uveitis.

Although inflammatory attacks may vary in the course of time, many patients will be able to recognize and describe signs and symptoms that define their own typical inflammatory attack. Patients may notice triggers for their attacks, such as emotional or physical stress, infections, cold exposure, vaccination or menstruation. Attack frequency may vary between and within patients. Auto-inflammation can lead to continuous inflammation, but inflammation-free intervals of several years are also possible. The same is true for the duration of inflammatory attacks, which can vary from continuous inflammation to episodes lasting only for a couple of hours to days.

The typical presentation of the classical monogenic autoinflammatory diseases, Schnitzler syndrome and adult onset Still's disease is described below. It is good to keep in mind that with improvement of techniques used for detection of genetic mutations, atypical presentations of the classical autoinflammatory diseases are increasingly seen.

Figure 4. Typical facial dysmorphism and skin rash in CAPS. A shows the typical frontal bossing, saddle back nose and mid-facial hypoplasia in a 3-year old child carrying a N477K-mutation in NLRP3. B: typical skin rash. Picture published with parental consent and reproduced with permission from Gattorno et al. J Clin Immunol. 2008; 28(suppl 1):S73-83. © J Clin Immunol



Familial Mediterranean fever

FMF is the most common autoinflammatory disease, especially in some populations. Prevalence is the highest in patients originating from around the Mediterranean basin, such as Arabs, Armenians, Turks and non-Ashkenazi Jews. Its inheritance is complex. Like in most autosomal dominant disease, gain-of-function mutations give rise to the disease. However, in FMF, a single mutant allele is usually insufficient to cause disease, whereas the presence of two affected alleles is likely to cause disease. Therefore FMF is mainly, but not exclusively, inherited in an autosomal recessive fashion. Most patients with FMF develop symptoms in infancy, but adult onset FMF has been described. A typical FMF attack starts with a prodromal phase with chills and malaise, followed by spiking fever that lasts 1-3 days. Attacks may be triggered by physical or emotional stress, infections or, in women, the menstrual cycle. Fever is accompanied by serositis: peritonitis, pleuritis, pericarditis or arthritis may be present. Due to sterile peritonitis, it is not uncommon for FMF patients to have had a healthy appendix removed because of suspected appendicitis. In boys, sterile periorchitis may mimic testicular torsion. Arthritis mainly affects large joints, such as knees, hips and ankles. Arthritic attacks can be protracted and joint symptoms may persist for days to weeks after fever has disappeared. Skin rash can be present. An erysipelas-like erythema located on the lower extremity is a rare but pathognomonic symptom of FMF. Protracted febrile myalgia syndrome is a very rare but severe manifestation of FMF. It is characterized by severe debilitating pain in the large muscle groups that may last for several weeks. IL-1 inhibition seems to be effective. (Mercan et al 2016)

Before the introduction of colchicine, proteinuria and renal failure due to secondary amyloid A (AA) amyloidosis developed in 75% of FMF patients. Since the introduction of effective therapy, the incidence of amyloidosis has decreased. In the past a 'type 2' FMF has been described in patients presenting with AA-amyloidosis associated with *MEFV* mutations in the absence of inflammatory attacks. It is now more commonly thought that these patients probably did have inflammatory attacks prior to the occurrence of amyloidosis, but that they were atypical and thus not recognized by patient and/or doctor.

Cryopyrin-associated periodic syndrome

Before the discovery of mutations in *NLRP3*, three different phenotypes that now fall in the CAPS spectrum were distinguished: familial cold autoinflammatory syndrome (FCAS), Muckle Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID, which is also known as chronic infantile neurologic, cutaneous and articular syndrome (CINCA)). Over the years, the CAPS-spectrum has extended and phenotypes with overlapping features are seen more and more. CAPS usually has its onset in infancy or early childhood. Mild CAPS phenotypes are characterized by short fever attacks that usually last up to 24 hours and can be induced by exposure to cold. A non-pruritic urticariform skin rash, arthralgia and conjunctivitis are common. Moderately severe phenotypes are associated with longer fever episodes, lasting up to several days. Progressive sensorineural hearing loss may be present. On the most severe end of the CAPS spectrum are the NOMID/CINCA phenotypes. Inflammatory symptoms, such as fever or skin rash may be present from birth or early infancy. Patients may have typical dysmorphias with frontal bossing, saddle nose and mid-face hypoplasia.(Figure 4) Bony overgrowth that predominantly affects the knees, hands and feet can be present.(Figures 5 and 6) Neurological symptoms, such as headache, papilledema, vision loss, hydrocephalus or aseptic meningitis are common in severe phenotypes.(Figure 7) Mental retardation and seizures have been described. Before adequate treatment was available, secondary amyloidosis was seen in approximately 25% of patient with moderate-to-severe CAPS.

CAPS is an autosomal dominant disease and a positive family history with fitting complaints in a first-degree relative can be helpful in the diagnosis, but mutations can also appear *de novo* and in about a third of patients disease is caused by somatic mosaicism.

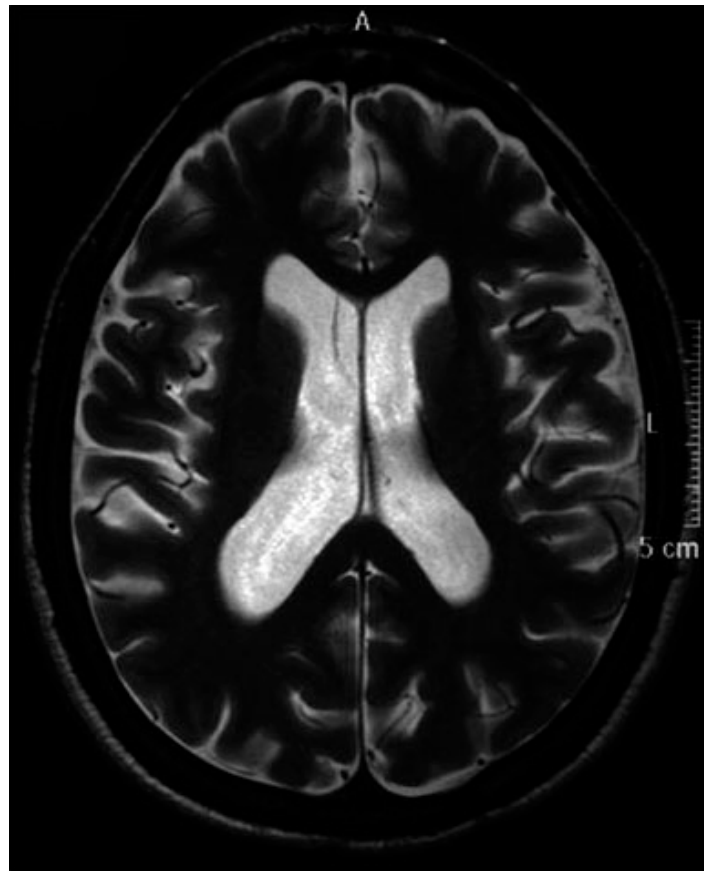
Figure 5. Bony overgrowth of the patella in CAPS. Picture reproduced with permission from Gattorno et al. *J Clin Immunol.* 2008; 28(suppl 1):S73-83. © J Clin Immunol



Figure 6. Finger clubbing in an adult CAPS patient. Picture reproduced with permission from Gattorno et al. *J Clin Immunol.* 2008; 28(suppl 1):S73-83. © J Clin Immunol



Figure 7. Cerebral atrophy and ventriculomegaly in CAPS. Picture reproduced with permission from Gattorno et al. *J Clin Immunol.* 2008; 28(suppl 1):S73-83. © J Clin Immunol



Mevalonate kinase deficiency

Diseases associated with *MVK*-mutations form a phenotypic spectrum. Before the genetic cause was known, the hyperimmunoglobulin D and periodic fever syndrome (HIDS) and mevalonic aciduria (MA) were considered to be separate diseases. HIDS is now regarded as the least severe end of the MKD spectrum and is characterized by fever attacks that last up to a week with onset in early infancy. A typical feature of HIDS is that the first fever attack may be triggered by childhood vaccination. Symptoms that accompany fever are abdominal pain, vomiting, diarrhoea, lymphadenopathy, skin rash, oral aphthous ulcers, arthralgia or arthritis. Typically, serum immunoglobulin D (IgD) is elevated in these patients. On the most severe end of the MKD spectrum lies MA, a disease present from birth or early infancy, characterized by failure to thrive, psychomotor retardation, ataxia, cataract and facial dysmorphism. Fever may be present. Before the introduction of adequate therapy, many patients with MA died in early childhood. Phenotypes with overlapping features are increasingly seen and *MVK* mutations overlap between severe and mild phenotypes. MKD is an autosomal recessive disease and a positive family history can be helpful. The risk of amyloidosis in MKD is around 6%, depending on the specific *MVK* mutations involved. (ter Haar 2016)

Besides these clear inflammatory phenotypes the spectrum of diseases associated with mutations in *MVK* has recently expanded. Mutations in *MVK*, that may overlap with mutations found in 'classical' MKD, have been

described in patients with retinitis pigmentosa, early onset ulcerative colitis, the skin diseases disseminated superficial actinic porokeratosis and porokeratosis of Mibelli, cyclic neutropenia and macrophage activation syndrome. (Mulders-Manders et al, 2015)

Tumour necrosis factor receptor associated periodic syndrome

An important feature distinguishing TRAPS from the autoinflammatory diseases described above is the length of the inflammatory attacks. In TRAPS, inflammatory episodes last for several days to weeks. Fever can be accompanied by abdominal pain, arthralgia, skin rash (a migratory rash that moves from the distal to the proximal parts of an extremity is very typical, figure 8) and myalgia. Periorbital oedema is another distinguishing but rare symptom of TRAPS. Chest pain due to pleuritis or myalgia is common. Ocular symptoms including conjunctivitis, periorbital pain, uveitis and iritis can be present. Disease onset is in childhood in most patients, but adult onset

TRAPS is autosomal dominantly inherited, so positive family history can be helpful. In the past, AA amyloidosis was an important long-term complication of TRAPS, affecting up to 25% of untreated patients

Figure 8. Erythematous skin overlying an area with fasciitis in TRAPS. Picture reproduced with permission from Gattorno et al. J Clin Immunol. 2008; 28(suppl 1):S73-83. © J Clin Immunol



Schnitzler syndrome

Schnitzler syndrome is characterized by late onset inflammation, with a median age of onset of 51 years. It is characterized by a non-pruritic urticarial skin rash, which can be accompanied by fever, bone pain, arthralgia or arthritis. Symptoms are progressive. The presence of monoclonal IgM or IgG paraprotein is a distinctive

feature, but symptoms can precede the presence of the M-protein for several years. Schnitzler syndrome is a non-hereditary disease. 15% of patients with Schnitzler syndrome develop Waldenström's macroglobulinemia within 10 years after the diagnosis.

Adult onset Still's disease

AOSD is characterized by fever, accompanied by arthralgia or polyarthritis and pharyngitis. A salmon-coloured skin rash, predominantly affecting the trunk and extremities is characteristic. Other symptoms are lymphadenopathy, hepatosplenomegaly, elevated liver enzymes, pneumonitis, and pleuritis. Beside high inflammatory markers (CRP), thrombocytosis, and neutrophilia, elevated serum ferritin levels are common in AOSD. A severe complication is the macrophage activation syndrome, which is a life-threatening disease, presenting with strongly elevated ferritin levels, coagulopathy, the absence or disappearance of thrombocytosis, and elevated liver enzymes.

The natural course of AOSD is highly variable. Some patients experience a single inflammatory episode, while in others episodic relapse of inflammation is present, and in some patients AOSD is a chronic disease.

4. Diagnostic workup for suspected autoinflammation

Thorough history taking and physical examination are the cornerstones of diagnosing autoinflammatory diseases. Focus should lie on the fever pattern, associated symptoms, triggering factors and family history. Experienced physicians with high exposure to these diseases may be able to diagnose some of these by pattern recognition, but clinical overlap is common. Patients should be seen during an inflammatory attack to validate symptoms and inflammation. Inflammatory markers, such as C-reactive protein (CRP) or serum amyloid A (SAA) should be measured during an inflammatory attack. Outside an attack, CRP and/or SAA may also be elevated, indicating smouldering subclinical inflammation. When during a clinical inflammatory attack no inflammatory markers are present, autoinflammation can be ruled out as the cause for the complaints. Further laboratory investigation should be guided by signs and symptoms present and should be aimed to exclude other causes for the inflammation. Although IL-1 β is central to the pathogenesis of the classical autoinflammatory disorders, serum levels of IL-1 β do not reflect the level of inflammation and should therefore not be used to test for the presence of autoinflammation. Diagnosis relies on recognition of the clinical picture and, increasingly, on detection of underlying genetic abnormalities. Laboratory investigations that may be helpful to distinguish autoinflammatory diseases are serum IgD, M-protein and ferritin. IgD is typically elevated in MKD, but it is neither sensitive nor specific: some MKD-patients never have elevated IgD and IgD may also be elevated in other inflammatory conditions, including FMF. Elevated IgA can be present in MKD. Schnitzler syndrome is characterized by the presence of monoclonal M-protein, typically IgM, but IgG paraproteinemia can also be present. As ferritin is an acute phase reactant, it may be elevated in patients with any inflammatory disease, but very high levels in combination with a fitting clinical picture are typical for

AOSD. Measurement of urinary mevalonic acid during febrile attacks can support a diagnosis of HIDS with high sensitivity. (Jeyaratnam 2015). However, the technology to detect mevalonic acid is not widely available. Measurement of MVK-activity in patient cells is the gold standard to diagnose mevalonate kinase deficiency, but the method is only available in very few highly specialized research laboratories. Therefore diagnosis does not depend on enzymatic studies.

Table 1. Diagnostic criteria for familial Mediterranean fever (FMF). Sensitivity and specificity are >95% and >97%, respectively.

Tel-Hashomer criteria (Definite diagnosis: 2 major criteria OR 1 major and 2 minor criteria. Possible diagnosis: 1 major and 1 minor criterion)

Major criteria

Recurrent febrile episodes associated with peritonitis, pleuritis or synovitis
AA-amyloidosis without a predisposing disease
Favourable response to colchicine

Minor criteria

Recurrent febrile episodes
Erysipelas-like erythema
Positive history of FMF in a first-degree relative

Livneh criteria (1 major criterion OR 2 minor criteria)

Major criteria

Typical attacks* of:

- Peritonitis (generalized)
- Pleuritis (unilateral) or pericarditis
- Monoarthritis (knee, hip or ankle)
- Fever

Minor criteria

1-2 incomplete attacks\$ affecting one or more sites:

- Abdomen
- Chest
- Joint
- Exertional leg pain

Response to colchicine

* Typical attack: ≥ 3 episodes with rectal temperature $\geq 38^{\circ}\text{C}$ lasting 12-72 hours

\$ Incomplete attack: recurrent painful attacks that do not fulfil all criteria for typical attacks (lower body temperature OR shorter or longer duration OR abdominal pain without peritonitis OR localized abdominal attack OR arthritis in other joints than specified).

Adapted from:

Soar et al. Tel Hashomer criteria for the diagnosis of FMF. First international conference on FMF. London and Tel Aviv: Freund publishing house. 1997

Livneh et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis rheum. 1997

Table 2. Diagnostic criteria for Schnitzler syndrome¹**Major criteria (≥ 1 present)**

(Chronic) urticarial rash

Monoclonal IgM or IgG

Minor criteria (≥ 2 present)

Intermittent fever

Arthralgia or arthritis

Bone pain

Lymphadenopathy

Hepato- or splenomegaly

Elevated erythrocyte sedimentation rate

Leukocytosis

Bone abnormalities (radiological or histological)

¹ Only when other causes have been excludedAdapted from: de Koning et al. Diagnostic criteria for Schnitzler syndrome. *Semin Arthritis rheum.* 2007

5. Diagnosis

CAPS, FMF, MKD and TRAPS can be confirmed by genetic analysis with detection of mutations in their respective causative genes, but mutation-negative forms of these diseases have been described, just like FMF or MKD associated with heterozygous mutations, possibly because mutations are not picked up with the current diagnostic techniques. Diagnostic criteria with high specificity are available for FMF (Tel-Hashomer (Sohar et al, 1997) or Livneh criteria (Livneh et al, 1997), table 1), Schnitzler syndrome (de Koning et al, 2007) (table 2) and AOSD (Yamaguchi criteria (Yamaguchi et al, 1992), table 3) and recently new sets of diagnostic clinical criteria for FMF, MKD, TRAPS and CAPS have been proposed (table 4), which have a sensitivity and specificity of 80-96 and 89-92%, respectively. (Federici et al, 2015) In FMF, a positive reaction to treatment with colchicine may be an additional clue that FMF is present and can therefore be used as a diagnostic test. Further recommendations for the genetic confirmation of FMF can be found in the most recent SHARE guidelines. (Giancane et al, 2015) As described in the section on patho-physiology, detection of R92Q- (R121Q) or P46L- (P75L) mutations in TNFRSF1A does not confirm TRAPS, as these mutations are present in low frequency in the general population. Diagnostic multi-gene panels that enable simultaneous sequencing of dozens or even hundreds of autoinflammation-associated genes are increasingly available and may be helpful in the diagnostic workup, as these will be less time consuming than doing multiple consecutive monogenetic analyses and may lead to the identification of new autoinflammatory diseases.

Table 3. Yamaguchi criteria for the diagnosis of adult onset Still's disease (AOSD)¹ (≥5 present of which ≥2 major criteria)**Major criteria**

Fever >39°C for ≥1 week
 Arthralgia or arthritis for ≥2 weeks
 Typical salmon-coloured rash
 Leukocytosis >10x10⁹/L with >80% polymorphonuclear cells

Minor criteria

Sore throat
 Recent and significant lymphadenopathy
 Hepatomegaly or splenomegaly
 Elevated liver enzymes
 No antinuclear antibodies (ANA) and rheumatoid factor (IgM)

¹AOSD can only be diagnosed when other causes are excluded.

Adapted from: Yamaguchi et al. Preliminary criteria for classification of adult Still's disease. J. Rheumatol. 1992.

Table 4. Eurofever criteria for the diagnosis of FMF, MKD, CAPS and TRAPS

Familial Mediterranean fever		Mevalonate kinase deficiency		Cryopyrin-associated periodic syndrome		TNF-receptor associated periodic syndrome	
Characteristic	Score	Characteristic	Score	Characteristic	Score	Characteristic	Score
Episodes < 2 days	9	Onset <2 years of age	10	Urticarial rash	25	Periorbital oedema	21
Chest pain	13	Aphthous stomatitis	11	Sensorineural hearing loss	25	Episodes >6 days	19
Abdominal pain	9	Generalized enlarged lymph nodes or splenomegaly	8	Conjunctivitis	10	Migratory rash	18
Turkish, Armenian, Non-Ashkenazi Jewish or Arab ethnicity	22	Painful lymphadenopathy	13	No exudative pharyngitis	25	Myalgia	6
Italian, Spanish or Greek ethnicity	7	Diarrhoea (sometimes/often)	20	No abdominal pain	15	Affected relatives	7
No aphthous stomatitis	9	diarrhoea (always)	37			No vomiting	14
No urticarial rash	15	No chest pain	11			No aphthous stomatitis	15
No enlarged cervical lymph nodes	10						
No episodes >6 days	13						
Cut-off ≥60		Cut-off ≥42		Cut-off ≥52		Cut-off ≥43	

Adapted from: Federici et al. Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. Ann rheum dis. 2015.

6. Treatment

Colchicine

The drug of first choice in FMF is colchicine (Ozen et al, 2016), as this drug is the only drug that has been proven to protect patients against the development of secondary AA amyloidosis. Its mechanism of action in FMF is unknown. On average, a dose of 1.0-1.5mg/day, which can be taken in a single daily dose or divided in multiple doses (Ozen et al, 2016), is effective. Side effects are predominantly of gastrointestinal origin, such as diarrhoea, nausea and abdominal pain. It is important not to stop colchicine when it is clinically ineffective or when side effects are present. In all patients the highest tolerated dose should be continued because of colchicine's protective effect against amyloidosis. In the few patients in whom colchicine is truly ineffective (in most patients ineffectivity will more likely be caused by incomplete compliance rather than true colchicine-resistance) addition of IL-1 inhibition can be very effective. Colchicine can be safely used during conception, pregnancy and lactation as is illustrated by multiple cohort studies.

Colchicine can also be used as a diagnostic test in patients with high suspicion of FMF. When colchicine is effective in a patient from a high-risk population and with a compatible clinical picture, FMF is the most likely diagnosis, even when no *MEFV*-mutations are found. During colchicine therapy, monitoring of liver enzymes and creatinin kinase (CK) should be checked regularly, especially in patients with decreased kidney function, as these patients are more susceptible for side effects and toxicity. (Giancane et al, 2015, Ozen et al, 2016)

Interleukin 1 targeting inhibition

The use of interleukin-1 targeting drugs in autoinflammatory diseases is described in detail in the in-depth discussion 2 that accompanies this chapter.

As outlined earlier in this chapter, overproduction of the pro-inflammatory cytokine IL-1 β is the most important feature in the pathophysiology of many autoinflammatory diseases. This is reflected by the positive effects of IL-1 inhibiting drugs in these diseases. The first IL-1 targeting drug to be widely available was anakinra, a recombinant IL-1 receptor antagonist. It has been shown to be effective in CAPS, FMF, MKD, TRAPS, Schnitzler syndrome and AOSD (Ter Haar et al, 2013, ter Haar et al, 2015, Ben Zvi 2016)* and has become standard of care, except for FMF, in which colchicine is the drug of first choice (see the section on this drug later in this chapter). The use of anakinra may lead to instant cessation of inflammation in autoinflammatory diseases. (Figure 9) and because of this it can also be used as a diagnostic test for IL-1 mediated inflammation. When signs of autoinflammation are present and other causes have been excluded, anakinra may be initiated. If it is effective, autoinflammation becomes a more likely diagnosis. An alternative for anakinra is canakinumab, a long-acting specific anti-IL-1 β monoclonal antibody. It has proved effective in Systemic JIA and CAPS. (Lachmann et al. 2009; Ruperto et al 2012) Based on the preliminary results of a large

double blind placebo controlled trial canakinumab has now also been registered for the treatment of, TRAPS, MKD and colchicine-resistant FMF.

The third IL-1 targeting drug available is rilonacept, a construct of two extracellular chains of the IL-1 receptor complex fused to the Fc-proportion of IgG. It has been approved for the treatment of CAPS and has been shown to be effective in colchicine resistant FMF.

The most common side effect of IL-1 inhibiting drugs is increased susceptibility for infections. Mild upper respiratory tract infections are the most common and severe infections are rare. With the use of anakinra, local injection site reactions are common. These can be extremely painful and this may hamper therapy.

Figure 9. Rapid effect of anakinra in a patient with CAPS. On day 0 before start of anakinra an urticarial rash is seen, which is completely absent one day after the first injection (day 1). Picture reproduced with permission from Gattorno et al. J Clin Immunol. 2008; 28(suppl 1):S73-83. © J Clin Immunol



Interleukin-6 inhibition

When anti-IL-1 therapy is ineffective in patients with an autoinflammatory disease, tocilizumab can be tried. Tocilizumab is a monoclonal antibody against the interleukin-6 (IL-6) receptor that has been registered for the treatment of rheumatoid arthritis and systemic onset juvenile idiopathic arthritis (SoJIA) and has shown to be effective in Schnitzler syndrome, AOSD, MKD and TRAPS. Side effects are increased susceptibility for infections, elevated liver enzymes and haematological abnormalities. IL-6 is an important cytokine in the production of CRP. Because of this, during tocilizumab treatment, CRP cannot be used to monitor disease activity.

Corticosteroids

Corticosteroids may be effective in autoinflammatory diseases such as AOSD, MKD, TRAPS and CAPS, but their effect is less than the effects of anti-IL-1 therapy (Ter Haar et al, 2013, ter Haar et al, 2015)* and side effects are common and may be severe. Because of this, corticosteroids are not preferred as maintenance treatment for patients with autoinflammatory diseases. However, in patients with infrequent episodes of TRAPS or MKD attacks may be managed with a short course of corticosteroids.

TNF-inhibition

There are no prospective trials comparing the effects of IL-1 inhibition and drugs that target TNF, such as etanercept or adalimumab. These may be effective in some patients with TRAPS (Ter Haar et al, 2013), but their effect may decline over time and because of this anti-IL1 treatment is preferred. (ter Haar et al, 2015) Anti-TNF may be used as a rescue drug in other anti-IL-1 resistant auto-inflammatory diseases. It has shown to be effective in over half of patients with MKD (ter Haar et al, 2015) and in AOSD or FMF anti-TNF may be effective, but its effect is generally less than the effect of colchicine (in FMF) and anakinra, and in AOSD it may even lead to exacerbations of the disease. (Kaneko et al, 2010)

7. Follow up

All patients with an (suspected) autoinflammatory syndrome should be followed up regularly for the evaluation of treatment and detection of drug side effects and complications. The most common complication of autoinflammatory diseases is secondary amyloidosis. This is described into more detail in in-depth discussion 1 accompanying this chapter. Periodical measurement of urinary protein should be performed in all patients with (suspected) autoinflammatory diseases to screen for secondary renal amyloidosis, although the risk of this is highest in FMF, TRAPS and moderate to severe CAPS and relatively low in MKD, Schnitzler syndrome and AOSD. CAPS can be complicated by vision loss and patients with moderate to severe CAPS are at high risk of developing sensorineural hearing loss. Because of this, periodical ophthalmologic and audiometric evaluation should be performed. MKD and AOSD can be complicated by the potentially fatal macrophage activation syndrome, also known as secondary haemophagocytosis. This syndrome is characterized by pancytopenia, liver failure, coagulopathy and neurological symptoms. Patients are generally very ill with fever and inflammation. ESR may be deceptively normal or even low because fibrinogen is consumed in the coagulopathy. Its cause is unknown. In patients with Schnitzler syndrome, M-protein should be measured regularly as 15% of these patients develop Waldenström's macroglobulinemia after 10 years.

8. Other rare auto-inflammatory syndromes like interferonopathies, granulomatous and pyogenic diseases.

8.1. Interferonopathies

Type 1 interferons (interferon alfa (IFN- α) and interferon beta (IFN- β) are important pro-inflammatory cytokines that play a role in host defence against intracellular pathogens. Their secretion is induced by stimulations of pattern recognition receptors, such as the Toll-like receptors (TLR). Type 1 interferons bind the interferon- α receptor (IFNAR) located on the cell surface and stimulation of IFNAR leads to activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, inducing transcription of interferon-stimulated gene (ISG) resulting in a consequent immune response.(Lee-Kirsch et al, 2015)

The term type 1 interferonopathies was first used in 2011 to describe a group of hereditary disorders associated with abnormal upregulation of type 1 interferons. Since the introduction of this term, the number of type 1 interferonopathies has been expanding rapidly. Most of them are very rare and therefore not all type 1 interferonopathies are described here. Examples of type 1 interferonopathies are:

- STING-associated vasculopathy (SAVI). This is an early onset disease with predominant vasculopathy, characterized by necrotic skin lesions on the face, fingers and toes, ears and nose, accompanied by fever episodes and interstitial lung disease or lung fibrosis.
- Proteasome associated autoinflammatory syndromes constitute an expanding group of disorders is caused by mutations affecting component proteins of the immunoproteasome. Clinically these are characterised by recurrent fever and various combinations of nodular skin rash, panniculitis, lipodystrophy, myositis and central nervous system involvement. An example is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE). It is an autosomal recessive disease characterized by early-onset recurrent fever, associated with skin lesions, swelling of eyelids and lips, failure to thrive, growth retardation, lipodystrophy, arthropathy and myositis. Visceral inflammation may be present. As it was first described in 1939 it is not newly identified, however, it was only recently classified as an autoinflammatory disease when it was found out that mutation in the gene encoding low molecular weight protein 7 (LMP7) cause CANDLE. LMP7 is a subunit of the immuno-proteasome; mutations lead to decreased proteasome activity and consequently increased production of proinflammatory cytokines. High dose steroids are very effective in CANDLE.
- Aicardi-Goutières syndrome. This rare disease is characterized by neonatal onset leukoencephalopathy, dystonia, seizures, fever, developmental delay and microcephaly. Other symptoms include liver enzyme elevation, arthritis, thrombocytopenia, lymphocytopenia, presence of antinuclear antibodies (ANAs) and cold-induced skin lesions. The pheno-type may differ largely between patients from one family. At least seven different genes that cause Aicardi-Goutières syndrome have been described.

- Retinal vasculopathy with cerebral leukodystrophy: this is an autosomal dominant disease characterized by cerebrovascular events, dementia and loss of vision. Disease onset is in early adulthood. Other symptoms may be headache, glomerulopathy and Raynaud's phenomena.
- Familial chilblain lupus (FCL). FCL is a very rare form of cutaneous lupus erythematosus with early childhood onset. Characteristic symptoms are red-blue skin lesions on the fingers, toes, nose, cheeks and ears. Other symptoms include the presence of ANAs, lymphopenia and arthralgia.

The optimal treatment for type-1 interferonopathies is unknown. Drugs targeting IFN- α or β , IFNAR or the JAK/STAT pathway may be effective and can be tried in these patients.

8.2 Granulomatous autoinflammatory syndromes

8.2.1 Blau syndrome

Blau syndrome, which is also known as familial juvenile systemic granulomatosis, is an autosomal dominant disease characterized by a triad of arthritis, dermatitis and uveitis due to non-caseating granulomatous inflammation. Disease onset is usually during the first years of life. Fifty percent of patients develop cataract and approximately one third eventually develops secondary glaucoma. Blau syndrome is caused by mutations in the gene encoding nucleotide binding oligomerization domain containing 2 (NOD2), a receptor able to recognize certain bacterial cell wall components and upon recognition upregulates NF- κ B, leading to an inflammatory response. It is also involved in autophagy and apoptosis. At least 17 mutations in NOD2 are associated with Blau syndrome and mutations in NOD2 are also found in early-onset sarcoidosis and Crohn's disease.

8.3. Pyogenic autoinflammatory syndromes

8.3.1 Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome

Pyogenic sterile arthritis (PAPA) syndrome is an autosomal dominant disease characterized by sterile arthritis, pyoderma gangrenosum and cystic acne. Disease onset is in childhood, with pyogenic oligoarthritis as presenting symptom. This sterile arthritis eventually leads to synovial and cartilage destruction. Skin lesions appear in the second decade of life. Acne, ulcerative skin lesions mimicking pyoderma gangrenosum, skin abscesses and hidradenitis are symptoms of PAPA syndrome.

Mutations in the gene encoding proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1) cause PAPA syndrome. PSTPIP1 is able to bind pyrin, forming a complex regulation the inflammasome.

PAPA syndrome is usually responsive to oral glucocorticoid treatment. Steroid resistant patients may benefit from anti-TNF or anti-IL-1 therapy.

8.4 Other autoinflammatory syndromes

8.4.1. Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome.

Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome was first described in the late 1980s. (Marshall et al, 1987) It may be the most common autoinflammatory diseases, but it is difficult to estimate its incidence as it is underrecognized. PFAPA is a disease with a usual onset before the age of 5. Its clinical picture is characterized by frequent and recurrent episodes of fever, accompanied by pharyngitis, cervical adenitis and aphthous stomatitis. Other symptoms are headache, vomiting, abdominal pain, arthralgia and myalgia. Symptoms usually cease before or during adolescence; the cause for this is unknown. PFAPA has been described in adults, but it is uncertain whether these cases represent the same disease. Little is known on the pathogenesis of PFAPA and no genetic defect has been found so far.

The only evidence based therapy in PFAPA is (adeno-)tonsillectomy. However, follow up of these studies has been short. Most patients benefit from short courses of corticosteroids during attacks, but their use may increase attack frequency. (ter Haar et al, 2015) A small trial showed that colchicine may reduce attack frequency in PFAPA. (Butbul Aviel et al, 2016) Other treatments that have been reported in small numbers of patients are cimetidine, and anakinra.

8.4.2. NLRP12-associated periodic syndrome

The NLRP12-associated periodic syndrome (Jeru et al, 2008) presents with recurrent fever, accompanied by urticarial skin rash, myalgia, arthralgia, sensorineural hearing loss, aphthous ulcers, lymphadenopathy and/or abdominal pain. Attacks may be triggered by exposure to cold, physical exertion or fatigue and the phenotype can resemble CAPS.

The protein NLRP12 is part of the nucleotide binding and leucine-rich repeat containing protein family, just like NLRP3, the protein involved in the pathogenesis of CAPS. Just like NLRP3, NLRP12 is able to form an inflammasome by combining with ASC and procaspase-1 and is involved in the up-regulation of NF- κ B. Mutations may interfere with this, leading to upregulation of the proinflammatory pathway.

8.4.3. Deficiency of interleukin-1 receptor antagonist (DIRA)

Deficiency of interleukin-1 antagonist (DIRA) is a disease with neonatal onset. It is characterized by multifocal osteomyelitis, periostitis and pustules, which may be local or generalized. (Aksentijevich et al, 2009)

DIRA is caused by mutations in the gene encoding interleukin-1 receptor (*IL-1RN*), leading to deficiency of the IL-1 receptor antagonist, which normally functions as an inhibitor of circulating IL-1 α and β . Treatment with recombinant human IL-1RA (anakinra) is very effective in DIRA.

8.4.4. NLRC4 associated autoinflammatory syndromes

Gain of function mutations in the gene encoding the inflammasome protein NLRC4 give rise to a spectrum of autosomal dominant diseases. Mildly affected patients have recurrent urticariform rash with conjunctivitis myalgias and arthritis. The other extreme of the clinical spectrum is characterised by severe sterile enterocolitis and susceptibility to the potentially lethal macrophage activation syndrome. (Canna et al 2014) Interleukin-18 and its downstream mediator gamma-interferon (IFN γ) appear to central to its pathogenesis.

8.4.5. NLRP1-associated autoinflammation with arthritis and dyskeratosis is an ultra rare disorder due to mutations in the gene encoding NLRP1, which is another inflammasome protein. The clinical phenotype includes diffuse skindyskeratosis, autoinflammation, autoimmunity, and arthritis. (Grandemange et al 2016)

8.4.6. *Deficiency of the interleukin-36 receptor antagonist (DITRA)*

Deficiency of the interleukin-36 receptor antagonist (DITRA) is a rare autosomal recessive disease associated with episodic fever, skin rash and pustular psoriasis, (Marrakchi et al, 2011) Mutations in the gene encoding the IL-36 receptor antagonist cause DITRA and deficiency of the receptor for the pro-inflammatory cytokine interleukin-36 leads to this inflammatory phenotype. Corticosteroids, retinoids, cyclosporine, methotrexate, anti-TNF and anakinra may all be effective in DITRA. Recently, ustekinumab was shown to be effective in two therapy resistant patients. (Bonekamp et al 2017)

8.4.6. *Majeed's syndrome*

The first report on the autosomal recessive Majeed's syndrome described a clinical picture with chronic recurrent multifocal osteomyelitis, congenital anaemia and inflammatory dermatitis. Majeed's syndrome is caused by mutations in the gene encoding lipin-2 (LPIN2). The exact function of this protein is unknown, but besides its role in inflammation, it also plays a role in lipid metabolism. Oral steroids can be effective. IL-1 blockade has been shown to effectively control inflammation in some cases.

8.4.7 Haploinsufficiency of A20 and related disorders of ubiquitinylation

Another rare autosomal dominant autoinflammatory disease is caused by loss-of function mutations in *TNFAIP3*, encoding A20, a negative regulator of NF κ B and of the NLRP3 inflammasome. Patients have an early onset febrile disease that is somewhat similar to Behçet's disease, with ocular inflammation, oral and genital ulcers and polyarthritis, but may include organ specific autoimmunity as well. (Zhou et al 2016). It is one of an emerging group of autoinflammatory disorders in which protein ubiquitylation is disturbed.

8.4. Auto inflammation with immunodeficiency

DADA2

Loss-of function mutations in both alleles of *CECR1* encoding Adenosine Deaminase-2 (ADA2) are associated with a spectrum of vascular and inflammatory phenotypes, ranging from early-onset recurrent stroke to systemic vasculopathy or vasculitis combined with a mild immunodeficiency (hypogammaglobulinemia) and hepatosplenomegaly. Patients with ADA2 deficiency (DADA2) have significantly diminished ADA2 activity in plasma. Treatment is directed to prevention of recurrent infections with antibiotic prophylaxis and/or immunoglobulin substitution. (Zhou 2014, Navon-Elkan 2014) Inflammation might be treated with anti-TNF. Anticoagulants are given to prevent strokes.

SIFD

A syndrome of congenital sideroblastic anaemia (CSA) associated with B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD), is caused by partial loss of function mutations in *TRNT1*, the gene encoding the CCA-adding enzyme essential for maturation of both nuclear and mitochondrial transfer RNAs. (Chakraborty 2014)

9. Conclusion

Autoinflammatory diseases are rare diseases characterized by chronic or episodic inflammation. Many various phenotypes have been described. CAPS, FMF, MKD and TRAPS are the most best-known. Other autoinflammatory diseases are increasingly reported, but most of them are rare. Diagnoses are based on a clinical picture with signs and symptoms of inflammation and sometimes with the help of detection of genetic abnormalities. Interleukin-1 targeting drugs are very effective in most classical autoinflammatory diseases. Exceptions are FMF, where colchicine is the drug of first choice, and the interferonopathies, where drugs targeting IFN or the JAK/STAT pathway are most effective. The main long-term complication of autoinflammatory diseases is AA amyloidosis.

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module

Autoinflammatory syndromes

EULAR on-line course on Rheumatic Diseases

Joost Frenkel and Elizabeth Legger

A previous version was coauthored by Véronique Hentgen, Anna Simon, Karin Mulders-Manders, Caroline Galeotti, Roberta Caorsi, Marco Gattorno, Katia Stankovic, Maria Antonietta Pelagatti, Gilles Grateau



IN-DEPTH DISCUSSION I

AA Amyloidosis in auto inflammatory diseases

One of the most serious complications of auto inflammation is the development of AA amyloidosis. Although the incidence of this potentially life-threatening disease has decreased since the introduction of targeted anti-inflammatory therapy, it is still an important long-term complication of these diseases.

Pathogenesis

Amyloidosis is caused by deposition of insoluble fibres in the extracellular matrix with disruption organ structure and organ function. In AA amyloidosis the amyloid fibrils consist of insoluble degradation products of the acute phase reactant serum amyloid A (SAA). The transcription of the hepatic protein SAA depends on several proinflammatory cytokines, amongst others IL-1 and IL-6. Therefore AA amyloidosis, which is also known as secondary amyloidosis, is associated with long-term systemic inflammation. The normal serum concentration of SAA is <10mg/L. During systemic inflammation this concentration can increase 1000-fold. There is a significant association between the duration of elevated SAA serum levels and the development of AA amyloidosis.

In AA amyloidosis, amyloid depositions primarily affect the kidneys. Other organs such as heart, liver, bone marrow and spleen may also be affected. Involvement of intestine, skin, thyroid, testes or adrenal glands is rare and only seen in patients with long-term untreated amyloidosis.

Epidemiology

The incidence of AA amyloidosis in auto inflammatory diseases has been studied before targeted treatment was available. The risk of developing amyloidosis varies between diseases, with the highest risk for patients with familial Mediterranean fever (FMF). In the pre-colchicine era over half of FMF patients developed amyloidosis. In untreated TNF-receptor associated periodic syndrome (TRAPS) amyloidosis was present in 10-20% of and in cryopyrin-associated periodic syndrome (CAPS) incidence was 25% with higher incidence in patients with the clinical phenotype Muckle-Wells syndrome than in familial cold auto inflammatory syndrome. AA amyloidosis is rare in mevalonate kinase deficiency (MKD): approximately 10 patients with hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) have been published worldwide (Obici 2012). AA amyloidosis is also rare in Schnitzler syndrome. (De Koning Semin Arthr Rheum 2007) It is unclear why some patients with the same level of inflammation never develop AA amyloidosis, while others do. There may be an association with polymorphisms in the SAA-gene or certain genotypes.

There can be a prolonged period of time between onset of inflammation and presentation of AA amyloidosis, but in some patients amyloidosis develops rapidly. In a cohort of 46 patients with an auto inflammatory disease (FMF, CAPS, TRAPS or MKD) and amyloidosis, median time between onset of symptoms of auto inflammation and diagnosis of AA amyloidosis was 23 years. (Lane 2013) In this cohort, median age of onset of amyloidosis was 38 years with a 7-year-old with FMF as youngest patient.

Clinical features

Signs and symptoms of AA amyloidosis depend on the localization of the amyloid deposit. As a general rule, kidneys are the first and often only symptomatic organs in AA amyloidosis. Renal AA amyloidosis will be subclinical in most patients, with proteinuria as the sole manifestation. Progression of amyloid mass can lead to progressive proteinuria, decreased kidney function or nephrotic syndrome. If left untreated, end stage renal failure will eventually occur. Nephrotic syndrome or kidney failure may be the presenting symptom in patients with prior unrecognized auto inflammatory disease. This is usually due to underreporting of symptoms by these patients, presence of atypical symptoms or under-recognizing of inflammation by treating physicians; absolute absence of any signs of inflammation before development of AA amyloidosis is extremely rare or probably even non-existent. Even so-called “type II FMF” (FMF presenting with amyloidosis before typical signs and symptoms of FMF) is likely due to this mechanism.

The gastrointestinal system is the second most commonly involved. Intestinal AA amyloidosis is characterized by abnormal bowel movement, usually with diarrhoea, sometimes with constipation. Advanced intestinal AA amyloidosis leads to chronic malabsorption.

Involvement of other organs is very rare in AA type amyloidosis and is usually only seen in very advanced stages. Amyloid deposition in liver or spleen may lead to hepato- or splenomegaly or elevated liver enzymes. Cardiac amyloidosis may present as rhythm disturbances, myocardial infarction, heart failure or sudden death.

Diagnosis

As outlined previously, proteinuria is often the first and the most important sign of AA amyloidosis. Therefore, all patients with an auto inflammatory disease should be screened for the presence of amyloidosis at least yearly with a urinary protein evaluation. Proteinuria >0.5 grams per day indicates glomerular dysfunction and is an indicator for the presence of renal AA amyloidosis.

When proteinuria (or nephrotic syndrome or decreased kidney function) is present, a kidney biopsy should be considered to confirm the diagnosis of AA amyloidosis. Congo red staining of biopsy samples shows apple-green birefringence at polarized light microscopy. Immunofluorescence microscopy can prove the presence of amyloid A fragments in the biopsy specimens.

Screening for amyloidosis in other organs should only been done in the presence of amyloidosis-related signs or symptoms, as these organs are involved in patients with advanced amyloidosis.

Serum amyloid P (SAP) scintigraphy is only available in specialized centres. In this nuclear medicine technique the serum amyloid P component is radiolabelled with a radioactive isotope. Radiolabelled SAP localizes rapidly and specifically to visceral amyloid deposits and detects systemic AA amyloidosis with 100% sensitivity. (Hawkins Europ J Nucl Med 1995)

Prevention and treatment

AA amyloidosis used to be considered incurable. However, now that very effective anti-inflammatory treatment is available for auto inflammatory diseases, it has been shown that disease progression can be halted with adequate control of inflammation. In some cases, amyloid mass and organ dysfunction may even regress with adequate treatment. Goal of therapy is a serum SAA level <10mg/L. In patients with AA amyloidosis, it is recommended to perform regular measurements of serum SAA concentrations, even in the absence of inflammatory symptoms, since subclinical acute phase response can persist and should be avoided. SAA is the best marker to use; if SAA measurement is not available, CRP can be used as a surrogate.

Treatment of the auto inflammatory disorders is not discussed in detail here. In brief, in FMF, colchicine is the treatment of first choice. The usual effective dose is 1.5 to 2.0 mg daily. In patients with inadequate response or intolerance to colchicine, interleukin-1 (IL-1) inhibitors such as anakinra or canakinumab can be added to improve control of inflammation. Colchicine should be continued in all patients in the highest tolerable dose because it is the only drug with proven protective effect against AA amyloidosis in FMF.

In CAPS, TRAPS and MKD inhibition of IL-1 leads to stable disease or regression of amyloid mass in most patients with AA amyloidosis. (Lane 2013)

In patients with end stage renal failure dialysis or kidney transplantation may be necessary. After kidney transplantation strict control of inflammation is necessary to prevent recurrence of amyloidosis in the allograft. It is difficult to estimate the risk of recurrence of amyloidosis after kidney transplantation. Lane et al reported a subgroup of 13 patients with an auto inflammatory disease who had undergone kidney transplantation because of amyloidosis, with a median follow-up of 6.38 years. Amyloidosis recurred in 2 patients (15%) with graft survival of 6.08 and 17 years in these patients. (Lane 2013) Median time from diagnosis of amyloidosis to transplant was 4 years.

Even in patients with end-stage renal failure on dialysis, it is still relevant to control the inflammation. Reversion of lost kidney function is unlikely, but blocking progression of AA amyloidosis is still important to prevent other organ damage, especially gastrointestinal.

Patients with inadequate response to IL-1 inhibitors may be switched to interleukin-6 (IL-6) inhibiting therapy with the humanized IL-6 receptor antibody tocilizumab. Lane et al treated 14 patients with chronic inflammation and AA amyloidosis, who did not respond to other therapies, with tocilizumab. All 14 patients

had reduction of proteinuria. Regression or stabilization of amyloid depositions on SAP-scintigraphy was seen in 64% and 29%, respectively. (Lane 2015) Tocilizumab has also been shown to be effective in reduction of proteinuria and improvement of renal function in patients with amyloidosis secondary to rheumatoid arthritis. (Courties 2015) In a cohort with 11 patients with FMF, tocilizumab was effective in reducing proteinuria 73% of patients, (Yilmaz 2015) but serum creatinine decreased only in 45% of them.

Prognosis

Although studies are lacking, life expectancy for patients with auto inflammatory diseases seems similar to the general population when adequate control of inflammation is achieved. In patients with AA amyloidosis survival is impaired with a median survival of 19 years after diagnosis of amyloidosis (Lane 2013) – although this study primarily included patients in whom AA amyloidosis was diagnosed over 20 years ago, when fewer anti-inflammatory biologicals were available.

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Autoinflammatory syndromes

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IN-DEPTH DISCUSSION II

Interleukin-1 inhibitors

The common pathogenic feature of autoinflammatory diseases is a consequent increased activity of the innate immunity, resulting in increased production of proinflammatory cytokines. Of these, interleukin-1 beta (IL-1 β) has been proven to be the most important factor that causes the clinical symptoms of autoinflammation, especially in the classical periodic fever syndromes. In some of the recently discovered rare autoinflammatory syndromes, the pathophysiological mechanisms of disease is different: for instance, hyperactivation of type-1 interferon signalling in proteasome disorders and of the IL-18/ γ -interferon pathway in NLRC4 related disease.

Pro-IL-1 β needs to be activated by multiprotein complexes called inflammasomes. Activation of inflammasomes leads to rapid conversion of pro- IL-1 β to the biochemically active mature IL-1 β . There are several types of inflammasomes activated by distinct stimuli and affected in different autoinflammatory diseases. The NLRP3 inflammasome is the best studied and is involved in the pathogenesis of CAPS. It is normally formed when inflammatory stimuli (bacterial compounds and other danger associated molecular patterns) are present. The NLRC4-inflammasome is physiologically involved in the detection of gram negative bacteria, whereas the pyrin inflammasome, involved in the pathogenesis of familial Mediterranean fever (FMF) and mevalonate kinase deficiency (MKD)

As IL-1 β is central to the pathogenesis of many autoinflammatory diseases, anti- IL-1- targeted therapy has been tried and found to be effective in an increasing number of autoinflammatory disorders .

Currently there are three IL-1 targeting drugs that are commonly used in autoinflammatory diseases.

The first widely used anti-IL-1 drug was anakinra (Kineret), which has been approved for clinical use in humans by the American FDA since 2001 and the European EMA in 2002. Anakinra is a recombinant form of the human IL-1 receptor antagonist. It blocks the biological action of IL-1 β and IL-1 α by competitive binding to the IL-1-type 1 receptor. Anakinra is available as subcutaneous injections, with a half-life of 4-6 hours, making daily subcutaneous injections necessary.

In most autoinflammatory diseases subcutaneous administration of anakinra leads to significant reduction of symptoms in 24-72 hours. Anakinra has been found to be safe and effective in both children and adults with different autoinflammatory diseases. The only placebo-controlled studies of anakinra in autoinflammatory disease have been in systemic JIA and in FMF. However, it has been shown in case series to effectively reduce the frequency, severity and duration of inflammatory attacks in cryopyrin associated periodic syndrome (CAPS), mevalonate kinase deficiency (MKD), Adult onset Still's disease, Schnitzler syndrome, TNF-receptor associated periodic syndrome (TRAPS). Anakinra is often used on a daily basis, in the standard dose of once daily 100 mg (adults) or 1 to 8 mg/kg (children). Younger children and those with severe inflammation tend to require higher doses. On demand therapy (i.e. anakinra is only started at the first signs of an inflammatory attack and is only continued for a few days) has been shown to be beneficial several cases of MKD and TRAPS.

Anakinra is generally so effective that it can also be used as a diagnostic tool: a quick clearly positive clinical response to anakinra points towards an IL-1 mediated autoinflammatory origin of the symptoms.

The major side effects of Anakinra are local pain at injection and transient local injection site reactions with subcutaneous infiltrates, which mostly occur during the second or third week of treatment. The exact mechanism behind these infiltrates is unknown and in most cases, they disappear during the next two or three weeks even when anakinra is continued. However, these local infiltrates can be extensive and painful and might form a reason to discontinue treatment in some patients. Other, less frequent side effects of anakinra are increased susceptibility to common infections (mostly skin and respiratory tract infections) and headache. Neutropenia and liver enzyme abnormalities have also been seen with anakinra. The incidence of opportunistic infections is rare; two cases of tuberculosis have been reported.

When subcutaneous anakinra leads to insufficient reduction of symptoms, a short course of daily intravenous infusion of 300 mg anakinra is safe in adults and could be helpful, although this approach is not scientifically proven.

To overcome the burden of daily, sometimes painful injections associated with treatment with anakinra, canakinumab (Ilaris®), a long acting anti-IL-1 β therapy, could be an alternative. Canakinumab is a humanized monoclonal antibody against IL-1 β and is thus able to directly bind to IL-1 β , preventing its biochemical action. Canakinumab has been approved for human use in the USA by the FDA since 2009 for the treatment of CAPS in both children >2 years of age and adults and for the treatment of systemic onset juvenile idiopathic arthritis (SoJIA), followed by approval by the EMA in Europe in the same year. In 2016, it was given a breakthrough designation for the treatment of MKD, TRAPS and colchicine-resistant FMF, based on preliminary study results and has now been registered for use in these indications as well as adult onset Still's disease in both the USA and Europe. Canakinumab has a half-life time of about 26 days, which translates in a dosing scheme of a single subcutaneous injection of 150 mg (adults) or 2-4 mg/kg (children) every two months in CAPS. Canakinumab is effective in reducing the frequency, duration and severity of inflammatory attacks in CAPS, TRAPS, MKD and colchicine resistant FMF and SoJIA and has also been effectively used in a limited number of patients with Schnitzler syndrome. However, the yearly dose needed in SoJIA, MKD, FMF and TRAPS tend to be higher than in CAPS. Unlike anakinra, canakinumab is associated with fewer local injection side reactions. Its major side effects are increased susceptibility to infections (mostly skin and respiratory tract), dizziness and abdominal pain. Canakinumab is very expensive at 5-10x the cost of anakinra.

A third available anti-IL-1 therapy is rilonacept (Regeneron). It has been approved for the treatment of CAPS since 2008 in the US and 2009 in Europe, but is not commonly used in the latter. Rilonacept is a dimeric fusion protein which consists of the ligand binding domains of the extracellular part of the human type 1 IL-1 receptor and IL-1 receptor accessory protein linked to the Fc portion of human IgG1. Rilonacept is able to bind

both IL-1 α and IL-1 beta and therefore prevents their biochemical action. It is available as subcutaneous injections which have to be injected every week due to its half life time of just over 7 days. The major side effects of rilonacept are local injection side reactions (erythema, bruising, pruritus, pain), increased susceptibility to infections (mostly respiratory tract) and headache. Placebo controlled studies have been performed in CAPS and colchicine resistant FMF only.

Off label use of IL-1 antagonists has been reportedly effective in an increasing number of disorders in which

Several new drugs targeting IL-1 are being developed and are likely to be introduced for common use in the next few years. Currently, the costs of IL-1 blockade are so high as to be unaffordable for patients in many countries. However, when disease cannot be controlled by NSAID's, steroids or -in the case of FMF- colchicine without intolerable side effects, there is sadly no effective alternative to IL-1blockade in IL-1 mediated autoinflammatory disease.

Few cases illustrate that the use of IL-1 targeting drugs during conception and pregnancy may be safe, but data is scarce and because of this it is advised that patients using IL-1 targeting drugs and considering getting pregnant should be counselled towards stopping IL-1 inhibitors.

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Pain: mechanisms and management

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LEARNING OBJECTIVES

- Describe and explain the neurophysiological basis of nociception
- Differentiate between the different forms of nociception
- Describe and explain the mechanisms underlying inflammatory pain
- Describe and explain the pharmacological action of the principal drugs used in pain treatment
- Evaluate different forms of pain in a clinical context
- Describe and explain the multidimensional nature of pain in diagnosis and management of pain

1 Introduction

Previously thought to be a simple sensory experience, current literature suggests pain is a complex neuropsychological phenomenon. Its universality indicates that it has an important function to protect the organism from dangerous and noxious external events. In this sense, pain is protective, as it promotes avoidance of such harmful stimuli. It may even promote wound healing. However, when pain is the dominant symptom in a clinical setting, provoking suffering and incapacity, it is termed 'bad' or 'maladaptive'. This state may be called 'pain disease'. Pain is often classified into acute and chronic states. Acute pain, usually refers to short-lived, protective pain as described above, whereas chronic pain is maladaptive and can lead to disability. However, this is an oversimplification as pain is often a combination of chronic and recurrent acute pains and is rarely a single consistent experience.

In the context of scientific study and medical treatment, it is important to define pain and its underlying mechanisms as well as how it is perceived (nociception). The International Association for the Study of Pain (IASP) (1979) defines pain in the following terms: *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."* Pain is also described as a subjective experience in which an individual's past experiences partly determine the current experience of pain. Functional imaging has revealed that pain also has a strong association with emotional state and is described often in terms of 'suffering'. It is beyond the scope of this chapter to cover the entire extent of these influences, but it is important for the clinician to be aware of these influences in the evaluation of the patient's symptoms and in the elaboration of a management plan. In 1999, Ronald Melzack coined the term 'neuromatrix of pain' to suggest the processing of pain that occurs in the higher cortical centres. Melzack combined the biopsychosocial experience of pain and hypothesized the interactions of neural mechanisms of pain perception (Melzack, 1999). In summary this states that the brain has the job of integrating neural information coming from the body with prior experiences of pain, including emotions, into one experience. Since then, clinicians have recognized the success of using an integrative approach to the management of pain.

In rheumatology, pain is the most common presenting complaint of our patients. Often it is accompanied by overt physical manifestations of disease, affecting the articular and non-articular connective tissue. It may also be a major clinical symptom in the absence of obvious, defined pathological abnormalities, such as in fibromyalgia, or when the pathological source of nociceptive stimulation is not easily delineated, as in chronic regional pains such as low back pain. In a majority of patients complaining of chronic pain in general practice there is no clearly definable physical cause (Rajapakse 2014). The management of such pain is an increasing problem for clinicians as approximately 40% of patients felt that their pain was managed inadequately in a survey published previously (Breivik et al, 2006). Furthermore, recent studies show that conventional treatments for pain, such as paracetamol and opiates, may have low efficacy for chronic pain and in fact may

not be worthwhile in these patients due to the troublesome side effects (Shaheed et al, 2016, Roberts et al, 2015). Therefore, to better understand the concepts underlying pain and its management, this chapter will cover our current understanding of the neurophysiological mechanisms underlying nociception, the clinical manifestations of different types of pain, as well as the biopsychosocial approach to the management of pain.

2 The neuroanatomy of pain

The common pathway of all pain perception is the transmission of neuronal signals from peripheral sensory organs/preterminal nociceptor to the spinal cord where synaptic processing occurs. The signals are then transmitted along the spinothalamic and spinoparabrachial pathways to higher centres in the somatosensory cortex (anterior cingulate cortex, pre-frontal cortex), after passing through the thalamus where the sensation of pain evokes behavioural, physiological, and emotional/affective responses.

2.1 Nociceptors and nociception

Nociception—the detection of tissue damage and the process that transforms the triggering stimulus to neural signals—is mediated by the generation and transmission of electrical signals from peripheral nerve terminals along unmyelinated C-fibres and thinly myelinated A δ fibres when they are activated by receptors which are sensitive to either heat, cold, protons, or mechanical stimuli. It is important to clarify the terms hyperalgesia, hypersensitivity and allodynia as these are used frequently in this chapter. Hyperalgesia refers to increased pain response to a noxious stimulus. Hypersensitivity, in pain, is defined as increased neuronal activity due to a non-noxious stimulus. Allodynia is a painful response to a non-noxious stimulus.

Multiple nociceptive receptors are found in these peripheral nerve endings and they can act singly or in collaboration to mediate a particular painful sensation (figure 1). In general, these receptors are non-selective cation channels that are activated by physico-chemical changes and not by electrical alterations of the cell membrane. Once activated, they open to allow sodium and calcium ions to flow into the nerve terminal, producing an inward current that depolarises the membrane. The receptors of the transient receptor potential (TRP) family, which includes the capsaicin receptor (responding to chilli pepper) (TRPV1), are one example that have been studied in detail. The TRPV1 receptor was the first to be cloned and led to the subsequent identification of others within this receptor family. They have a common structure possessing six transmembrane domains and function as ion channels on specific stimulation. As summarised in table 1, the expression of these receptors is not restricted to neural tissue and TRPV1 is found in other tissues such as neutrophils and mast cells. However, their high level of expression in nerves and the experimental behavioural evidence from mice with deletions of specific receptors strongly support their different roles in nociception (reviewed in Levine and Alessandri-Haber, 2007).

Other receptors are the sensory neuron-specific acid gated ion channel ASIC (acid sensing ionic channel) (Waldmann et al, 1997) and the ATP-activated ion channel P2X. They are found on sensory neurons and contribute to nociception when cells are damaged to release intracellular ATP (Cook and McCleskey, 1997).

Neurokinins are neurologically active peptides known to facilitate mechanisms of inflammation and pain. Substance P was the first peptide to be shown to be specific for small sensory afferents and belongs to a family of small neuropeptides that include neurokinin A. Approximately half of C fibres and 20% of A δ fibres are estimated to contain substance P. It acts through the NK (natural killer) family of receptors that are most abundant on dorsal horn neurons. Experiments showed that, when activated, these receptors facilitate hyperalgesia.

Figure 1 Nociceptors found on sensory nerve endings that mediate painful stimuli. Different nociceptors respond to distinct stimuli to trigger receptor activation and transmission to the afferent neuron. The transient receptor potential (TRP) family includes multiple members that are activated by physical or chemical stimuli to produce an afferent signal. The sodium channel Nav1.8/1.9 is located at the nerve endings and modulates the threshold of activation of the nerve.

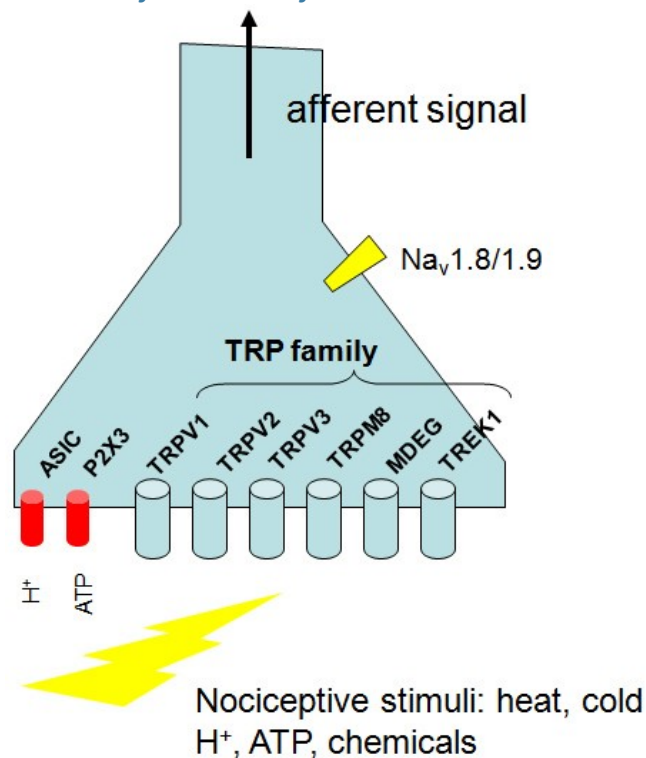


Table 1 The TRP family of nociceptors

Name	Agonists	Expression
TRPV1	Vanilloid compounds (capsaicin) Camphor, NO Moderate heat (>43°C)* Low pH (<5.9)	DRG Mast cells, keratinocytes Bladder epithelium, brain
TRPV2	High temperature (52°C)	DRG, Aδ fibres
TRPV3	Warm temperature (>34°) Repetitive heat stimulation Thyme, cloves	DRG, brain, skin (mice), spinal cord
TRPV4	Hypotonicity Heat >27°C Low pH Endocannabinoids	Cochlear cells DRG Cutaneous Aδ and C fibres
TRPA1	Cold (8–26°C) Menthol, eucalyptol	DRG
TRPM8	Mustard oil, garlic Ginger	Inner ear, DRG

**Prostaglandins increase the sensitivity of this receptor by lowering the activation temperature to ~37°C. DRG, dorsal root ganglion; NO, nitric oxide; TRP, transient receptor potential.*

2.2 Peripheral neurons

Action potentials are generated at the peripheral endings of nociceptive nerve fibres embedded in the tissues in response to the appropriate nociceptive stimulus to be transmitted centrally. The locations of these nerve endings include superficial structures such as the skin, cornea, and mucosa as well as internal structures such as the joint, muscle, and pericardium. Some tissues that do not have pain innervation are cartilage and bony matrix (as opposed to the periosteum).

Anatomically, there are two broad groups of sensory fibres: myelinated A fibres and unmyelinated C fibres. Most small diameter cutaneous sensory fibres (type Aδ or C) are nociceptive, with the majority of type C fibres being polymodal (responding to several forms of noxious stimuli such as heat, cold, mechanical pressure, and chemicals). Type Aδ fibres, being myelinated, are more rapid (conduction velocity of 2–30 m/s). In contrast, type C fibres are of small diameter (0.2–1.5 μm), unmyelinated, and therefore transmit their information slowly (≤2 m/s). Due to their faster conduction and less diffuse receptive fields, Aδ fibres are responsible for conduction of sharp pain, while type C fibres respond to multiple nociceptive signals and are responsible for the sensation of ‘burning’ or ‘aching’ pain.

2.3 Spinal cord

Peripheral sensory neurons transmit their signals along nerve fibres to nerve terminals in the dorsal horn of the spinal cord. The cell bodies of these peripheral neurons are located in the dorsal ganglia and trigeminal

ganglion (for the face). In the spinal cord, afferent nerve terminals transmit their signals to ascending neurons that project to the brain, either in a monosynaptic connection or through a network of interneurons. Interneurons can have excitatory as well as inhibitory properties (figure 2). Interneuronal networks transmit nociceptive information and also modulate that information and pass it on to other spinal cord neurons, including flexor motor neurons and nociceptive projection neurons—for example, certain patterns of stimulation can lead to enhanced reflex actions and to sensitisation of projection neurons and increased nociceptive transmission. Other inputs result in the inhibition of projection neurons. The balance of these excitatory and inhibitory processes is the basis of whether information is presented to the brain as nociceptive or not and will partially determine how it is perceived (formerly gate control) (Melzack and Wall, 1965).

2.4 Spinal cord transmission

Glutamic acid is an amino acid and the most abundant excitatory neurotransmitter in the nervous system. Glutamate is released from the spinal cord during peripheral nociceptive stimulation of small afferent neurons, and it acts on specific receptors on spinal neurons. These receptors include the α -amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) receptors. The AMPA receptor is an ion channel and is found in high concentrations in the dorsal horn and is probably the main mechanism of synaptic transmission in the dorsal column.

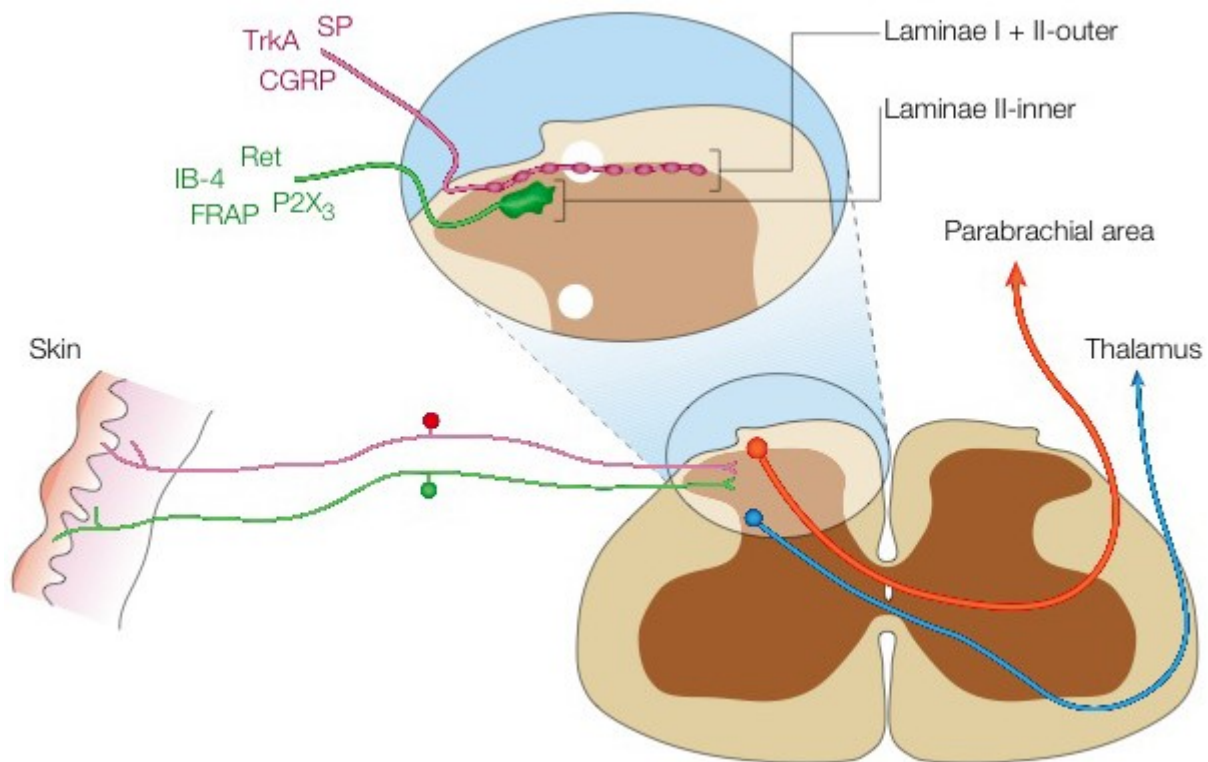
2.5 Projection neurons

Nociceptive projection neurons transmit information to a number of regions of the brainstem and diencephalon (Willis and Westlund, 1997). Some of these projections are discussed in more detail.

2.5.1 Spinothalamic tract

Based initially on clinical studies of spinal cord damaged patients and subsequently confirmed in experimental studies in animals, the spinothalamic tract conveys the sensations of pain, cold, warmth, and touch. Animal studies showed that most of the spinothalamic neurons project to the contralateral thalamus, but a small fraction projects ipsilaterally. The cells of origin are concentrated in laminae I and V of the spinal cord dorsal horn, their axons crossing the midline in the ventral grey commissure and then ascending in the ventral and in the ventrolateral quadrant. After passing through the brainstem, the axons terminate in the lateral thalamus (figure 2).

Figure 2 Neuroanatomy of pain projections. CGRP, calcitonin gene-related peptide; SP, substance P. (Reproduced with permission from Hunt and Mantyh, *Nat Rev Neurosci* 2001;2:83–91.)



2.5.2 Spinomesencephalic tract

The spinomesencephalic tract includes several projection systems that terminate in different areas in the midbrain. The cells of origin of the spinomesencephalic tract are distributed in the spinal cord in a manner similar to that of the cells of origin of the spinothalamic tract, derived largely from neurons in the dorsal horn, and terminate in the parabrachial and periaqueductal grey matter. This tract has also been termed the spinoparabrachial tract. Neurons in these areas in turn project into forebrain regions such as the hypothalamus and amygdala. These areas are capable of modulating the affective dimensions of pain and controlling autonomic activity (Hunt and Mantyh, 2001).

2.5.3 Thalamus

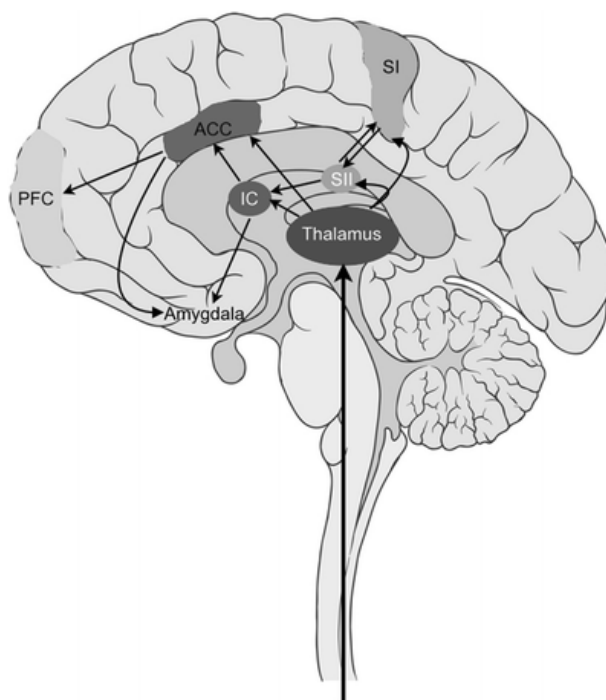
Axons from the spinothalamic tract synapse at 3 different regions within the thalamus: posterior thalamic nuclei, intralaminar and ventral posterior lateral thalamus (VPL) (Millian, 1999). The posterior nuclei and VPL share somatotopic connections with the primary somatosensory cortex, thereby suggesting that it's associated with the localisation of pain stimulus. Neurons from the intralaminar nuclei synapse in various areas of the limbic system. This suggests that these connections are predominantly concerned with the affective-

motivational component of pain. The spinothalamic tract projects to the brain stem reticular formation and then to the thalamus. These connections extend to the cortex from the thalamus.

2.5.4 Cerebral cortex

Recent evidence from mainly functional brain imaging studies supports the view that various cortical and subcortical structures including medial prefrontal cortex, anterior cingulate cortex (ACC) and insular cortex participate in pain perception. These areas are collectively termed 'pain matrix'. Animal studies have shown responses to nociceptive stimuli in cortical neurons, and imaging studies have demonstrated pain-associated responses in a number of cortical areas. Indeed, functional imaging of the brain using positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and electrophysiological (EEG and magnetoencephalography) techniques have provided novel insights of brain activation in a number of painful states (eg, arthritis, neuropathic pain, fibromyalgia) (Tracey, 2008). A meta-analysis from human studies showed that the S1 and S2 cortical regions, insular, ACC, the prefrontal cortex, and the thalamus were activated during pain (Apkarian et al, 2005). Other regions, such as the basal ganglia, cerebellum, amygdala, hippocampus, and areas within the parietal and temporal cortices, can also be activated, depending upon the particular set of circumstances for that individual. The contextual associations of these areas are described below.

Figure 3 (Jones 2012) shows connections between areas collectively known as the human pain matrix. IC = insular cortex, SI SII = primary & secondary somatosensory cortex, ACC = anterior cingulate cortex, PFC = prefrontal cortex.



As simplified in figure 3, the somatosensory cortex is associated with the lateral component of the pain matrix. This pathway is concerned with the sensory- discriminative component of pain. This includes the quality (burning, stinging, stabbing etc.), intensity and location of the pain. These are facilitated by connections between the lateral thalamus, posterior insular cortex and somatosensory cortices (SI and SII) (Kulkarni et al. 2002). The medial pathway is concerned with the affective-motivational processing of pain. This includes the computing of the emotional and unpleasantness experience attached to pain. These processes are facilitated by neurons between the medial thalamus, ACC and insular cortex. This pathway also mediates the response aspects of pain such as prediction, learning, attention, avoidance and anticipation of pain. These are a result of connections that exist between the medial thalamus, prefrontal motor cortex and brain stem structures such as the periaqueductal grey area.

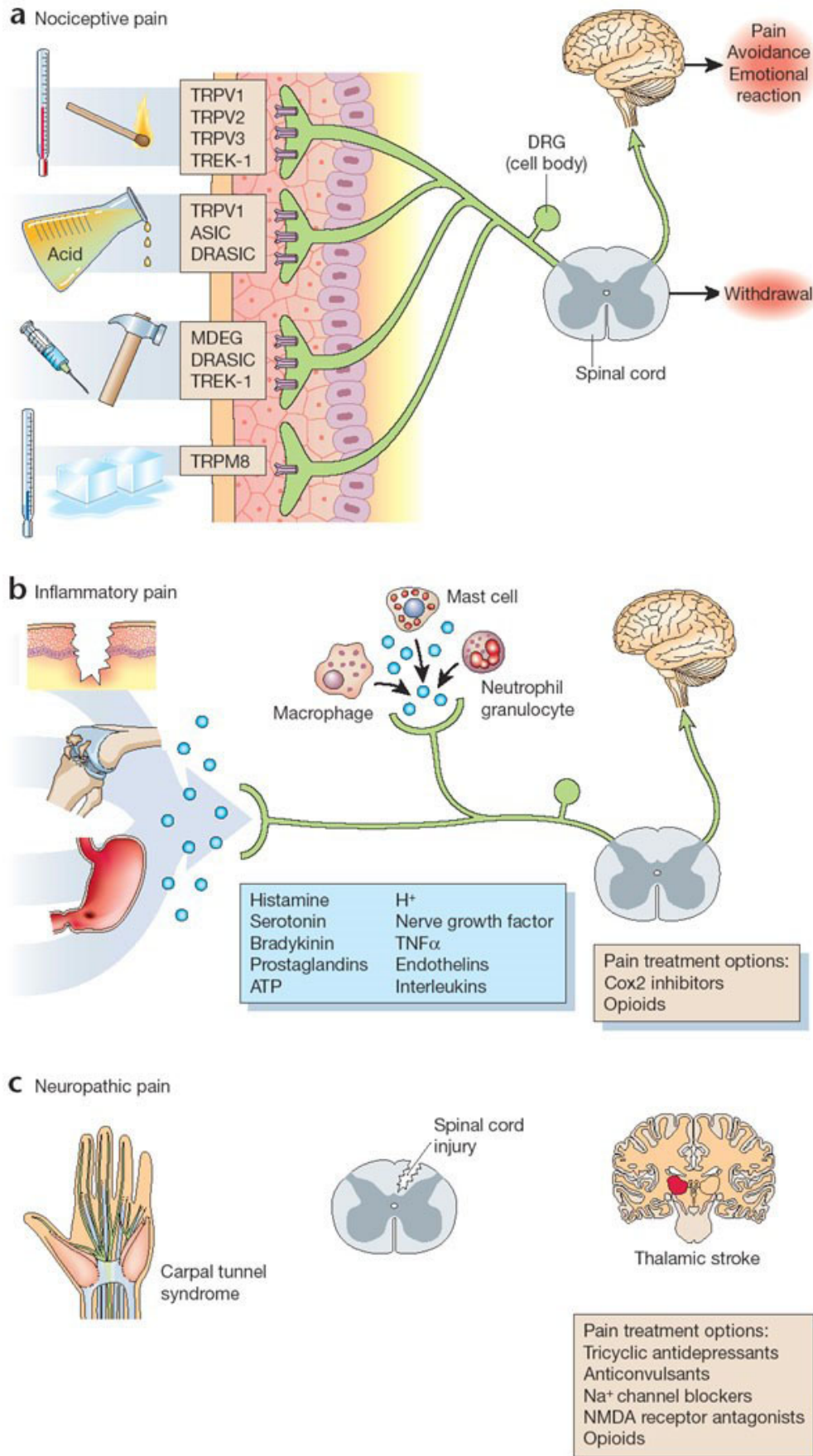
2.5.5 Limbic structures

Pain is often accompanied by motivational-affective and autonomic responses, such as an increase in the heart rate and blood pressure, endocrine changes, increased attention, arousal, anxiety, and emotional distress (suffering). The neural pathways that mediate these changes consist mainly of projections from the intralaminar nuclei, from the thalamus, and the reticular formation to the limbic system (hypothalamus, amygdala, and anterior thalamic nuclei).

3 Neurobiology of pain

Much of our current understanding of pain has developed from the studies of Melzack and Wall, who laid the groundwork for an integrative approach to the neurobiology of nociception. We distinguish two distinct aetiological causes of painful sensations—nociceptive (tissue damage-related) which may or may not have an inflammatory component and neuropathic (nerve damage related) (figure 4)—that can be characterised by their clinical manifestations as well as their underlying neurobiological processes. Some authors have suggested a third category—functional pain that describes a painful sensation in the absence of an identifiable nociceptive stimulus (Woolf, 2004*). We also recognise increasingly that pain is not only associated with injury and inflammation, but can be modified by cognitive factors which influence the brain's processing of the sensory information - such as fear of damage, psychological distress (anxiety and depression) and catastrophising (Vogt 2005).

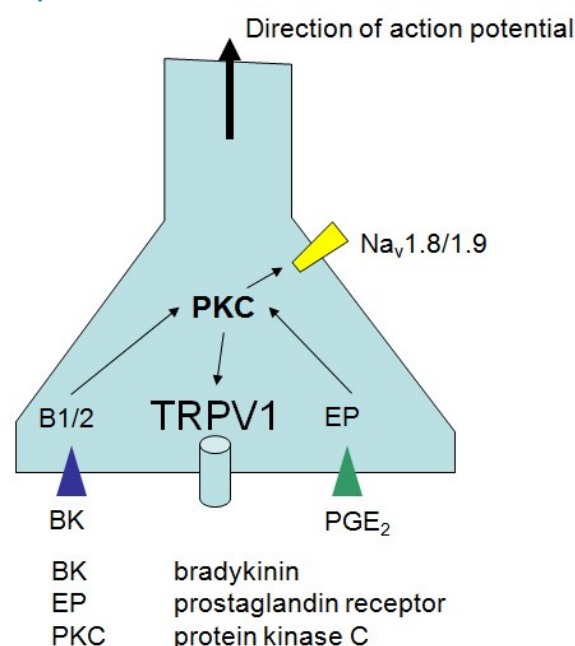
Figure 4 Different modalities of nociception. ATP, adenosine triphosphate; Cox2, cyclo-oxygenase 2; DRG, dorsal root ganglion; NMDA, N-methyl-D-aspartate; TNF α , tumour necrosis factor α . (Reproduced with permission from Scholz and Woolf, *Nat Neurosci* 2002;5:1062–7.)



3.1 Inflammatory pain

Nociceptor function is substantially modified in response to tissue damage, inflammation or injury to the nervous system, by altering the threshold and transmission properties of the sensory neurons. This modulation causes peripheral sensitisation (see below) and explains the clinical phenomenon of hyperalgesia (or hypersensitivity). In molecular terms, inflammatory mediators such as bradykinins and prostaglandins are capable of modifying the sensory neuron's threshold of activation by phosphorylation of ion channels and receptors causing peripheral sensitisation, a state of increased sensitivity to stimuli (figure 5). One of the best studied mechanisms is that of the prostaglandins, with prostaglandin E₂ (PGE₂) and prostaglandin I₂ (PGI₂) being the most relevant to nociception. The synthesis of prostaglandin metabolites from arachidonic acid is mediated by the cyclo-oxygenase enzymes COX-1 and COX-2 that can be upregulated in inflamed tissues. Prostaglandins signal through their specific receptors (the IP and EP1–4) that are present not only on peripheral sensory neurons, but also in the dorsal ganglia (see section on central processing of pain) (Zeilhofer and Brune, 2006*). Signalling leads to activation of intracellular kinases (protein kinase A (PKA) and protein kinase C (PKC) in particular) that phosphorylate ion channels in nerve endings to alter their reactivity. Inflammatory cytokines such as interleukin 1 β (IL-1 β) and tumour necrosis factor α (TNF α) also modulate pain perception and reduce the threshold of painful stimuli (Oprea and Kress, 2000). They are capable of inducing COX-2 expression that in turn leads to increased prostaglandin production, and hence explain some of the analgesic effects of non-steroidal anti-inflammatory drugs (NSAIDs) in conditions such as rheumatoid and osteo-arthritis.

Figure 5 Inflammatory mediators induce peripheral sensitisation. Inflammatory mediators, such as bradykinin and prostaglandin E₂, act through their receptors to modify terminal protein kinase C activity and the conductance of the sodium channel, resulting in lowering of the activation threshold of the TRPV1 receptor. TRP, transient receptor potential.



3.2 Neurogenic inflammation

Neural networks and inflammatory mediators interact bidirectionally and there is accumulating evidence that neurotransmitters can influence the inflammatory and immune response in experimental models. In man, the most clinically striking example is the reduction of synovial inflammation on the affected side of a rheumatoid arthritis patient who has suffered a stroke. Neuropeptides such as substance P and calcitonin gene related peptide (CGRP), released from peripheral nerve endings located in the joint, can have pro-inflammatory effects in arthritis, and their activity is regulated by neuropeptidases that inactivate them (reviewed in Schaible et al, 2005*). Furthermore, there is evidence that vagal nerve stimulation and release of acetylcholine has an anti-inflammatory effect mediated by its binding to specific cholinergic receptors on monocytes and macrophages (Tracey, 2009).

3.3 Neuropathic pain

Peripheral neuropathic pain may be caused by traumatic or compression peripheral nerve injury, peripheral neuropathy in metabolic conditions such as diabetes, nerve damage resulting from viral infections such as herpes zoster and rarely inflammatory conditions such as vasculitis, or lumbar radiculopathy due to a herniated lumbar or cervical disc are some examples of neuropathic pain caused by lesions of the peripheral nerve(s). Central neuropathic pain may occur in association with lesions of the spinal cord or the brain and is more commonly associated with sensory deficit (particularly pin-prick, heat and pinch). This may be caused by any kind of damage anywhere in the central nervous system but is more common with lesions of the pain system (spinothalamic tracts and pain matrix) and is most commonly caused by stroke and MS. Patients can experience either spontaneous pain or have symptoms of hyperalgesia or allodynia (painful sensation provoked by a normally innocuous stimulus such as light touch) within the territory of the neurological deficit. Cerebrovascular disease is increased in patients with inflammatory arthritis and post-stroke shoulder pain is present in approximately 50% of patients who have a stroke within the first six months. In those who receive prompt therapy for impingement (steroid injection) and nocturnal pain (low dose amitriptyline or gabapentin) the prognosis is reasonably good with approximately 70% resolution at six months. It is not clear why certain patients experience neuropathic pain and others not with similar lesions but peripheral and central sensitization is a common feature. Post-stroke shoulder pain is associated with changes in opioid receptor binding within the pain matrix.

4 Drug targets in the spinal and supraspinal neurotransmitter/receptor system

4.1 Opioids

Opioid receptors have a major role in the processing of nociceptive information in the periphery, the spinal, and supraspinal levels. Although opioid receptors were first characterised pharmacologically as mediators of

the analgesic effect of morphine and its derivatives, their presence in the nervous system indicates that they must have endogenous ligands. The first endogenous ligand that could be identified was enkephalin; now ligands for opioid receptors include β -endorphin, dynorphin, and the enkephalins, a family of peptides that are generated following processing of their respective precursors: proopiomelanocortin, prodynorphin, and preproenkephalin. Their binding to different opioid receptors mediates their actions, which are summarised in table 2. The fourth receptor is the so-called nociceptin receptor (also called ORL-1). It binds the endogenous peptide nociceptin and differs from other known receptors in that it is not antagonised by naloxone, a selective receptor antagonist.

Table 2 Classification of opioid receptors

Name	Endogenous agonists	Effects	Exogenous agonists	Antagonist
MOP-R (μ)	β endorphin enkephalins	Analgesia, respiratory depression, constipation, euphoria	Morphine	Naloxone
DOP-R (δ)	Enkephalins		Deltorphin	Naloxone
KOP-R (κ)	Dynorphins	Sedation, dysphoria	Enadoline	Naloxone
Nociceptin receptor (OPL-1)	Nociceptin	Anxiety, depression	Buprenorphine	

Opioid receptors are G-proteins with a typical seven transmembrane domain organisation and an extracellular binding site for its ligands. Receptor occupancy leads to modulation of K^+ and Ca^{2+} channels and a decrease in neuronal excitability. Opioids are generally recognised to inhibit neuronal activity. The location of the receptor in a neuronal circuit determines its effects. If the receptor is located presynaptically, it will inhibit neurotransmitter release. If located on the post-synaptic neuron, it will reduce neuronal firing. Furthermore, the nature of the neuron on which the receptor is sited influences the final effect. If the opioid receptor is located on an inhibitory neuron, it may have a paradoxical effect, leading to excitation. This is thought to account for effects such as vomiting and behavioural changes.

The different subclasses of opioid receptors are widely expressed on neuronal as well as non-neural tissues. They account for the analgesic effects of opioids as well as central side effects such as nausea, vomiting, respiratory sedation, and dependence. In addition, expression of opioid receptors in other tissues, such as the oculomotor nucleus and the smooth muscle of the gut, account for the side effects such as pupillary constriction and, for example, constipation encountered with opiate therapy. Recently, PET imaging using specific opioid receptor ligands has depicted the brain regions that are activated in different pain states (Henriksen and Willoch, 2008) providing evidence of release of endogenous opioids during pain and placebo analgesia. Moreover recent studies have identified adaptive increases in opioid receptor binding within the

pain matrix associated with increased resilience to pain (pain threshold and tolerance) in patients with arthritis (Brown et al 2015).

4.2 Catecholamines

Noradrenaline and adrenaline are released in the spinal cord when descending neurons (from the brain stem and diencephalic structures) are stimulated. They act through the classical adrenergic receptors ($\alpha 1$ and $\alpha 2$) located in the dorsal root ganglia and the dorsal horn, and modulate spinal afferent and efferent activity. In experimental systems, intrathecal injections of noradrenaline produced a potent analgesic effect in rats and in primates that is mediated primarily by the $\alpha 2$ receptor.

4.3 γ -Aminobutyric acid/glycine

γ -Aminobutyric acid (GABA) and glycine are the principal inhibitory neurotransmitters in the spinal cord, acting through their respective receptors. Activation of these receptors leads to an increase in chloride conductance and stabilisation of the transmembrane potential leading to reduced neuronal excitability. These inhibitory effects serve to reduce the transmission of nociceptive information in projecting neurons. It is postulated that benzodiazepines that augment the action of GABA reduce nociceptive reflexes in animals. However, there is no clear evidence of benzodiazepines being analgesic in humans.

4.4 Cannabinoids

Cannabinoid receptors (CB1 and CB2) are widely expressed in the brain and spinal cord as well as the peripheral nervous system. Their endogenous ligands are called endocannabinoids, of which anandamide is the prototype. At the physiological level, cannabinoid receptor signalling leads to inhibition of Ca^{2+} channels on both excitatory and inhibitory neurons in the spinal cord and elsewhere, and local delivery of CB agonists (to nociceptive neurons), thus producing an antinociceptive effect. However, a recent systematic review concluded that, based on current randomized control trial evidence, cannabinoids have no role in acute pain management (Stevens and Higgins 2017).

4.5 Cholinergic drugs

Acetylcholine and the cholinergic receptors (muscarinic and nicotinic) have been characterised in the spinal dorsal horn. The effects of cholinergic signalling on nociception are largely mediated by its secondary actions on glutamate, GABA, and noradrenaline receptor systems. They have been reported to have analgesic effects in selected animal models.

5 Pain mechanisms in rheumatic diseases

Rheumatic diseases commonly present with pain as a major symptom, typically involving articular and periarticular structures. In inflammatory arthritides such as rheumatoid arthritis or gout, clinical signs of inflammation are usually obvious and are commonly accompanied by systemic changes in inflammatory parameters. In degenerative arthritides such as osteoarthritis the sources of pain include the periosteum as well as low grade synovitis. The source of pain is more difficult to pinpoint in the spine, where nociceptive, neuropathic and psychological mechanisms are probably all involved in different forms of spinal pain. The situation is even more complicated in chronic pain states where there is evidence that neuroplasticity can play a role in the perpetuation of chronicity.

5.1 Inflammatory pain

A large number of factors released at the site of inflammation elicit pain when injected into peripheral tissues, either by reducing the threshold of nociceptor activation or by increasing the responsiveness of the nociceptor to suprathreshold stimulation. Of particular relevance to rheumatological pain syndromes are the roles of bradykinins, prostanoids, and cytokines, though other pathways such as protease activated receptor-2, histamine, and nitric oxide (NO) are also known to be involved.

5.1.1 Bradykinin

Bradykinin, a 9-amino acid peptide, is released from its precursor protein high molecular weight kininogen by the action of the protease kallikrein that is produced and released at the sites of inflammation or tissue damage. Upon binding to the B2 receptor, bradykinin activates sensory neurons via PKC-dependent pathways to sensitise the TRPV1 ion channel. The activity of bradykinin is terminated upon its degradation by the action of kininases that include angiotensin converting enzyme and aminopeptidase P.

5.1.2 Arachidonic acid derivatives

The generation of prostaglandins, in particular PGE₂, PGI₂ and PGD₂, from arachidonic acid by the action of the cyclo-oxygenases COX-1 and COX-2 plays a key role in inflammatory pain. COX-2 is not constitutively expressed in peripheral tissues (with the exception of the kidney and the brain), but is rapidly induced in cells such as macrophages, monocytes, and synoviocytes when they are exposed to inflammatory stimuli. The prostaglandins that are generated sensitise peripheral neurons to noxious chemical, thermal, and mechanical stimuli (see below, figure 6).

Interestingly, COX-1 and COX-2 are also expressed in the spinal cord and contribute to modulating nociception by the action of prostaglandins on prostanoid receptors that are expressed in DRG neurons. Part of the analgesic effect observed clinically during therapy with NSAIDs is explained by this central inhibition.

5.1.3 Cytokines

Proinflammatory cytokines modulate nociception peripherally by the induction of molecules such as cyclooxygenases (COXs) (see above) and by acting directly on sensory and central neurons. The best studied cytokines are IL-1 β and TNF α , but IL-6 and leukaemia inhibitory factor (LIF) have also been implicated. The administration of small doses of TNF α in the mouse footpad induced hyperalgesia and an effect on neuronal transmission was also demonstrated (Hori et al, 1998; Schafers and Sorkin, 2008). In addition to direct neuronal effects, IL-1 β and TNF α also modulate the secretion of cytokines by glial cells and act as an additional modulator of central pain perception (Hess et al, 2011*). Recent clinical trials are targeting nerve growth factor (NGF) in chronic pain patients. Several humanized anti-NGF monoclonal antibodies have produced significant pain relief in patients with osteoarthritis leading to functional improvements. However, there is no evidence to suggest effectiveness of anti-NGF monoclonal antibodies in neuropathic pain. Studies have also shown significant side effects related to these antibodies such as worsening of peripheral neuropathy and joint destruction in some patients. Due to this, the clinical trials were halted by the Food and Drug Administration (FDA). However, since then the FDA have lifted this hold and clinical trials for these drugs have restarted (Bannwarth and Kostine 2014).

5.2 Complex regional pain syndrome

Also known as algoneurodystrophy, complex regional pain syndrome (CRPS) contains features of both nociceptive and neuropathic pain. Two subtypes are recognised (see chapter on 'Regional pain syndromes'), and in CRPS type II, allodynia, hyperalgesia as well as vasomotor and cutaneous changes are common clinical features. These develop after nerve injury, and may persist for months or even years. It has been suggested that following injury, an aberrant tissue response associated with neuronal changes at the peripheral or dorsal horn level are at the basis of clinical symptoms (Marinus et al, 2011*).

5.3 Chronic pain

Chronic musculoskeletal pain poses a particular challenge in terms of diagnosis and treatment. In some cases, a clearly identifiable pathological cause can be found, but in many cases, the origin is either unclear (as in fibromyalgia) or it is extremely difficult (with the means currently available) to identify the exact structures that provoke nociception (eg, chronic low back pain). As discussed earlier, 'plasticity' or modification of neural pathways, either at the nerve terminal or in neural networks in the spine and the brain, can take place after an initial nociceptive stimulus, resulting in an altered threshold to subsequent stimuli or even give rise to spontaneous pain. Another additional factor is the cognitive/affective component as chronic pain can lead to psychological or affective changes that resemble depression. The question often raised is whether these affective changes precede the painful state, and whether the pain is of psychological origin. Psychological

distress is a risk factor for developing chronic widespread pain and psychological interventions are helpful once it is established (McBeth 2001).

5.4 Fibromyalgia: an example of functional pain

Fibromyalgia or chronic widespread pain is probably one end of a spectrum of somatoform pain disorders which range from chronic regional pain (irritable bowel syndrome, atypical facial pain, headache) to chronic widespread pain. These all tend to be associated with sleep disturbance, multiple symptoms and consulting, psychological distress and endocrine disturbance (endometriosis). It is a good example of functional pain, as opposed to the other aetiological categories detailed above. Recent neurophysiological and functional imaging studies implicate central sensitisation as a possible mechanism for the chronic perception of pain in the absence of obvious pathology. Testing showed a reduced threshold to cold pain in comparison to normal subjects (Desmeules et al, 2003) and enhanced activation of certain cerebral areas in fibromyalgia patients (Gracely et al, 2002), giving rise to the theory that central processing pathways are altered in fibromyalgia. The precise brain mechanisms are still unclear but recent studies have shown that in patients with fibromyalgia there is abnormal processing of pain expectation. This is associated with increased processing of pain expectation within the insula cortex, which is concerned with the emotional processing of pain, that is correlated with the extent of pain and tenderness. There is a corresponding reduction in processing of expectation within the dorsolateral prefrontal cortex that is inversely correlated with abnormal coping such as catastrophising (Brown et al 2013). Interestingly, similar findings were found in patients with chronic arthritis pain suggesting there may be common central mechanisms for more localized and widespread pain. However, the question of the role of depression in this disorder and how it can affect central pain processing is still not entirely resolved. However, when patients are given an eight week course of mindfulness-based cognitive therapy for their pain the unpleasantness of the pain, psychological distress and abnormal expectation-processing are all significantly improved (Brown et al 2003).

5.5 Depression and pain

The prevalence of major depression as a comorbid factor in chronic pain conditions is highly variable, depending on the underlying painful pathology. For example, in a study of chronic low back pain, depression was found in 72% of the subjects in a small study (Gallagher et al, 1995), while in a study on chronic pain, depression was present in 18%, compared to a prevalence of 8% in the general population (Magni et al, 1990). Although there is a certain 'chicken and egg' dilemma in determining if one preceded the other, it is well known that in chronic diseases with pain as a major symptom, depressive symptoms are frequently reported (Kroenke and Price, 1993) and are a risk factor for developing chronic widespread pain (McBeth 2001, MacFarlane 2001). Practically both drug and non-drug therapies for depression are effective for chronic pain and it is difficult to manage pain without active management of the depression.

6 Mechanisms of neuronal modification

6.1 Central mechanisms

6.2.1 Neuroplasticity and pain

The early concepts of the neurobiology of pain concentrated on transmitter/receptor mechanisms and the different neuronal connections that mediate nociception. Recent research has highlighted that these connections are not stable, but depend on dynamic processes that modify the circuits of neural transmission—hence the term plasticity. Many studies have concentrated on the modulation of neurotransmission at the spinal level, but there is also evidence to show that neuroplasticity can occur at a higher level that may explain the interactions between cognition, behaviour, and pain perception, which are frequently observed in clinical practice.

6.1.2 Top-down modulation and alpha waves

One of the commonest frequencies of brain waves is alpha waves (8-12Hz). Early investigations showed that alpha waves are associated with an idle resting state, as alpha increases when an individual closes their eyes and no stimulus is provided. However, more recent theories suggest that alpha waves represent a gating mechanism in the brain, specifically that alpha waves are emitted when the brain inhibits regions that are not relevant to the specific task an individual is currently focused on. This may be a method of streamlining information transfer and increasing efficiency. Further evidence suggests that alpha waves specifically from the frontal regions of the brain (frontal alpha) show an increase in power during top-down modulation of incoming stimuli. Studies have shown increases in frontal alpha after placebo administration which led to reduced nociception in patients. A more recent study by Ecsy et al. also showed that alpha waves can be trained to modulate the perception of pain (Ecsy et al, 2016). In this experiment, participants were given auditory and visual stimuli at 3 different alpha frequencies (8, 10 and 12Hz). These participants, compared to controls, reported a significant reduction in pain ratings which were independent of other factors recorded in the study. Although still in the early stages, this shows that alpha wave entrainment is possible and could be a potential treatment method in the future.

6.2 Peripheral sensitisation

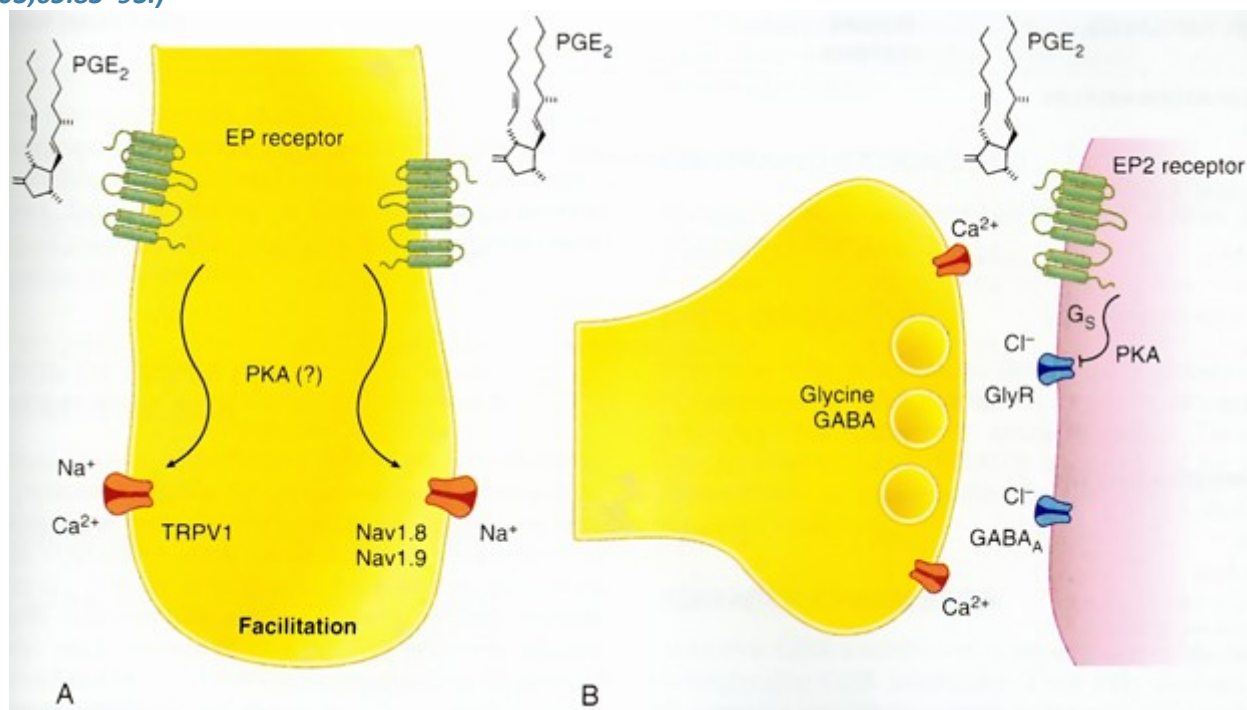
Nociception can be modulated by tissue damage or inflammatory mediators (bradykinin and PGE₂) or chemicals released from damaged cells (ATP, H⁺ ions). These agents sensitise the nociceptor so that the activation threshold is lowered. In the case of PGE₂, binding to its receptor leads to activation of intracellular protein kinases that in turn are able to alter the activity of receptors as well as ion channels. For example, the TRPV1 channel is normally activated at around 42°C, but when phosphorylated, its threshold of activation is reduced to near normal body temperatures. Furthermore, sensitisation is facilitated when ion channels (in

particular sodium channels) that are exclusively expressed on nociceptors are activated by phosphorylation, resulting in an increase firing of the nociceptor, generating more action potentials (figure 5).

6.2.1 Wind up

‘Wind up’ describes the phenomenon whereby the action potential output from the dorsal horn neuron increases progressively on repeated low frequency nociceptive stimulation. Biochemically, repetitive stimulation leads to the co-release of substance P with the transmitter glutamate, resulting in activation of cation channels and a prolonged postsynaptic depolarisation lasting tens of seconds. In humans, an example of this phenomenon is the increase of perceived pain when a subject is stimulated repeatedly with heat stimuli of the same intensity.

Figure 6 Prostaglandin E₂ (PGE₂) facilitates central sensitisation. (A) PGE acting through prostaglandin receptors modifies sodium channels (Nav1.8, 1.9) and nociceptor threshold to facilitate nociceptive signalling. (B) PGE acts on the post-synaptic neuron to increase GABA and glycine induced signalling. GABA, α -aminobutyric acid. PKA, protein kinase A. (Reproduced with permission from Jones et al, Br Med Bull 2003;65:83–93.)



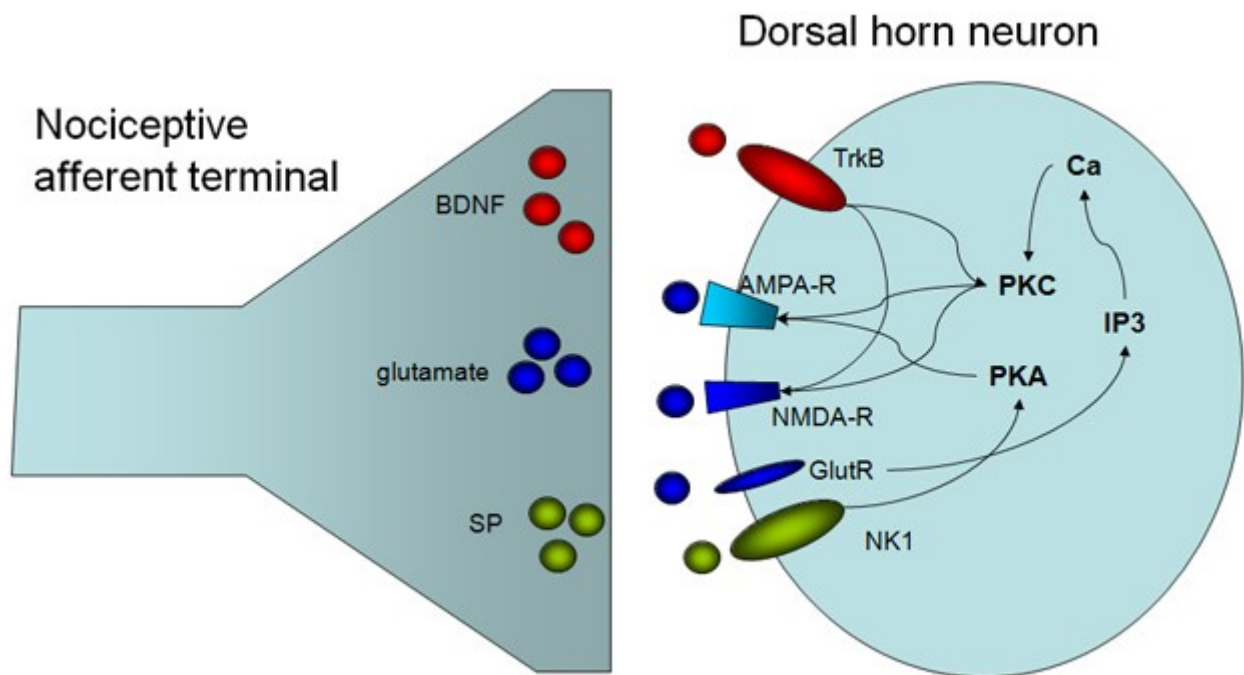
6.2.2 Central sensitisation

Similar to the processes already outlined in peripheral sensitisation, central neurons (located in the dorsal horn of the spinal cord) can be sensitised. The results of central sensitisation are the amplification and facilitation of synaptic transfer of signals to dorsal horn neurons. An example for amplification is the ability of a usually subthreshold stimulus to activate the dorsal horn neuron after the neuron has been conditioned by a brief and intense nociceptive stimulus. Facilitation is the term that describes the increase in synaptic

transmission in response to a stimulus that did not originate from the nociceptor, such as to a low threshold mechanoreceptor. The clinical correlates of sensitisation and facilitation are the phenomena of hyperalgesia and allodynia.

A key receptor that mediates this effect is the glutamate-activated NMDA receptor. During central sensitisation, receptor phosphorylation leads to increased expression of the NMDA receptor on the synaptic membrane and hence its response to glutamate. The resultant increase in receptor responsiveness to glutamate increases cellular excitability. This means that it can be activated by signals that are normally below the threshold of activation (figure 7). Inhibition of the NMDA receptor by the short acting anaesthetic ketamine can block this process and reduce central hypersensitisation.

Figure 7 Molecular mechanisms of central sensitisation at the dorsal horn. Central sensitisation of dorsal horn neurons by action of neurotransmitters like SP and BDNF to alter the phosphorylation of receptors by PKA and PKC. The result is the lowering of the threshold of activation by glutamate release. BDNF, brain derived neurotrophic factor; PKA, protein kinase A; PKC, protein kinase C; SP, substance P.



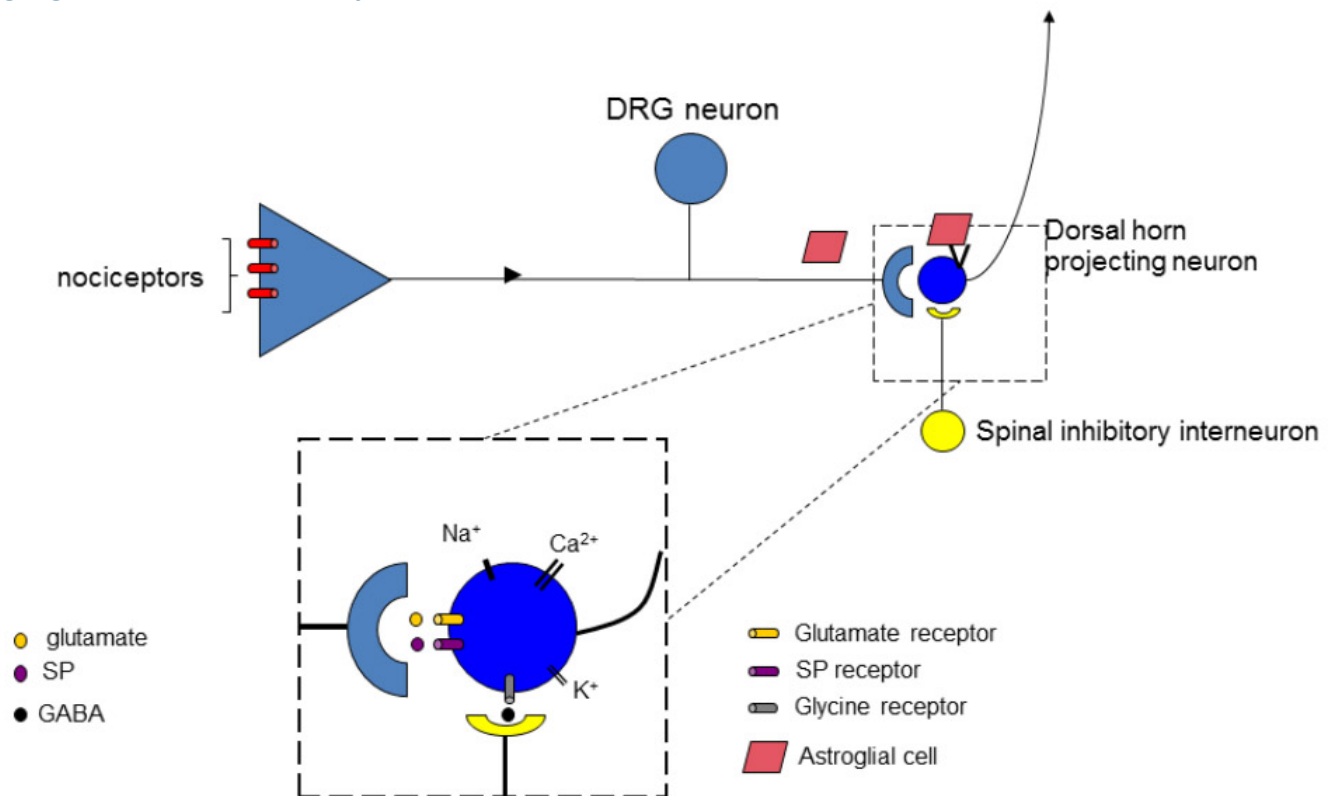
After the early changes in receptor thresholds, subsequent modifications to central neurons occur through transcription of new proteins or increased expression of existing proteins. For example, central neuronal expression of COX-2, induced by $\text{TNF}\alpha$ and $\text{IL-1}\beta$, results in increased PGE2 production locally (figure 6).

6.2.3 Neuronal connections and supporting cells

Other mechanisms that play a part in neuronal plasticity in pain include the loss of neuronal inhibition, the rearrangement of synaptic contacts, and interactions between microglial cells and neurons. During loss of inhibition, inhibitory interneurons in the spine may either become less active or even undergo cell death (figure 8). In animal studies, hyperalgesia from inflammation and neuropathic pain can be improved by GABA

mimetics such as diazepam (Paul 2013). Synaptic rearrangements have been shown to take place following nerve injury. In experimental models, sprouting of new connections from injured A δ fibres have been demonstrated to generate new anatomical projections (Shortland and Woolf, 1993). These phenomena are thought to be influenced by neurotrophic factors such as nerve growth factor (NGF) and glial cell-derived neurotrophic factor (GDNF). Most recently, the interactions between neurons and cells of its supporting matrix, the microglia, have been intensively studied. Instead of a passive supportive role, glial cells are now known to release cytokines including IL-1 β , transforming growth factor β (TGF β), IL-6, and IL-10 in response to inflammatory signals. Indeed pain responses can be substantially reduced in most animal models by interfering with this inflammatory process (Chang 2016).

Figure 8 Dorsal horn neuronal network. Interactions between afferent neurons, dorsal horn cells and inhibitory neurons modulate dorsal horn transmission to the central nervous system. DRG, dorsal root ganglion; GABA, α -aminobutyric acid; SP, substance P.



7 Evaluation of pain

7.1 Pain assessment

As pain is first and foremost a subjective sensation, its assessment relies on the patient's experience. Pain evaluation is a common ingredient in the disease assessment tools used in rheumatology (for example, subscales in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) for osteoarthritis, the Disease Activity Score (DAS) for rheumatoid arthritis, and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score for ankylosing spondylitis). Most of these scores measure pain in a graduated manner,

using a device such as a 10 cm Visual Analogue Scale (VAS), the Numerical Rating Scale (NRS) or the Verbal Rating Scale (VRS), and integrate the results with other measures of disease activity to provide an overall score. However, this type of assessment is based on the assumption that pain is a uni-dimensional experience. That is clearly an oversimplification towards the patient's own perspective. A more comprehensive pain assessment scale that evaluates a number of dimensions of pain qualitatively has been developed by Melzack and is widely used in clinical studies. The McGill Pain Questionnaire (MPQ) was developed to assess the affective and sensory experiences of the patient and has been validated in different languages as well (Melzack and Katz, 2006). This instrument has further given rise to an abbreviated version, the Short Form McGill Pain Questionnaire, that has good correlation with the MPQ itself (Dudgeon et al, 1993). However, mostly such detailed pain assessments as the short McGill have been used for research purposes depending on the resources available. The most important aspect of the clinical assessment is listening to the patient and providing time for them to tell their story. Most patients with chronic pain will have a history of psychological distress and often childhood or adolescent abuse. Trust and calm listening are required for the patient to feel listened to. This in itself may be the first time this has occurred and may have a therapeutic effect. The second aim is to establish the spatial and temporal characteristics of the pain or pains. Many patients will have more than one types of pain. Then try to establish the main driver of the chronic pain. In other words is it mainly nociceptive, neuropathic or psychologically maintained. The latter is mainly a matter of clinical judgement and needs to be confirmed by a thorough clinical examination. Neuropathic pain is relatively easy to identify as it will be accompanied by pain in the distribution of neurological deficit and is often associated with allodynia. The only other situation where allodynia may occur is the whole body allodynia (to light pressure and sometimes touch and brush) associated with fibromyalgia. Often regional pains are not associated with any obvious pathology. If there is no other evidence of arthritis these may develop over time into more widespread pains. However, at the time of consultation they may be difficult to characterize other than with a label of chronic regional pain. In these patients it is important to assess psychological co-morbidities and refer for cognitive therapy if appropriate. Antidepressants are not appropriate for mild to moderate depression as a first line to therapy. The presence of obvious tissue damage-such as arthritis is usually clinically evident in the small to medium sized joints and x-rays are rarely helpful (particularly in osteoarthritis) if there is no evidence of arthritis clinically. Widespread pain either with or without widespread tenderness can be provisionally diagnosed as fibromyalgia. However, it is worth excluding thyroid, calcium and inflammatory muscle disorders (thyroid function, calcium, alkaline phosphatase and creatine phosphokinase). Vitamin D is always worth checking as patients with fibromyalgia are frequently vitamin D deficient although the pain rarely resolves with Vitamin D therapy.

By the end of the clinical assessment it should be possible to make a clinical assessment of the most likely drivers of the chronic pain. This is a helpful construct for the patient but should be reassessed if the symptoms change.

Explanation of the patient's symptoms is probably the most important part of the consultation. Any associated pathologies should be explained in simple and jargon-free terms. In the absence of any physical cause of chronic pain the author finds it useful to explain chronic regional and widespread pain in the following way; 'Pain is sometimes associated with physical damage such as arthritis but more frequently is not associated with physical damage. In chronic widespread pain the brain is under a lot of stress and this is associated with the brain always expecting bad things to happen including pain. This is associated with the widespread pain. Although there is no magic therapeutic wand to get rid of the pain, these fine tuning problems can be helped by talking therapies. Sweaty exercise is also helpful as this activates the natural opiate system in the brain. So these two types of therapy allow you to take more control over how you feel including your pain.'

7.2 Evaluation of the biosocial complexity

Chronic pain engenders affective and psychosocial consequences that may play a role in the pain experience of the patient. Symptoms of depression are commonly reported in patients with chronic pain even though the patient does not have an overt psychiatric disorder—for example, there is a strong correlation between pain intensity and symptoms of anxiety and depression in patients with rheumatoid arthritis (Dickens et al, 2002). Although most chronic pain patients are not clinically depressed, assessments of biopsychosocial factors are appropriate in a clinical comprehensive assessment and may also have a role in management. Many studies of chronic pain conditions (such as low back pain and cervical pain) have shown that a multidimensional assessment and management approach provides better results than a uni-dimensional approach. However, there is not one single instrument that has been found to be applicable to the different chronic pain conditions. In low back pain, Waddell and colleagues have developed an assessment of non-organic factors based on a limited number of clinical signs (Waddell and Burton, 2005), but this is not validated in other conditions of musculoskeletal pain. Many different assessment instruments have been developed and validated, some of them being disease specific and others generic. Examples of the latter include the general health status instrument SF-36 that has been applied in many different clinical conditions (Ware et al, 1980). Another instrument, the Intermed evaluation scale, has proven clinical utility as an assessment tool in chronic rheumatological conditions and may be helpful in selecting patients for more specific treatments (Stiefel et al, 1999; Koch et al, 2001).

Sleep disturbances are often present in chronic pain patients, a typical example being fibromyalgia. The mechanisms are poorly understood, but chronic fatigue due to sleep disturbance probably plays a primary role. Interestingly, patients with chronic low back pain also report significant levels of sleep disturbance (Kelly et al, 2011). It has been suggested that sleep disturbance should be assessed as a distinct item in clinical trials in fibromyalgia.

8 Non-pharmacological Management of Pain

8.1 Neurobiological effects of exercise

Non-pharmacological treatment approaches have shown to decrease pain and improve function by significantly. Exercise treatment regimes are often recommended when managing pain related symptoms and these can vary depending on the pathology and the location of pain. Exercise treatment regimes are often recommended as part of a rehabilitation programme tailored to individual patients and have shown up to a 30% reduction in pain and up to a 20% improvement in function (Turk D et al, 2011). Further studies have revealed neurobiological relationships between exercise and pain. As discussed earlier, chronic pain can be as a result of increased inflammatory cytokines. Inflammatory markers such as TNF- α and IL-6 are also increased acutely after exercise (Cooper et al, 2016). This increase in cytokines from exercise is thought to trigger a robust anti-inflammatory cascade which ultimately results in an increase of anti-inflammatory markers. Overall, long term regular exercise leads to an increase in anti-inflammatory cytokines and a decrease in pro-inflammatory markers. Furthermore, exercise has shown to increase endogenous opioids in brainstem regions important to pain processing. This suggests that exercise may reverse neuropathic pain by upregulating endogenous opioids. Although there is variability of analgesic effects in non-healthy individuals, exercise is still viewed as beneficial in reducing pain in disease and should be considered as one of the first treatment options as it is a relatively safe approach.

8.2 Psychological therapies

Psychological approaches to the management of pain are generally split into two categories: theoretically-based approaches and specific techniques (Turk D et al, 2011). The commonest theoretical approaches include operant conditioning, mindfulness-based therapy and cognitive-behavioural therapy. These types of approaches focus on patient coping, adaptation, self-management and reduction of disability associated with symptoms. This is achieved by cognitive therapy, relaxation and hypnosis to enable patients to take control of their symptoms and develop an active and resourceful attitude towards their pain. By replacing feelings of hopelessness with control, patients can avoid catastrophizing and feeling demoralised towards their pain. Meta-analyses and systematic reviews show that psychological therapies result in modest benefits in improvement of pain and physical and emotional functioning. However, the most amount of benefit is seen when they are included as part of a rehabilitation programme. Rehabilitation programmes do not follow a specific format, but use an integrated approach led by a multidisciplinary team. Components of a rehabilitation programme include physical rehabilitation, exercise therapy, behavioural treatment, cognitive restructuring via education, vocational rehabilitation and pharmacological approaches. One of the main advantages of non-pharmacological approaches is its relative safety when compared to pharmacological treatments. This is due to the side effects of analgesic drugs. It is important to note that multiple meta-

analyses report that rehabilitation programmes result in reduced healthcare use and a significant reduction in pain by as much as 37% in one analysis (Hoffman et al, 2007). The current evidence suggests that rehabilitation programmes may be as effective as traditional pharmacological therapies and therefore patients with resistant symptoms should be considered for such options.

9 Pharmacology of analgesics

9.1 NSAIDs and COX-2 inhibitors

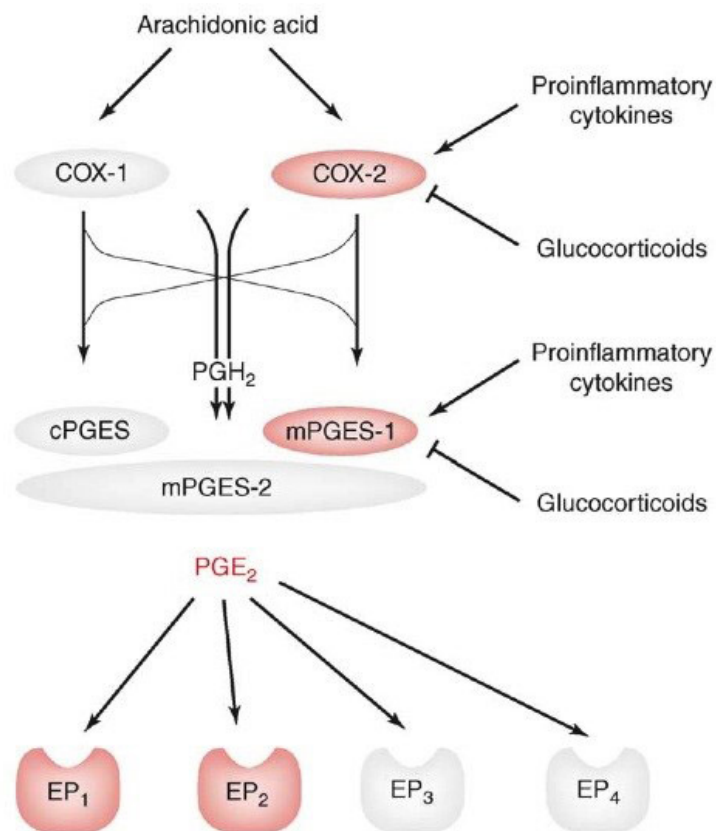
NSAIDs are the most commonly used agents in the treatment of pain. Their many facets of action are still under investigation decades after the initial discovery by Vane of the ability of aspirin-like drugs to inhibit prostaglandin synthesis (Vane, 1971). This discovery opened the door to the pharmacological study of antipyretic analgesics and the subsequent discovery of the two isoforms of cyclo-oxygenase, COX-1 and COX-2, providing a rational understanding of the pharmacological action of NSAIDs (table 3). As already detailed above, prostaglandins, in particular PGE₂, enhance nociception by acting on peripheral nerve terminals as well as acting centrally. COX inhibitors are used routinely in clinical practice for their antipyretic as well as analgesic effects. Both enzymes (COX-1 and COX-2) metabolise arachidonic acid to the two prostaglandin precursors PGG₂ and PGH₂. Through the action of PGE₂ synthases—enzymes that are bound to microsomal membranes and are closely coupled to the COX enzymes—the precursors are converted to PGE₂ (figure 9).

Table 3 Pharmacological properties of common non-steroidal anti-inflammatory drugs

Class	Name	T _{1/2}	pKa	Protein binding (%)	Maximum daily dose in adults
Low potency/fast elimination	Aspirin	20 min	3.5	>80	6 g
	Salicylic acid	2.5–7 h	2.9	>90	6 g
	Ibuprofen	2–4 h	4.4	99	3.2 g
	Mefenamic acid	1–2 h	4.2	>90	1.25 g
High potency/fast elimination	Ketoprofen	0.5–2 h	4.2	99	300 mg
	Diclofenac	1–2 h	4	99	200 mg
	Indomethacin	2.6–11.2 h*	4.5	99	200 mg
Intermediate potency/intermediate elimination	Diflunisal	8–12 h	3.8	98	1 g
	Naproxen	13–15 h	4.1	99	2 g
High potency/slow elimination	Meloxicam	18–36 h	4.9	>99	15 mg
	Piroxicam	14–160 h	5.1	>99	40 mg

*Presence of enterohepatic circulation.

Figure 9 Prostaglandin (PG) synthesis from arachidonic acid. Summary of the role of cyclo-oxygenases in PGE₂ production and the differential expression of COX-2 during inflammation. COX, cyclo-oxygenase. (Reproduced with permission from Zeilhofer and Brune, Trends Pharmacol Sci 2006;27:467–74*.)



The understanding of the physiopathological actions of prostaglandins and their inhibitors in nociception has been facilitated by knock-out of the different COXs and the receptors (reviewed in Brune and Zeilhofer, 2006; Zeilhofer and Brune, 2006*). COX-1 knockout mice did not show a nociceptive phenotype whereas COX-2 deficient mice showed impaired nociceptive reflexes. Mice deficient in the prostaglandin receptors EP₁, EP₂, EP₃, and EP₄ showed reduced nociception in a number of experimental settings. EP₂ deficient mice also showed no hyperalgesia after intrathecal injection of PGE₂, suggesting that this receptor has a central role as well.

9.2 COX-2 inhibitors

Aspirin (acetylsalicylic acid) is the prototypic COX inhibitor and serves as a useful paradigm for our understanding of the mechanisms of action of this class of drug, though it only has a minor place in the treatment of pain in clinical settings. Its molecular mechanism of action is the irreversible inactivation of the COX enzyme's active site by acetylation. However, aspirin has a higher affinity for COX-1 than COX-2. Moreover, as de novo synthesis of COX-1 does not occur in platelets, the prominent antiplatelet effects and gastrointestinal (GI) toxicity in comparison with other non-steroidal agents is explained. The differences in tissue distribution of the two forms of COXs as well as their different transcriptional regulation supported the notion that, in inflammatory states, COX-2 mediated production of PGE₂ accounts for the known clinical effect

on nociception as well as cellular effects on, for example osteoclasts, T lymphocytes as well as dendritic cells that can play a part in the inflammatory site (Anderson et al, 1996). The first generation of NSAIDs inhibited to a varying extent both COX-2 and COX-1, and were termed non-selective COX inhibitors.

Based on the roles of COX-2 in inflammation, pharmacological inhibitors that are selective for COX-2 inhibitors (COXIBs) are expected to show a somewhat better therapeutic profile. However, one must not forget that COX-2 is also produced constitutively in the kidney, brain, and blood vessel wall. Mice that are deficient in COX-2 demonstrated renal impairment and developed atherosclerosis. Development of selective COX-2 inhibitors as therapeutic agents was greeted with initial enthusiasm, based on the proposition that these drugs should be devoid of relevant GI toxicity, but show efficacy in different painful conditions. Clinical studies confirmed there was a lower incidence of GI side effects with these drugs; however, the incidence of cardiovascular side effects (stroke, myocardial infarction, thrombosis) was significantly increased in some studies where the control group received the conventional non-selective NSAID naproxen. This difference is not seen in comparison with diclofenac or ibuprofen. Different mechanisms have been proposed to account for these observations: the inhibition of prostacyclin production by COXIBs, hypertension, fluid retention, and effects on endothelial function. As a consequence, several drugs were withdrawn and the development of others suspended. As of the time of writing, only celecoxib and etoricoxib are still marketed.

Indeed, the cardiovascular side effects observed in the COXIB clinical studies have raised the question of whether conventional NSAIDs can also pose a cardiovascular risk. Several long term studies investigating the cardiovascular risk of selective and non-selective COX inhibitors demonstrated that all compounds, even acetaminophen, were associated with an increased risk of cardiac infarction and other cardiovascular damage.

The cardiovascular side effects are probably linked to the inhibition of endothelial production of prostacyclin (Grosser et al, 2006*). Naproxen appears to differ from all other selective and non-selective COX inhibitors as this compound is not associated with an increased incidence of myocardial infarction (at high doses) in a meta-analysis of published randomised trials (Kearney et al, 2006*). Pharmacologically, naproxen can significantly inhibit COX-1 activity in platelets in the short term, down to levels observed on treatment with low dose aspirin, and interfere with platelet aggregation (Capone et al, 2007). However, naproxen is not devoid of upper GI tract toxicity (Rahme and Nedjar, 2007) and it has also been reported to cause significant lower GI toxicity, even when given together with a proton pump inhibitor (Goldstein et al, 2005). These findings have clinical and therapeutic implications, as recent guidelines by the European Medicines Agency (EMA) have stated that traditional non-selective NSAIDs are contraindicated in patients who have had two or more GI bleeds, and should be used with caution in patients with known cardiovascular risks. As already indicated previously, COXIBs are contraindicated in patients with known cardiovascular risks, though they may be used in patients who have GI bleeding risk. The unresolved question is how to treat a patient who presents both cardiovascular and GI bleeding risks. Expert opinion suggests that it may be better in this situation to prescribe a combination

of a traditional non-selective NSAID, a proton pump inhibitor, and low dose aspirin. This option, however, is questionable as a recent large population study indicates that this combination may blunt the cardioprotective effect of aspirin (Charlot et al, 2011).

The side effect profile of NSAIDs is also similar, the most important being GI, renal, cardiovascular, and central nervous system side effects. Table 4 provides a summary of the side effects that are encountered with NSAID therapy and the putative mechanisms. COXIBs were not detailed specifically, but they share some of the properties detailed (eg, effects on renal function). COXIBs may be safer in terms of bleeding risk in the setting of concomitant anticoagulation and may have a safety advantage in patients who have known aspirin-induced asthma. As the selectivity of inhibition of COX-1/COX-2 varies between agents, some of these drugs may also have an antiplatelet effect, though nowhere near that obtained with aspirin. It is notable that most NSAIDs are acidic molecules with similar degrees of plasma protein binding. Compounds do, however, differ in two properties—potency and pharmacokinetics—that can alter their effectiveness in a given patient or clinical situation.

9.3 Paracetamol

Paracetamol (acetaminophen) is an aniline derivative and is a non-acidic antipyretic analgesic. It is a weak inhibitor of COX-2 in vivo and ex vivo, which explains its (weak) antipyretic effect (Graham and Scott, 2005; Hinz et al, 2008). As an analgesic, it is less potent than NSAIDs and has to be given at relatively large doses with relative safety. Its main toxicity is on the liver. Liver toxicity is due to its benzoquinone metabolite, mediated by the hepatic enzyme CYP450, which can bind covalently to DNA and structural proteins in hepatocytes to produce necrosis. It has recently become obvious that paracetamol not only shares all side effects of NSAIDs, but in addition induces liver damage at therapeutic doses (Brune et al, 2009; Brune and Hinz, 2011). Recent metaanalysis of trials in chronic pain has cast some doubt about the long-term efficacy of paracetamol (Roberts et al, 2015) when compared to placebo treatment. This raises issues about its place in chronic pain management. One of the problems is that patients with arthritic pain may have a combination of acute recurrent pain and chronic unremitting pain. It is not always clear from drug trials which pains are being targeted. Paracetamol or combinations with low dose opiates such as codeine have been a traditional first line of treatment where patients can make their own choices of when they take them. There is currently no obvious alternative oral therapy for this first step in self-managed analgesia. We probably need to understand more about patient's needs and motivations at this initial level of analgesia, but one possibility is exploring the possibility of prescribing placebo by mutual consent, as we know that placebo has potent and long-term benefits with relatively few side-effects (Colloca and Benedetti, 2005)

Table 4 Side effects of NSAIDs and COXIBs

Organ system	Proposed mechanism	Comments
Gastrointestinal <ul style="list-style-type: none"> • Gastric irritation • Upper GI bleeding • Lower GI bleeding 	Inhibition of gastroprotective effects of COX-1 activity in the upper GI tract Local effect of slow release drugs and enterohepatic circulation influences injury to the small intestine	Coexisting factors influence the risk of GI bleeding during NSAID therapy. Some of these factors are (1) previous bleeding, (2) age, (3) glucocorticoid therapy (Langman <i>et al</i> , 1994) and use of SSRIs Lower GI ulceration and bleeding are often silent but incidence may be greater than reported (Allison <i>et al</i> , 1992)
Renal <ul style="list-style-type: none"> • Oedema • Hypertension • Renal failure 	Renal vasoconstriction in subjects with pre-existing renal disease	The risk of acute renal failure is particularly high in the first 30 days following initiation of therapy (Schneider <i>et al</i> , 2006)
CNS <ul style="list-style-type: none"> • Depression • Cognitive dysfunction • Aseptic meningitis 		Cognitive dysfunction is frequently reported, but aseptic meningitis is a rare complication
Cardiovascular <ul style="list-style-type: none"> • Myocardial infarction • Heart failure 	COX inhibition can interfere with platelet function as well as endothelial vasodilator mechanisms (prostacyclin, NO production). In addition, renal effects of COX inhibition can lead to hypertension, a risk factor for atherosclerosis	There is considerable controversy about the risk of conventional NSAIDs. Certain COX-2 inhibitors, such as rofecoxib and valdecoxib, have been withdrawn from sale (McGettigan and Henry, 2006)
Haematological <ul style="list-style-type: none"> • Haemolytic anaemias • Bleeding 	Inhibition of COX-1 in platelets leads to reduced production of thromboxane A ₂ and platelet aggregation	NSAIDs can interact with anticoagulant therapy to exacerbate bleeding Neutropenia is infrequent but an association with NSAID therapy has been demonstrated (Strom <i>et al</i> , 1993)
Dermatological		Toxic epidermal necrolysis (Stevens-Johnson's syndrome) is rare. Risk appears greater with the oxicam class of NSAIDs (Mockenhaupt <i>et al</i> , 2003)
Hepatic <ul style="list-style-type: none"> • Liver enzyme alterations • Hepatitis • Liver failure 		Liver enzyme elevations are commonly encountered with NSAID therapy. Individual drugs and the clinical context may play a role (Furst and Anderson, 1993). Liver failure is infrequent (3.7/100,000 users) (Garcia Rodriguez <i>et al</i> , 1994), but high with paracetamol
Others <ul style="list-style-type: none"> • Foetal effects 		COX inhibition in pregnancy may result in the premature closure of the ductus arteriosus and bleeds

CNS, central nervous system; COX, cyclo-oxygenase; COXIBs, COX-2 inhibitors; GI, gastrointestinal; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Some superficial rheumatological conditions are amenable to local treatments applied to the joint and to periarticular tissues. The use of topical formulations of NSAIDs has grown over the last two decades, as topical formulations (in the doses used) do not have the toxicity profile of systemic administration. A small amount of drug enters the plasma after topical application, but the concentrations found in the subcutaneous tissues and joint fluid are within the therapeutic windows of the drugs studied. However, the joint fluid concentration after topical application remains significantly lower than that found after oral administration (Erdogan et al, 2006; Rainsford et al, 2008).

Currently, topical therapy can be applied directly to the skin, whereby the drug diffuses continuously through the skin to the symptomatic area. Randomised controlled trials in patients with different forms of osteoarthritis and soft tissue rheumatic disorders have shown that there is a small analgesic effect with these preparations, but the effect is only significant during the first 2 weeks. The side effect profile is similar to that found in placebo treated subjects, but shows more skin irritation. Ketoprofen preparations are associated with increased phototoxicity. In one meta-analysis, the number needed to treat to obtain a positive effect was calculated to be 4.6 (Lin et al, 2004*; Mason et al, 2004). Topical treatment has been recommended as a therapeutic option in the management of knee osteoarthritis (Jordan et al, 2003), but convincing data are from smaller joints—for example, in patients with osteoarthritis of the finger.

9.4 Opioids

The pain relieving effects of opium, derived from the poppy *Papaver somniferum*, were recognised by ancient healers. Our current therapeutic opioids are all derivatives of morphine. Derivates of opium are called opiates, and synthetic analogues are called opioids. Opioid drugs act through the opioid receptors whose physiological actions have already been described. The first opioid receptor to be cloned was the mouse δ receptor (DOP-R) in 1992 and this led to the identification of the μ (MOP-R) and κ (KOP-R) receptors. Cloning of the opioid receptors has allowed detailed studies of the different ligands (endogenous and exogenous) with the different receptors and their effects in vivo.

The analgesic and adverse effects of opioids are mainly mediated by their binding to the MOP-R, though there are some data to suggest that agonists for DOP-R also exert an analgesic effect. Experiments with knockout mice showed that MOR mediates all morphine's activities (including its side effects), whereas the KOR knockout mice had little effect on nociception, but showed stress-induced behavioural changes.

In clinical use, opioids are the most powerful analgesics available and their use is of immense therapeutic value. However, they are also associated with known pharmacological side effects. In rheumatoid arthritis, osteoarthritis and common rheumatological conditions, strong opiates are not a first-line choice. Combination effect opiates such as tramadol (combined opioid and 5HT effects) and tapentadol (combined opioid and noradrenergic effects) probably occupy an intermediate place although tapentadol is conventionally regarded

as a strong opioid. Physicians prescribing opioids should be aware of the common side effects that include dizziness which may lead to falls and fractures. Dose-dependent side effects include respiratory depression, euphoria, feeding, reduced GI transit, effects on anxiety, and endocrine and immune effects.

Prolonged use can, however, produce ‘tolerance’, a physiological phenomenon resulting in a diminished analgesic effect or ‘dependence’—the necessity for continued drug intake in order to prevent the symptoms of opioid withdrawal.

The main opioids in routine clinical use are summarised in table 5; their ‘analgesic equivalence’ is presented in table 6. Many opioids have multiple forms of administration, ranging from oral to topical, and detailed knowledge of the features of each route of administration, as well as the drug’s suitability, is required for optimising treatment. The main pharmacological aspects of some of these drugs are detailed in the section below.

Table 5 Functional classification of opioids

Full agonists	Morphine Fentanyl Hydromorphone Codeine (via its metabolite morphine) Methadone Tramadol Pethidine
Partial agonists	Buprenorphine Pentazocine Butorphanol
Agonists–antagonists	Nalbuphine Nalorphine
Full antagonists	Naloxone Naltrexone

Morphine, hydromorphone and codeine are opiates. The others are opioids. For explanation, see text.

Table 6 Equianalgesic doses of opioids

	Dose with analgesic activity equivalent to 10 mg morphine
Pethidine	100
Codeine	90
Dihydrocodeine	60
Tramadol	50
Oxycodone	7.5
Hydromorphone	2
Methadone	1
Buprenorphine	0.3

9.5 Strong opioids

Morphine remains the standard to which all other opioids are compared in terms of clinical efficacy and tolerance. It is most often prescribed orally or by subcutaneous injection, but can also be injected directly into sites such as the epidural space and the spine. Following absorption, morphine is metabolised to its glucuronide derivatives.

Morphine-6-glucuronide has an analgesic effect, whereas morphine-3-glucuronide accounts for the adverse effects. The balance between these two major metabolites can be altered by conditions such as renal failure. Hence morphine should be used with care in that situation.

Other strong opioids include oxycodone, hydromorphone, and buprenorphine. Oxycodone is a semi-synthetic derivative that has become the most widely prescribed opioid worldwide, marketed as a single substance or in combination with paracetamol. It has a higher bioavailability after absorption and is metabolised by liver cytochrome P450 to oxymorphone (Kalso, 2005). Buprenorphine is another semi-synthetic derivative that has partial agonist activity for the MOR and antagonist activity for the KOR.

Currently, the drug is given by sublingual or transdermal administration to overcome high first-pass metabolism and has a half-life of around 37 h. As it is mainly eliminated by hepatic metabolism, there is less risk of toxicity when it is used in patients with renal impairment. Because of its partial agonist activity it is much less likely to cause respiratory depression and can also be started at low doses as a patch.

It must be emphasised that all strong opioids possess similar pharmacologic side effects to those of morphine (nausea, vomiting, respiratory depression, etc), so the same caution applies whenever they are prescribed, though there may be slight differences in effects such as itching (less with oxycodone) and respiratory depression.

9.6 Weak opioids

Codeine is an alkaloid of opium that is metabolised in the liver to glucuronide derivatives of morphine, and to morphine itself (2–10% of the codeine dose), which accounts for its analgesic effects. This latter step is mediated by CYP2D6, an enzyme that is lacking in 9% of the Caucasian population, which accounts for the lack of analgesic effect in some patients. When given with other medications that inhibit CYP2D6 (such as citalopram and fluoxetine), the effectiveness of codeine may be impaired.

Tramadol is not an opioid in the classical sense, as it acts on the MOR as well as on serotonergic and noradrenergic neurotransmission. It is used widely as a mild analgesic and has the advantage that, at equianalgesic doses, it results in less constipation than morphine and causes less dependence and respiratory

depression. However, nausea and vomiting are common side effects and tramadol may cause postural hypotension due to its 5HT effects. The new drug tapentadol is very similar in its pharmacological profile.

9.7 Neuropathic pain and mode of action of anticonvulsant analgesics

Damage to peripheral nerves frequently results in spontaneous pain and/or enhanced nociception and is a frequent problem confronting physicians. Examples are persistent nerve root pain after herpes zoster neuropathy, lumbar disc surgery, phantom limb pain, and painful peripheral neuropathies in the context of systemic diseases. In these examples, there is no evidence of an ongoing nociceptive stimulus, and the persistence of pain could be explained by prior nerve damage leading to long term remodelling of nociceptive transmitters and neuronal circuits (see section 6.1 on plasticity). Clinical management of these conditions is often complex, requiring multiple pharmacological interventions and sometimes even invasive procedures, such as spinal cord or brain stimulation.

No single pharmacological class has been found to be universally effective, but among the pharmacologic agents, anticonvulsant drugs, tricyclic antidepressants and opiates have a place. Indeed, since the discovery of phenytoin, physicians have treated pain syndromes empirically with available anticonvulsants. Examples include carbamazepine and more recently gabapentin and pregabalin. Randomised controlled trials, however, are still scarce and inconclusive.

9.8 Mode of action of anticonvulsant analgesics

Phenytoin acts by blocking voltage-gated sodium channels, inhibiting the repetitive firing of injured nerves and suppressing spontaneous discharges, while carbamazepine acts on voltage-gated sodium channels in a voltage- and frequency-dependent manner. Gabapentin is a structural analogue of GABA and binds to the $\alpha 2\delta$ subunit of the voltage dependent Ca^{2+} channel. It inhibits high-threshold calcium currents in cultured neurons and inhibits the release of excitatory amino acids, such as glutamate, through its actions on the calcium channel (Fink et al, 2000). Finally, gabapentin also interacts with the NMDA receptor. The pharmacological properties of the commonly used agents are summarised in table 7. In clinical use, both phenytoin and carbamazepine have narrow therapeutic windows, and side effects such as somnolence and dizziness are common. Gabapentin has similar side effects, but in clinical practice does not seem to be as disabling as the other agents. Pregabalin is an analogue of gabapentin and its pharmacological actions are similar.

Table 7 Properties of commonly used anticonvulsants in neuropathic pain

	t_{1/2} (h)	Therapeutic dose (in neuropathic pain), mg/day	Clinical evidence for efficacy in randomised controlled trials
Phenytoin	6–24	<300	Diabetic neuropathy Mixed neuropathy Fabry's disease
Carbamazepine	25–65	100–1200	Diabetic neuropathy Trigeminal neuralgia Post-herpetic neuralgia
Gabapentin	5–7	900–2400	Phantom limb pain Mixed neuropathy Diabetic neuropathy Spinal cord injury pain Guillain-Barré syndrome
Pregabalin	6	100–300	Diabetic neuropathy Post-herpetic neuralgia

9.9 Role of antidepressants in pain management

Because chronic pain patients often manifest depressive symptoms, empirical therapy with antidepressants was introduced. Their initial positive effects led to further randomised clinical trials that confirmed an analgesic effect. The principal question in the use of antidepressants for treatment of pain is whether the analgesic effect is linked to the antidepressive action of these drugs. Because the analgesic effects come on prior to changes in mood they have been traditionally considered to have analgesic effects in their own right.

As the pharmacological spectrum of antidepressive drugs increases, so does our understanding of their mechanisms of action in pain. Not all antidepressants show the same efficacy in pain management, and from meta-analyses of published data it is now recognised that mixed inhibitors of serotonergic and noradrenergic transmission are more effective than agents that work on single pathways.

The proposed mechanisms of action of antidepressants include the activation of serotonergic and adrenergic pain inhibitory circuits that descend from the midbrain and brainstem to the dorsal horn, but other pharmacological actions (on acetylcholinergic transmission, on the NMDA receptor as well as on ion channels) have also been described (reviewed in Watson *et al*, 2006).

Currently, three main classes of antidepressants are in use: the tricyclic antidepressants (TCAs), the selective serotonin-reuptake inhibitors (SSRIs), and the combined serotonin-noradrenaline reuptake inhibitors (SNRIs). A review of the use of these agents in a randomised controlled trial setting in different pain states showed that the most effective class for pain are the TCAs in a wide variety of settings (neuropathic pain, arthritis pain,

headaches). This class of drugs include amitriptyline, nortriptyline, trimipramine, and ritanserin. Side effects common to this class include anticholinergic effects, sedation, and orthostatic hypotension, though some agents (such as amitriptyline and trimipramine) are more sedative than others (Watson *et al*, 2006; Wise *et al*, 2007*). In general, SNRIs have a better side effect profile, but their effects on pain may not be as potent as TCAs. SSRIs appear to be the least effective in pain indications, but would treat depression as a co-existing pathology.

10 Conclusion

The priority when assessing patients with chronic pain is to define and assess any underlying disease process. However, assessment of the likely drivers of the chronic pain can go in parallel to this process. With the awareness that in most cases there will not be a clear relationship between any defined disease process and the patients pain symptoms. The choice of analgesics and non-drug therapies for chronic pain is therefore not based less on the disease process, but more on the presumed physiological drivers of pain in an individual patient (i.e. is it mainly nociceptive, neuropathic or psychologically maintained). This is mostly based on clinical assessment and judgement rather on objective tests and where there is uncertainty, it is fine to share this with the patients. It is also vital that the underlying disease causing pain is assessed and treated in the most effective way possible, and in the case of rheumatic diseases, treatment targeting the inflammatory and immune processes can alleviate pain significantly. However, in clinical day-to-day settings, it is important that patients made aware of both the physical and psychological components that may affect their pain and their response to this. In practice, most patients will start with simple and safer analgesics with or without some advice about exercise. There is relatively little evidence-based guidance as to what types of therapies should be embarked on in which order. This will in many cases be determined by what resources the clinician has access to. However, much will be determined by the patient's biases about therapy. Greater engagement is likely if the patient and clinician are enthusiastic about the type of treatment offered. In practice there is no evidence for one particular type of therapy (drug, exercise/physiotherapy or cognitive therapy) being uniquely effective in any type of chronic pain. In back pain there is evidence for a stepped approach being effective. In authors experience it is generally better to offer a choice of all of these types of therapy and to allow the patients choice to influence combinations of therapy that they engage with. Although resources are an issue in some health communities, especially access to CBT, a great problem is the patients continued engagement with effective therapies over time, which relies on a good therapeutic relationship between the health care professional and the patient. This requires deliberate allocation of adequate time in whatever clinical setting the patient is being advised in.

In acute painful states, a step-up approach with a combination of analgesic agents is often applied. Initial therapy is usually with an NSAID. Many guidelines suggest paracetamol alone or in combination with an NSAID or opioid. Recent evidence, however, suggests that these combinations may have disadvantages as there is not

only no gain in effectiveness, but even an increase of unwanted drug effects (Doherty *et al*, 2011*). A combination with a weak opioid may be tried. There is no evidence that combining two different NSAIDs augments the effect and indeed it may increase the incidence of adverse effects. If pain relief is insufficient with weak or intermediate opioids such as codeine or tramadol, consideration should be given to the use of strong opioids such as morphine and its derivatives, though the evidence base for their efficacy is mainly based on short term studies. In the past 10 years, morphine-like drugs have been more widely used and this has raised questions about the risk of tolerance, addiction, and withdrawal symptoms, particularly in chronic therapy (Ballantyne and Mao, 2003). The additional use of antidepressants and anticonvulsant classes of drugs needs careful clinical assessment and the patient may benefit from a multidisciplinary team assessment. The weight gain and other side-effects associated with these should be discussed with the patient.

The optimum long term management of chronic pain should aim to rely as much as possible on self-management. The role of the health care professional is to facilitate this process and to empower the patient along this path in a non-judgemental way. This may comprise regular exercise, using the principles learned from CBT and other adjunctive activities such as meditation, hypnosis, yoga and tai-chi. Any activities which facilitate reduced social isolation such as art-therapy and group recreation are likely to be helpful. Likewise the use of therapies where the evidence for being better than placebo is questionable (e.g. acupuncture, TENS) should be discussed, based on the patient's needs, costs and potential to do harm. As placebo represents the brain taking control of symptom expression which should be encouraged if it is neither costly or harmful.

The optimal drug therapies are with relatively safe analgesics that the patient can make their own decisions about on a daily basis. Drug holidays are likely to be useful in avoiding long-term side-effects such as dependence. The patient should be as well educated about both their condition and the effects of different therapies as possible to the point where they confident in making decisions about their own pain management.

One frequently posed question of who should provide this service for patients with musculoskeletal and neuropathic pain ? There is no definitive answer to this question, but in the authors view this should be a collective health-care community activity which, however, does require some leadership either in primary or secondary care. Where there is not diagnostic uncertainty then all the appropriate management can be provided in primary care with opportunities for review in secondary care where necessary. Where there is diagnostic uncertainty it may be appropriate that this should be provided in secondary care. In practice a partnership between primary and secondary care is often effective as patients with chronic pain represent a significant demand in primary care which is sometimes difficult to meet. The essential issue is that whichever health care professional takes on this primary responsibility, that sufficient mutual trust and confidence is established to facilitate optimal long-term management aimed at eventual self-management. The principles of chronic pain management are sufficiently simple that all health care professionals can engage with this central

aspect of medical care in a co-ordinated way. Delegation to any particular branch of the health-care system is likely to result in that branch being overwhelmed.

Technical advances using smart self-monitoring, more effective and safer analgesics and smart neurotherapeutics such as neuro-feedback are likely to make this task much easier in the future.

SUMMARY POINTS

- **Nociception is the fundamental biological process underlying pain perception and involves activation of neural pathways that ascend from the periphery to the brain.**
- **The information processed within pathways transmitting nociceptive information is not fixed and can be modified at each level of processing.**
- **The perception of pain is a balance of nociceptive inputs from the body and what the brain is expecting. As such cognitive and affective influences have a major influence on how pain is perceived.**
- **There are powerful control mechanisms from higher brain areas such as the prefrontal cortex that occur naturally.**
- **Neuroplasticity of pain transmission is an important mechanism in chronic pain.**
- **Inflammatory mediators, like prostaglandins and cytokines, modify nociception at the level of the nerve and the brain.**
- **Ion channels on neurons play an important role in nociception and are modified by many different classes of analgesics.**
- **The analgesic effect of non-steroidal anti-inflammatory drugs is through inhibition of PGE2 synthesis.**
- **Opioids relieve pain by binding to opioid receptors that alter ion channels and neuronal excitability.**
- **Tricyclic antidepressant drugs have a superior analgesic effect to serotonin-reuptake inhibitors.**
- **Integrated management using drug and non-drug therapies should be aimed at the eventual goal of self-management.**
- **The more empathic you are with your patients the more likely you are to enhance these powerful mechanisms.**
- **There are powerful control mechanisms from higher brain areas such as the prefrontal cortex that can influence the perception of pain that occur naturally that can be enhanced by drug and non-drug therapies.**

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module

EULAR on-line course on Rheumatic Diseases

Pain: mechanisms and management

Alexander So, Anthony Jones, Nadeem Jamal

A previous version was co-authored by Alexander So, Jiten Patel, Sylvie Revaz, Jean Dudler, Kay Brune, Haiko Sprott, Christian Roux, Silvano Adami, Emmanuel Biver



IN-DEPTH DISCUSSION I

Analgesia and pregnancy

There is currently a wealth of literature on the use of anti-rheumatic drugs and DMARDs during pregnancy. Despite this, there is little information on the treatment of pain during the same period, other than the very specific period of labour.

However, virtually every woman will have some degree of musculoskeletal discomfort during pregnancy; and it is estimated that as many 25% of them will have at least temporarily disabling symptoms of some type. Low back pain is one of the most common complaints of pregnancy. It will affect 50% of all pregnant women, being more common in patients with previous back pain. There are numerous other musculoskeletal conditions that may warrant the prescription of some analgesia, excluding patients suffering from inflammatory diseases. It is important to note that any pharmacotherapy may prove problematic during pregnancy, as we remain concerned about any potential risks for the unborn child. Most of the published data are in the form of case reports and small retrospective studies. Nevertheless, sufficient evidence has been accumulated to be able to recommend a safe drug treatment option in most clinical situations. It is important to have some common knowledge to help our patient to make an informed decision.

Paracetamol

Paracetamol is safe throughout the pregnancy and lactation period. Although it does cross the placental barrier, no teratogenic effects have ever been attributed to paracetamol in therapeutic doses. Paracetamol remains the analgesic of choice throughout all stages of pregnancy. Some studies have suggested pharmacokinetic changes during pregnancy. However, this does not appear to be clinically relevant as paracetamol can be used at the usual dosage in this setting. Similarly, excretion in milk is minimal (<2% of the ingested dose) and represents less than 5% of the infant therapeutic dose. Breastfeeding does not represent any contraindication to its use.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The story is not as straight forward with the NSAIDs as for paracetamol. For a thorough review the reader could refer to a recent article by Ostensen et al (2006). Nevertheless, NSAIDs can be used during most of the pregnancy with relative security and are considered Category B medications by the FDA. Broadly, NSAIDs are contraindicated during the third trimester of pregnancy but considered as acceptable before this time point. In addition, aspirin and naproxen may increase the risk of bleeding during early pregnancy.

NSAIDs are contraindicated from gestational week 32 onwards, and one should be cautious about their use between gestational week 20 and 32 as they can promote premature closure of the ductus arteriosus and subsequent foetal pulmonary hypertension, or induce renal insufficiency and oligohydramnios. They also potentially increase the risk of foetal haemorrhage and postpartum bleeding by inhibiting platelet aggregation. Despite the fact that these adverse effects appear rapidly reversible within 48 hours, it is best to avoid them during this period.

Before week 20, NSAIDs can be prescribed without too many concerns. There is currently no evidence of teratogenicity and several population-based cohort and case-control studies have failed to demonstrate any increased risk of congenital malformations with the use of NSAIDs during the first trimester. However, one should warn the patient of a possible slight increased risk of miscarriage due to the effect of prostaglandin inhibition on implantation and placental circulation, an effect related to some cases of transient infertility related to the use of NSAIDs.

Finally, most NSAIDs are excreted in very small quantities in breast milk. Though they have the potential to displace bilirubin and therefore increase the risk of jaundice and kernicterus, breastfeeding is generally regarded as an acceptable risk in patients on NSAID therapy. Nevertheless, one should choose agents with a good safety profile: such as ibuprofen, mefenamic acid and naproxen. Feeding immediately before a dose may also help to minimize the infant exposure to the drug.

COX-2 inhibitors (coxibs)

Though most animal data showed that COX-1 and COX-2 inhibitors have the same effects during pregnancy, there is presently insufficient data to recommend the use of any coxibs during pregnancy or breastfeeding. Mouse knock-outs for the two different isoforms demonstrated dramatically different effects on bone consolidation, a fact to bear in mind before assuming that prescribing a COX-2 specific inhibitor will be absolutely similar to prescribing a non-specific NSAID for the foetus.

Tramadol

Tramadol is usually regarded as safe during pregnancy in most European countries. However, embryotoxic and foetotoxic effects have been demonstrated in mice, rats and rabbits treated with maternally toxic doses. These effects include decreased foetal weight, skeletal ossification and increased supernumerary ribs and have led certain countries to recommend avoiding this drug during the first trimester. However, no foetal toxicity was observed with doses that were not maternally toxic, and no teratogenic effects were observed at any doses. Similarly, certain countries also advise avoidance of tramadol during the last trimester for fear of potential neonatal respiratory depression. Globally, it appears that tramadol is a generally safe alternative if it is needed during pregnancy. We should probably be more careful during breastfeeding as active metabolites are excreted into human milk in amounts that could expose a nursing infant to potential toxic levels if the mother is on full-dose tramadol. Choosing the lowest effective dose and informing the mother of risk should prove adequate in these situations.

Major opioids

Interestingly, major opioids are probably the analgesic drugs where the most data are available in the context of pregnancy, as methadone has been given since the 1960s in pregnant patients with opiate addiction.

Despite the fact that some neonates may display opiate withdrawal syndromes, outcome measures support the safe use of this type of analgesic medication in pregnancy. Methadone, buprenorphine and slow release morphine have been used with adequate safety information in pregnant opioid-addicted women, and thus appear reasonable alternatives for pregnant women in intractable pain, regardless of substance addiction. It is also important to note that methadone is an efficient medication for pain, including neuropathic pain.

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module

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IN-DEPTH DISCUSSION II

Peripheral pain mechanisms in osteoarthritis

Joint pain due to osteoarthritis (OA) is common and with prevalence reaching up to one third of the adult population. Current pharmacological treatments of OA joint pain are often ineffective and side effects of the commonly prescribed drugs may pose a therapeutic challenge, especially when used in an elderly population with multiple comorbidities. There is therefore a need to advance our understanding of the causes and mechanisms that mediate joint pain in OA. In the normal joint, both joint (except for cartilage) and peri-articular structures include many sensory nerve fibres that are able to detect and transduce mechanical and nociceptive stimuli. In the presence of local inflammation, the activation threshold of these afferents is significantly decreased to allow nociception even with low level stimuli (Sprott H, 2008).

Pain and prediction of structural progression in osteoarthritis

There appears to be no real correlation between pain intensity and structural damage in OA as assessed by standard radiology. Up to 40% of individuals with severe radiographic changes are symptom-free (Davies et al, 1992). In addition, there is an inconsistent relationship between the magnitude of radiographic changes and the severity of joint pain and disability (Creamer et al, 1999). It is well documented that changes in knee pain do not correlate with the loss of cartilage, but do moderately correlate with synovitis (Hill et al, 2007; Felson et al, 2007). Moreover, radiographic OA and pain appear to be independent predictors of cartilage loss, as described by Saunders et al 2011 (Saunders et al, 2011). An index of different demographic variables (age, sex, and BMI) seems to be the best predictor for the development of knee and hip OA (Schett et al, 2009). Other attempts such as the index to ring finger (2D:4D) ratio (a longer ring finger than index finger is a risk factor for knee OA), elevated synovial fluid IL-15 (early knee OA), or elevated VCAM-1 levels (severe OA) also illustrate interesting approaches regarding this specific topic (Ferraro et al, 2010; Schett et al, 2009; Scanzello et al, 2009).

Peripheral nociception in osteoarthritis

Local inflammation of the synovial tissue is a feature of the symptomatic OA joint. Synovial fibroblasts have the ability to secrete an array of cytokines, chemokines and growth factors and therefore have the capacity to induce pain in nerves, modulate inflammation and promote matrix degradation (Table 1) (Ritchin, 2000). The result is local hyperalgesia. For that reason, the synovial fibroblast has recently moved into the focus of peripheral pain research. Initially, mechanical stimuli, e.g. movement, cause pain exacerbation (Rackel et al, 2010). This is followed by the development of peripheral sensitization, previously demonstrated in an animal model (Brenn et al, 2007). Silent nociceptors become accessorially activated and amplify these mechanisms (Schaible and Grubb, 1993). Other nociceptive molecules/receptors, such as protons and/or prostaglandins, will then be activated (Wendler and Baewald, 2004), e.g., the intra-articular Prostaglandin E2 level will increase (Table 1). Inflammation and matrix degradation will be enhanced, as shown by Attur et al (Figure 1).

Experimental targets to treat local pain in OA

Currently, there is little information available about local pain mechanisms in synovial tissue. Different pain receptors, such as opioid receptors and the TRPV1 receptor, well described in the CNS (see module 39) are found on synovial fibroblasts and they may play a significant role in peripheral nociception. The discovery of these new molecules has provided novel potential treatment targets in the painful joint. However, a comprehensive understanding of their contributions to pain generation is still lacking. There is, for example, very little data about therapeutic measures via the opioid system when injecting opioids intra-articularly which results in the clear inhibition of both pain and inflammation [reviewed in Janson and Stein, 2003; Gunji et al, 2000; Walker, 2003]. Innovative new targets are expected through other systems, e.g. the TRPV1 or the P2X4 receptor system (Sprott H, 2008; Krause et al, 1995; Engler et al, 2007; Reisch et al, 2005).

Future treatment strategies in osteoarthritis

Future local therapeutic treatment strategies may be based on these new scientific findings, such as intra-articular opioid application (Likar et al, 1997; Takeba et al, 2001; Kalso et al, 2002; Stein et al, 1999; Zeidan et al, 2008), antibody or anti-cytokine approaches (Lane et al, 2010; Chevalier et al, 2009), specific pain receptors (Piepoli et al, 2009), or even by using products of nature like cherry or pomegranate juice (Conolly et al, 2006; Hadipour-Jahromy and Mozaffari-Kermani, 2010). Due to these findings, it is becoming increasingly clear that OA is not simply a degenerative disease but also possibly a disease with systemic inflammatory components (Aigner, 2007).

For this reason, different experimental therapies have been tried and have provided promising results. Etanercept-treated rats showed significantly less mechanical hyperalgesia than saline-treated rats at the injected knee joint, which can be explained by its direct action on neuronal targets rather than an attenuation of the inflammation (Boettger et al, 2008). Other anti-TNF alpha-directed drugs as well as anti-IL-1 or anti-IL-6 approaches may act similarly (Table 2). Cytokines are able to activate NGF and TRPV1. Clinical studies have proved their efficacy and side-effect profile; in previous phase III clinical studies, anti-NGF was found to be very effective in treating OA related pain, but the severity of OA in these patients was accelerating and therefore these studies were stopped (Schaible, 2010). Applying TRPV1 antagonists enhances analgesic activity but also attenuates antagonist-induced hyperthermia (Honore et al, 2009). Bisphosphonates might be able to reduce joint pain and reduce subchondral bone loss in OA (Buckland-Wright and Messent, 2007). The results of autologous chondrocyte or mesenchymal stem cell transplantation as a potential cure are currently being discussed (Minas et al, 2009).

It is becoming increasingly apparent that pain associated with OA is at least partly mediated by central mechanisms as well as peripheral pathology. Preclinical and clinical evidence from experimental sensory testing and functional imaging studies suggest a significant role for excessive nociceptive ascending

transmission resulting in the development and maintenance of central sensitisation (Lluch Girbes et al, 2013). This process has become a target for new pharmacological and non-pharmacological therapies. Randomised controlled trials involving the centrally acting drug duloxetine (an SNRI), have demonstrated analgesic effects in adults with knee osteoarthritis (Abou-Raya et al, 2012; Chappell et al, 2009). Alongside such pharmacological approaches, Cognitive Behavioural Therapy and Neuroscience Education should be considered (Lluch Girbes et al, 2013). It is currently believed that our understanding of the mechanisms of central sensitisation in OA remain in their infancy. However, with the increasing body of evidence supporting central mechanisms in OA it is likely that new central targets will be revealed.

Figure 1: Type II collagen degradation in OA cartilage is augmented by PGE₂. Human OA cartilage was incubated with or without PGE₂ (10uM), with or without the MMP inhibitor Ilomastat (5 ug/ml) for 72 h in serum-free medium. Degradation products of type II collagen were determined in the supernatant using the C1,2C ELISA kit. IL-1 served as positive control. The data represents mean +/- SD (n = 3) performed with three individual patient cartilage explants cultures

(From Attur M et al (2008) Prostaglandin E₂ exerts catabolic effects in osteoarthritis cartilage: evidence for signalling via the EP₄ receptor. *J Immunol* 181:5082-8, 17. With permission.)

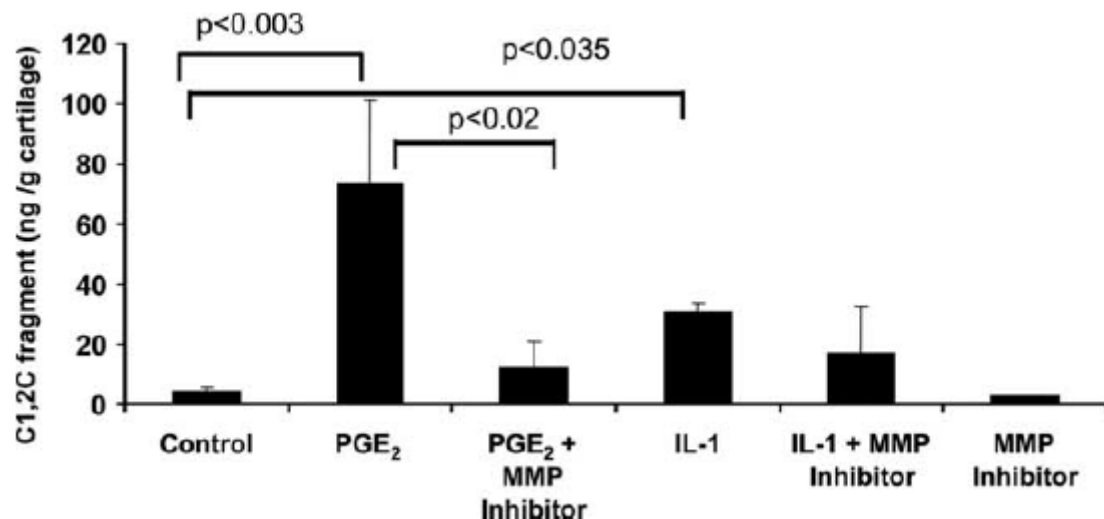


Table 1: Effector molecules released by synovial fibroblasts

Signal function	Effector molecules
Angiogenesis	IL-8, TGF- β , PDGF, GM-CSF, G-CSF, FGF, VEGF, EGF
Chemo-attractant	IL-8, IL-16, MCP-1, MIP-1 α
Pro-Inflammatory	IL-1, IL-6, IL-7, IL-8, IL-11, IL-15, LIF, PDGF, MIF, GM-CSF, TRX
Anti-Inflammatory	p55 TNFR, p75 TNFR, IL-10
Matrix degradation	PGE2, collagenase, stromelysin, 92 kD gelatinase, cathepsins B, L, and K
Inhibit matrix degradation	TIMP, TGF- β IL-11
Osteoclastogenesis	RANKL, VEGF
Bone formation	TGF- β , BMP-2

EGF, epidermal growth factor; FGF, fibroblast growth factor; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; IL, interleukin; LIF, leukaemia inhibitory factor; MIF, macrophage inhibitory factor; PDGF, platelet derived growth factor; RANKL, receptor activity of nuclear factor κ B ligand; TGF, transforming growth factor; TIMP, tissue inhibitors of metalloproteinases; TNFR, tumour necrosis factor receptor; TRX, thioredoxin; VEGF, vascular endothelial growth factor

(From: Ritchlin C (2000) *Fibroblast biology. Arthritis Res* 2:356–60. Published online 2000 June 23. doi: 10.1186/ar112, 11. With permission.)

Table 2: Selected targeted therapies in OA – open studies on clinicaltrials.gov

(Modified after Berenbaum F (2010) *Targeted therapies in osteoarthritis: a systematic review of the trials on www.clinicaltrials.gov. Best Prac Clin Res* 24:107-19, updated October 28, 2011)

Target	Drug	Phase
COX	Valdecoxib/Naproxen	IV
Serotonin/Norepinephrine	Duloxetine	IV
NGF	Tanezumab	III, terminated
FGF	AS902330	I
iNOS	SD-6010	II/III
Cathepsin K	Balicatib	II
Cathepsin S	JNJ 42160443	II
IL-1	Canakinumab	II
TNF α	Adalimumab	III

The targets suggest that episodes of pain are caused by episodes of joint inflammation.

For routine clinical management, the published EULAR management strategies to treat osteoarthritic hip and knee pain, which include pharmacological as well as non-pharmacological measures, should provide a framework for everyday work (see also recommended further reading).

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module

EULAR on-line course on Rheumatic Diseases

Rehabilitation aspects of rheumatic diseases

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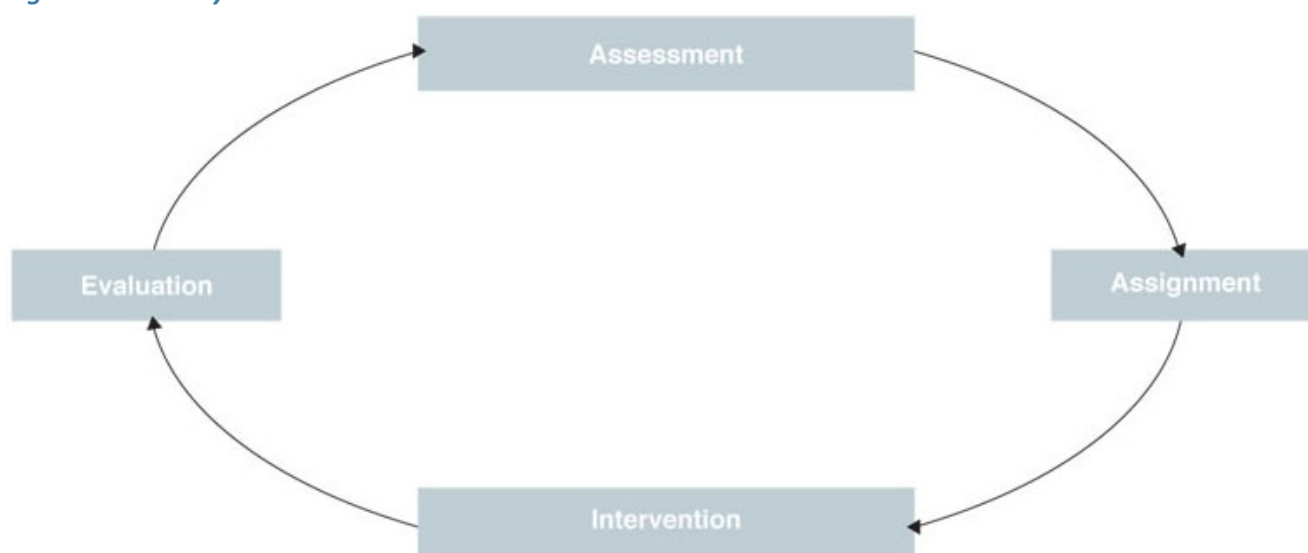
LEARNING OBJECTIVES

- Describe and explain the principles of rehabilitation and use them to devise an individually tailored management plan for patients with rheumatic conditions
- Identify rehabilitation needs and demonstrate appropriate understanding of the possibilities and limitations of rehabilitative treatment modalities for an individual patient
- Properly support patients on self-management skills including lifestyle changes, exercises, the application of activity pacing, and the use of orthoses and adaptive equipment
- Make a substantiated decision on when to refer a patient to a health professional or rehabilitation centre
- Make a valid evaluation of the results of a rehabilitative intervention

This chapter has been developed from the perspective of the rheumatologist and includes issues and tasks he or she needs to know and do with respect to rehabilitation needs of patients with rheumatic conditions.

Rheumatic conditions have a major impact on patients' lives, especially if pharmacological interventions are not available, or effects are small. Symptoms such as pain, stiffness and fatigue may, together with loss of function, causes limitations in daily activities, affect physical activity levels and participation in society. While rheumatologists are focused on controlling the disease process, the derived symptoms and structural damage, they should keep in mind that achieving and maintaining an optimal level of functioning is crucial to the patient's quality of life. This is the aim of the rehabilitation process. This process involves a comprehensive assessment, including collaborative goal setting, the allocation of treatment targets to specific interventions and health professionals, the performance of the interventions and the evaluation of results (the rehab cycle, figure 1) (Stucki and Sangha, 1998). In case of involvement of various health professionals, coordination of rehabilitative care is of the utmost importance.

Figure 1 Rehab-Cycle®.



Rehabilitative interventions include a wide range of modalities, such as physical activity and exercise, self-management support, orthoses, assistive devices, and physical modalities. These interventions can be provided as single treatment modalities, but are often combined in comprehensive rehabilitative management strategies, and are conducted either by the patient themselves, or in collaboration with one or more health professionals. Patient centred care is essential and requires that the patient's preferences, needs and values are considered. Most rehabilitation interventions assume behavioural change, which requires time, knowledge and strategies addressing behaviour change. This can be facilitated by using motivational interviewing, cognitive behavioural therapy (CBT) or theories, for example the Transtheoretical model of behaviour change, Social cognitive theory, Self-determination theory.

Given his or her central role in the management of patients with rheumatic conditions, it is very important that the rheumatologist understands the opportunities and limitations of rehabilitation and rehabilitation treatment modalities. The rheumatologist may advise patients on the optimisation of functioning and to decide when it is time to refer the patient to a health professional, rehabilitation specialist or rehabilitation team.

1 General introduction to rehabilitation

1.1 Definition and goals of rehabilitation

Rehabilitation is by the WHO defined, as a process aimed at enabling people with disabilities to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels. Rehabilitation provides disabled people with the tools to attain independence and self-determination” (World Health Organization, 2002). With respect to rheumatic conditions, this applies to management of the consequences of living with the disease, including pain, fatigue, stiffness, deformity, functional disability and physical inactivity. Rehabilitation usually implies the involvement of professionals other than the rheumatologist alone. The professionals most commonly involved in rheumatology rehabilitation are often referred to as the ‘multidisciplinary team’. The rheumatology multidisciplinary team usually comprises, in addition to the rheumatologist, professionals such as nurse specialists, physical therapists, occupational therapists, social workers, dieticians, podiatrists, psychologists, rehabilitation specialists or orthopaedic surgeons. One of the key elements of rehabilitation is patient participation which implies that the patient should be considered as an important member of the rehabilitation team. In daily practice, rehabilitation can be provided in many different ways, depending on the needs of the patient and the organisation and availability of healthcare professionals in the rheumatologist’s working situation. One mode includes the rheumatologist instituting rehabilitative treatment by himself or herself, with involvement of other health professionals in the hospital or in primary care, according to the patient’s problems (eg, give advice on exercise, write a prescription for a wrist splint, or refer a patient to a social worker). If a clinical nurse specialist is available in a rheumatologist’s practice, he or she could play a role in the coordination of this form of care. Another option is rehabilitative care provided by a multidisciplinary team consisting of professionals who are all working in the same rehabilitation centre or a hospital’s rehabilitation unit, under the medical supervision of a rheumatologist and/or rehabilitation specialist. With this form of multidisciplinary team care either group programmes or individual treatment or combinations of both are delivered. Patients with complex problems, complications and/or comorbidity may especially benefit from a comprehensive approach.

The decision on whether or not to refer a patient to a health professional, a rehabilitation specialist and/or rehabilitation team outside one’s own rheumatology unit depends on the nature and complexity of problems encountered and the local availability of rehabilitative services and/or agreements with rehabilitation

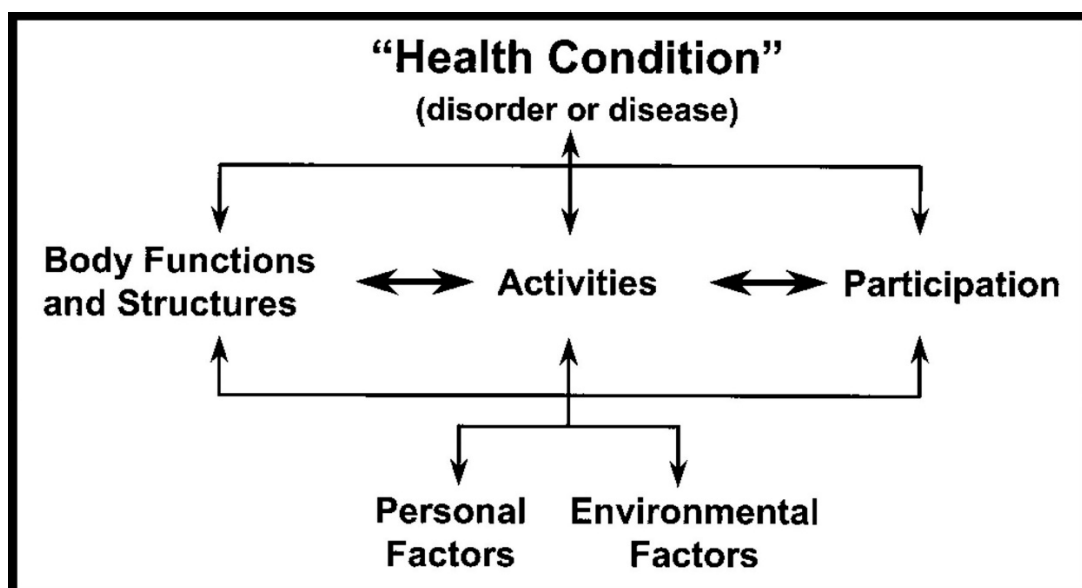
specialists. To make an informed decision, the rheumatologist must be aware of the most relevant problems and needs of the individual patient, and have a good understanding of the potential benefits, risks and limitations of rehabilitative treatment modalities. This includes the consideration of the specific knowledge and skills regarding the treatment of patients with rheumatic conditions of the health professionals involved.

1.2 A structured approach towards rehabilitative management

A structured approach is the key to a successful rehabilitation programme. This should comprise a careful assessment of problems and needs leading to clearly defined individual goals. These goals should lead to identification and provision of appropriate interventions and, finally, an evaluation of goal attainment.

The rehabilitation programme should be designed in close collaboration with the individual patient, to help to reach his or her goals for optimal level of functioning within different areas of disease consequences (figure 2). The World Health Organization International Classification of Functioning, Disability and Health (ICF) offers a useful tool to identify these areas (World Health Organization, 2002; Rauch et al, 2008*). This classification is structured in two parts, with two components in each: (a) functioning and disability (body functions and structures; activities and participation), and (b) contextual factors (environmental factors; personal factors). The following examples may be helpful to understand these concepts: body functions and structures: 'range of knee and hip movements'; activities and participation: 'ability to walk', 'dressing' or 'having a paid job'; environmental factors: 'architectural obstacles' or 'support from family and friends'; and personal factors: 'coping styles' or 'other health conditions'. Identifying the limiting and facilitating factors at each of these levels, and the potential to overcome them, and optimising the use of facilitators, is a key part of the assessment and an essential basis for planning and evaluating the interventions.

Figure 2 World Health Organization International Classification of Functioning, Disability and Health (ICF) model. (Reproduced courtesy of WHO.)



Rehabilitation is organised and managed differently in different countries. However, some key elements of the structure are considered important to improve quality of rehabilitation; there should be a structure for team communication, rehabilitation goals should be defined and evaluated, there should be a structure for patient involvement, and there should be a structure and a plan for follow-up after rehabilitation (Klokke et al, 2012).

2 Rehabilitative treatment modalities

2.1 Physical activity and exercise

Physical activity is defined as ‘any bodily movement produced by skeletal muscles that result in energy expenditure’ (Caspersen et al 1985). The American College of Sports Medicine (ACSM) states that ‘physical activity broadly encompasses exercise, sports, and physical activities done as part of daily living, occupation, leisure, and active transportation’ (*Garber et al 2011). Exercise is a subcategory of physical activity and is ‘planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective’ (Caspersen et al 1985). Exercise is a cornerstone of the rehabilitative management of rheumatic conditions and the prescription of exercise should take into account the following aspects:

- Objectives (eg, improvement or maintenance of cardiorespiratory fitness, various aspects of muscle functioning (strength, endurance), flexibility and/or specific activities such as walking, climbing stairs).
- The required intensity, number of repetitions and frequency for each type of exercise.
- Limitations and risks of exercises related to the individual patient’s underlying rheumatic condition and health status, including, for example, local joint inflammation, local joint damage, joint instability, the presence of joint prostheses or cardiovascular or pulmonary comorbidity.

Structured exercise programmes for patients with rheumatic diseases usually comprise a combination of exercises to increase cardiorespiratory fitness, muscle strengthening, flexibility and balance exercises, and training of specific movement patterns or daily activities. Exercise programmes can be performed individually or in group, under the supervision of a physical therapist (figure 4) or, after careful instruction, by the patients themselves (figure 3) at home, or by using community-based resources for exercises. The decision on the required nature and extent of supervision depends on the patient’s ability to modify the programme according to fluctuations in his or her health status and to recognise potential side effects of exercises, the physical and social accessibility of exercise facilities and, especially, the qualification of staff/instructors to deal with patients with rheumatic conditions.

Figure 3 Individual exercises, after instruction. Patient consent obtained.



Overall, there is high quality evidence for the effectiveness and safety of exercises in most rheumatic conditions (Sveaas et al 2017; National Collaborating Centre for Chronic Conditions, 2008*; Forestier et al, 2009*; Hagen et al, 2012; Hurkmans et al 2009; Swärdh et al 2016). Suitable forms of exercise are for example walking/hiking, running/jogging, cycling/bicycling, aerobic dance/group exercise, swimming/aquatic exercise, functional exercise, gym machines, rubber expanders or circuit interval training or some combination thereof (Swärdh et al 2016; Sveaas et al 2017; Westby 2001). Public health recommendations on exercise (*Garber et al 2011) can be used in the design of exercise programs for most patients with rheumatic conditions, with appropriate individual adaptations if needed. Rheumatologists have an important task in the education of patients with rheumatic conditions, in particular regarding the role of specific exercises related to individual impairments or limitations and with respect to general physical activity as part of a healthy lifestyle. Moreover, they should refer patients to appropriate professionals or services if they cannot achieve or maintain a sufficient amount of exercise or physical activity by themselves. The evaluation of an exercise prescription should comprise an assessment of its results versus the established goals and the occurrence of side effects, such as persistent pain on exertion or after the exercise sessions.

Figure 4 Supervised exercises. Patient consent obtained.



2.1.1 Public health recommendations on exercise

Evidence based public health recommendations to improve and maintain physical fitness and health states that all adults should perform a program consisting of cardiorespiratory, muscle conditioning, flexibility and balance exercises. Most adults should engage in moderate-intensity cardiorespiratory exercise for ≥ 30 min a day on ≥ 5 days a week for a total of ≥ 150 min a week, OR vigorous-intensity cardiorespiratory exercise for ≥ 20 min a day on ≥ 3 days a week for a total of ≥ 75 min a week, OR a combination of moderate-, and vigorous-intensity exercise. On 2-3 days a week respectively, adults should also perform muscle conditioning, flexibility and balance exercises. It is thus important to design the exercise program based on the individually stated objectives. A gradual progression of exercise volume (duration, frequency and/or intensity) is recommended. People who are unable to meet these recommendations can still benefit from performing less amount than recommended.

2.1.2 Cardiorespiratory exercises

Cardiorespiratory exercises are designed to increase or maintain cardiorespiratory fitness. Any activity that uses large muscle groups, can be maintained continuously, and is rhythmical and aerobic in nature is suitable. Moderate-intensity exercise means that the heart rate and breathing rate of a person is increased, and he or she may sweat but is still able to carry on a conversation. The perceived exertion should be rated 12-13 on a 6-20 RPE-scale (RPE=Rating of perceived exertion) or reach 46-63% VO_{2max} (VO_{2max} =percent of maximal oxygen uptake). Vigorous-intensity exercise means that a person is breathing rapidly and is only able to speak in short

phrases, with his or her heart rate being substantially increased and the person likely to be sweating. The perceived exertion should be rated 14-17 on a 6-20 RPE-scale or reach 64-90%VO_{2max} (*Garber et al 2011).

During the last years, increasing evidence shows that people with inflammatory rheumatic diseases are at increased risk of cardiovascular disease (Castaneda et al 2016, Peters et al 2010). Exercises to maintain or improve cardiorespiratory fitness are in general recommended for all chronic rheumatic conditions. In RA, exercise can have a positive effect on cardiac autonomic function, endothelial function and reduce cardiovascular risk factors (Metsios et al 2014; Stavropoulos-Kalinoglou et al 2013; Janse van Rensburg et al 2012). Patients may have coexisting conditions, such as cardiac or lung disease, related or not to their rheumatic disease. In addition, the presence of joint prostheses or other specific joint conditions may require the minimisation of some weight bearing activities and/or the avoidance of specific sports. In these cases expert advice from a cardiologist, pulmonologist or orthopaedic surgeon, and appropriate modification and careful supervision of the exercise programme, are needed.

2.1.3 Muscle conditioning exercises

Muscle conditioning exercises are designed to maintain or improve various aspects of muscle functioning, such as strength and endurance. A muscle conditioning exercise programme should include 8–10 strength-training exercises for major muscle groups, with 8–12 repetitions of each exercise, in 2-4 sets. An intensity between 20-80% of 1RM (RM=repetition maximum) depending on objective, experience and age is recommended (Garber et al 2011). The selection of exercises for therapeutic purposes depends on the specific impairments at the level of body functions and structures or on limitations in activities and participation of the individual patient. Dynamic muscle conditioning exercises should be used with caution in cases of unstable or mal-aligned joints, whereas isometric (static) muscle conditioning exercises may increase blood pressure.

2.1.4 Flexibility exercises

Flexibility exercises are prescribed to develop and maintain ROM within physiological limits. In general, flexibility exercises should include the joints most relevant to function and may preferably, in most rheumatic diseases, be performed daily (Garber et al 2011). Flexibility exercises are especially important in the case of local joint inflammation and pain, when there is a risk of developing contractures. Flexibility exercises are not to be prescribed in the case of joint instability, in particular of the spine (eg, cervical subluxation in patients with rheumatoid arthritis (RA)) or if a fracture is suspected (eg, osteoporotic fracture of the spine in patients with ankylosing spondylitis (AS)).

2.1.5 Balance exercises

Balance exercises are prescribed to reduce the risk of injury from falls in patients with rheumatic conditions who have a substantial risk of falls. Balance exercises may comprise standing-in-place exercises, either

combined or not combined with the use of a balance board, muscle strengthening exercises or gait training, or activities such as dancing. Tai chi is a popular form of alternative or complementary medicine which aims, among other goals, to improve or restore balance. Although the evidence for its effectiveness in rheumatic conditions is limited, conditional recommendations for tai chi in knee osteoarthritis have been issued (Hochberg et al 2012). Balance exercises are in general considered to be safe; however, a careful evaluation of the cause of balance problems and falls (eg, neurological or cardiac) is needed before their prescription.

2.2 Patient education and self-management support

Patient education has been defined as: ‘a planned learning experience using a combination of methods such as teaching, counselling, and behaviour modification techniques which influence patients’ knowledge and health behaviour’. Patient education can be provided individually or in groups. It is an interactive process assisting patients to participate actively in their health care, and providing them with information about available health services and their use (figure 5). Active participation in health care and effective self-management implies, for example, adherence to medication and exercises, and the use of orthoses or assistive devices and ergonomic techniques. Self-management support means providing education and supportive interventions to increase patients’ skills and confidence (i.e self-efficacy) in managing their rheumatic disease. This support is the responsibility of health care providers, however self-management skills, meaning performing the behaviours necessary to manage and live well with the rheumatic disease, is the responsibility of the patient (Brady et al 2006). Difficulties in applying these skills can have a decisive impact on a patient’s response to therapy and quality of life. The EULAR recommendations for patient education emphasizes patient education as an integral part of standard care (Zangi et al 2015). The proficient rheumatologist will be sensitive to these difficulties and provide advice or seek the assistance of a rehabilitation specialist or other professional if needed.

Figure 5 Individual patient education. Patient consent obtained.



Structured patient education in rheumatic diseases is based around three areas: (a) knowledge; (b) skills and behaviour; and (c) psychosocial support and coping (table 1).

With respect to knowledge, patients need an understanding of the basic concepts of anatomy and inflammation, as a prerequisite to understanding the objectives, limits and risks of drug therapy and non-pharmacological strategies such as exercises, activity pacing or weight reduction. In addition, patients need to understand the roles of the various healthcare providers involved in the management of their condition and, especially, acknowledge the importance of their own role in the management of their disease. Knowledge translation is enhanced if simple, non-threatening language is used, and written information is available for later review.

Self-management skills include specific behaviours, such as medication use, daily exercise regimens, the application of activity pacing techniques, and the usage of ergonomic techniques and adaptive devices.

The psychosocial and coping area pertains to helping patients feel more confident in being able to manage their rheumatic condition and to function in the conduct of daily tasks, thereby reducing feelings of anxiety, depression and helplessness.

Table 1 Content areas of structured patient education

Content area	Examples of specific content
Knowledge	<p>Anatomy, disease process, inflammation and risk of comorbidity</p> <p>Symptoms and signs of improvement or deterioration in rheumatic condition; understanding of disease monitoring</p> <p>Drug therapy: usage, effects, side effects</p> <p>Knowledge of activity pacing, aids, assistive devices, orthoses and ergonomic techniques to maximise function</p> <p>Understanding the benefits or risks of surgical interventions</p> <p>Health benefits of exercise and physical activity</p> <p>Understanding of where to find health professionals, community resources, patient/consumer organisations</p>
Skills and behaviours	<p>Performing exercises and achieving a sufficient level of physical activity</p> <p>Seeking insight into his/her own capacity and, through activity pacing, finding the individual balance between pain, fatigue and activity</p> <p>Making daily tasks easier by using adaptive devices, home or work adjustments, or using altered working methods</p> <p>Medication adherence and monitoring of side effects</p> <p>Seeking medical support in case of symptoms of drug side effects</p>
Psychosocial and communication dimensions	<p>Reducing anxiety and feelings of helplessness, increasing confidence for specific tasks or roles</p> <p>Communicating with healthcare providers, learning how and when to ask questions</p> <p>Eliciting support from partner or other family members</p>

Overall, there is high quality evidence for the effectiveness of educational interventions in patients with RA and osteoarthritis (OA) (Iversen et al 2010*; Knittle et al 2012), and to a lesser extent in AS (Vliet Vlieland and Li 2009) or other rheumatic conditions. The rheumatologist is in a strategic position to engage in patient education as part of his or her medical consultation. In case there is a need for additional education, this may be provided by other individual health professionals such as nurses, social workers, physical therapists, occupational therapists or psychologists. Patient education can also be provided by trained patients (patient partners). Patient education may also be provided in a group setting, either ancillary to medical care or in the community. It is also important for the rheumatologist to provide brief behavioural counselling to enhance patients' self-management skills. Rheumatologists have the opportunity to assess the patients' behaviour and beliefs, advice and provide information, use collaborative goal-setting, facilitate an action plan and arrange follow-up (Brady et al 2006).

2.2.1 Educational interventions promoting optimal function in everyday life activities

Educational interventions promoting optimal function in everyday life activities (known as joint protection) attempts to help patients plan, pace and carry out activities in such a way that pain is minimised and their energy level is maximised. Simple measures including performing tasks at a slower pace and breaking activities into smaller sections with periods of rest in between, proper body positions, adaptation of the work environment, and use of assistive devices can have a huge impact on the work load. Such measures can make a very important contribution towards reducing fatigue and pain, and increasing the patient's productivity and satisfaction.

The main guiding principles include the avoidance of positions and activities that are stressful for joints and cause pain and discomfort by using alternative body positions, working heights and working methods, using assistive devices, and finding the right balance between rest and activity. Evidence for the effectiveness of educational interventions promoting optimal function in everyday life activities (joint protection and energy conservation) is mainly available for RA (Steultjens et al 2004). In other rheumatic conditions the evidence is scarce (Stamm et al 2002; Spadaro et al 2008). The term 'joint protection' should be used with caution, as it reflects the opposite of what is desirable to communicate: the importance of keeping up activity and exercising to maintain movement and strength.

2.2.2 Aids and devices and adaptations of physical environment

Aids and devices and adaptations of physical environment can be used to ease pain, overcome joint limitations, compensate for muscle weakness, and enhance safety. The ultimate aims are to relieve suffering and increase function and independence.

There is a large variety of assistive devices to address the individual needs of patients in almost all areas of activity: personal care and protection, mobility, housekeeping, furnishing and adaptation of homes and other premises, communication, information and signalling, recreation, etc.

The interested rheumatologist can and should provide patients with useful advice in this respect, as it is an integral and important part of the management programme. If available, the patient should be referred to an occupational therapist or a physiotherapist for a more extensive consultation related to adaptations and information on assistive devices. Table 2 provides examples of activities, related aids, and assistive devices and home modifications relevant for rheumatic conditions.

With respect to upper extremity aids, pinch and grasp can be improved by building up handles on tools, cookware and eating utensils (figures 6 and 7). Grip can further be improved by using no-slip mats or cutting boards (figure 8). Power equipment, such as electric knives and tools, can substitute for decreased power grip and poor upper extremity strength. Reachers (figure 9) can be used to retrieve objects from floors and shelves. Long-handled brushes, combs and sponges can help with upper extremity grooming and perineal care. Buttonhooks, zippers with tabs, clothing and shoes with Velcro closures, elastic waist trousers, and V-neck pullovers can facilitate dressing. Sock cones and long-handled shoehorns ease the donning and doffing of socks and shoes, and dressing sticks assist those with impaired shoulder mobility.

Figure 6 Utensil with enlarged grip.



Table 2 Examples of assistive devices and adaptations to homes and furnishing (Adapted from Noaker JA. Enhancing functional ability: alternative techniques, assistive devices and environmental modification. In: Wegener ST, Belza BL, Gall EP, eds. Clinical care in the rheumatic diseases. Atlanta, Georgia: American College of Rheumatology, 1996)

Activity	Example of assistive device or adaptation
Personal hygiene	Enlarged-handle brush/comb Long-handled brush/comb Wash and dry bidet
Bathing	Long-handled bath sponge or brush Shower chair Bathtub seat–elevator Replacing bath with walk-in-shower
Dressing	Sock device Long-handled shoe horn Elastic shoe laces Replace closures with Velcro
Eating	Enlarged handle grips or cylindrical foam Rocker or angled knife Non-slip matting under plate
Transfers and mobility	Lift chair Elevated toilet seat or chair Grab bars Canes, crutches Rolling walker Electric mobility scooter (Electric) wheelchair Bicycle with electric support
Household	Loop scissors Reacher Electric can opener Long-handled non-wringing sponge or mop Tools with enlarged and cushioned handles Non-slip mats
Work and school activities	Large diameter pens Document holder Speaker phone or headset Ergonomic keyboard
Leisure activities	Gardening tools with cushioned handles Playing card holder

Figure 7 Utensil with bent and enlarged grip.



Figure 8 No-slip cutting board.

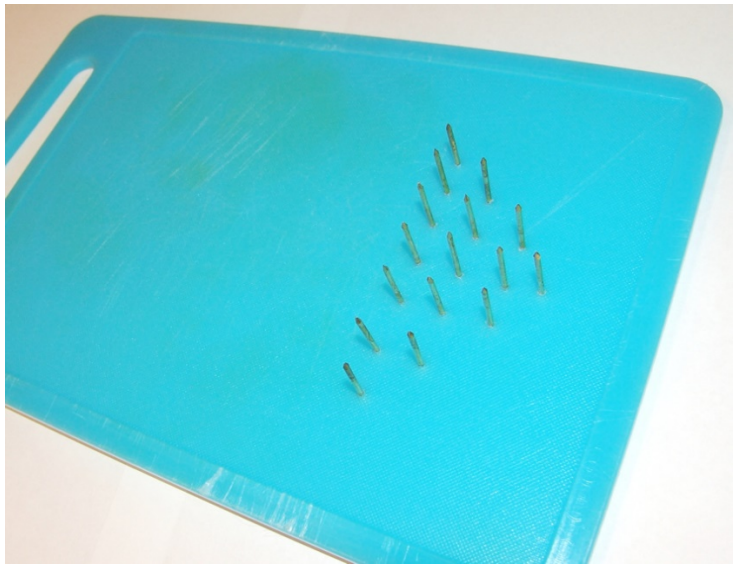


Figure 9 Reacher.



Concerning the lower extremity, rheumatologists ought to have some knowledge of canes, crutches and walkers, as they will be frequently used by their patients. These aids are aimed at improving gait and ease weakness, pain and instability in lower extremity joints.

Most assistive devices can usually be found by local suppliers or on the internet. The selection of the best tool will be more appropriately performed by the patient with the support of a trained professional, who will have specimens of various devices in his or her practice. If the rheumatologist provides assistance, a number of factors should be considered before advising on aids and assistive devices, including physical, social-emotional,

environmental, and financial factors (table 3). This consideration also includes potentially negative consequences of the use of assistive devices, such as making the physical disability more obvious for other people or the implicit idea that activities should be avoided because they could be harmful.

Overall, the literature on the effectiveness of adaptive devices is scarce (Tuntland et al 2009). Permanent and drastic adaptations to the home should always be carefully considered, and mainly be advised in case no improvement of the patient's health status can be expected in the short term.

Table 3 Factors to be considered in prescribing assistive devices (Adapted from Noaker JA. Enhancing functional ability: alternative techniques, assistive devices and environmental modification. In: Wegener ST, Belza BL, Gall EP, eds. Clinical care in the rheumatic diseases. Atlanta, Georgia: American College of Rheumatology, 1996)

Physical factors	Effects on pain, stiffness and joint stress Effects on energy and time expenditure Convenience (eg, easy to do, on/off) Frequency of use Substitution of activities
Social-emotional factors	Effect on independency in activities of daily living Cosmetic aspects Learning ability to use device
Environmental factors	Compatibility with environment of home/workplace Aspects with regard to instalment and maintenance of equipment
Financial factors	Commercial availability Insurance policies

2.3 Orthoses

The term 'orthoses' refers to 'any medical device added to a person's body to support, align, position, immobilise, prevent or correct deformity, assist weak muscles, or improve function'. In rheumatic conditions orthoses are usually used to relieve pain through reduction of strain or load on a joint or a decrease in its motion. They can also be used as a conservative modality to improve patterns of motion, or postoperatively to provide stability and ensure healing in an optimal position. Postoperative orthoses can both be static and dynamic. Orthoses are most commonly made or tailored by occupational therapists or prosthetists.

The aims of splints and the advised duration of their use should be communicated clearly to patients. Moreover, patients with rheumatic conditions may have more fragile skin due to their disease or to medications. Splint fitting, padding and lining can address this issue. The effects of immobilisation on the targeted joint, as well as adjacent joints, should be considered when prescribing splint wear. In all cases, splints should be removed periodically for ROM exercise and skin care.

The following sections present a core summary of important concepts that the rheumatologist should master regarding the most commonly used orthoses in his field.

2.3.1 Wrist orthoses

Wrist orthoses provide support for the wrist while allowing motion of the thumb and fingers. Indications for a wrist splint include wrist pain and synovitis or tenosynovitis (Adams et al 2005). Different types of wrist splints are available. Functional or working wrist splints permit movement of the metacarpophalangeal (MCP) joints and the finger joints. Working wrist splints are intermittently used during activities in which resistance, object weight or protracted positioning are likely to stress the wrist, with the aim of supporting joints and restricting motion; they are primarily thought to relieve pain and improve the performance of activities of daily living.

With resting splints, the MCP and finger joints are also immobilised, and these splints are to be worn intermittently during resting periods over the day and at night. Resting wrist splints are mainly prescribed to reduce pain and other signs of inflammation, and to a lesser extent to prevent contractures and preserve function.

A systematic review from 2014 concludes that working wrists splints reduce pain and improve grip in RA, but the effect on function is unclear (Ramsey L et al 2014)

With wrist splints, for most conditions, a functional position of 20° to 30° of extension of the wrist while wearing the splint is advocated, with the exception of carpal tunnel syndrome, where 10° extension is recommended. Wrist working splints have been found to reduce wrist pain during activities, but may also decrease dexterity and interfere with some daily activities such as working in water or in dirty conditions (eg, gardening). With the prescription of wrist splints, the potential benefits and adverse effects need to be discussed with the patient.

2.3.2 Finger orthoses

Finger orthoses are prescribed in the case of finger deformity or instability such as swan neck or boutonnière deformities in patients with RA. These deformities may interfere with pinch grip and fine precision activities. A swan neck splint prevents the proximal interphalangeal joint from hyperextension while supporting the volar surface (figure 10), whereas a boutonnière splint places the proximal interphalangeal joint in extension (van der Giesen et al 2009). Finger splints can be made from sterling silver or thermoplastic material, with no differences in effectiveness related to the material they are made of. Side effects of finger splints include pressure on bony edges, the development of rheumatoid nodules in RA patients, or paraesthesias in the finger tips.

Figure 10 Finger splints for swan neck deformity.



2.3.3 Thumb splints

The thumb accounts for 60% of hand function. When thumb movement is limited by pain, instability or deformity, hand function is greatly reduced. A common condition where thumb involvement is seen is OA of the first carpometacarpal joint. This condition is often associated with instability and pain, particularly during activities in which force is exerted by the thumb (eg, in applying pinch or three-point grip). In this case, a thumb support either covering both the thumb base and wrist or protecting only the thumb base can improve pain and function (Ye et al 2011*). The thumb should be placed in a functional position of opposition to the index finger. In addition, wrist and thumb interphalangeal joint motion should not be restricted (figure 11).

Figure 11 Thumb base splint.



Involvement of the MCP joint of the thumb can be seen in patients with RA. Splints to support the MCP joint of the thumb can improve pinching abilities by providing support and relieving pain. A so-called 'figure of eight' splint for this joint allows movement of the carpometacarpal and interphalangeal joints while providing lateral support and positioning the MCP joint for function.

Splints for hyperextension and lateral instability of the interphalangeal joint of the thumb follow the same guidelines as for the proximal interphalangeal joints of the fingers.

2.3.4 Knee braces

In particular in patients with knee OA, pain and disability may be due to an abnormal distribution of forces as a result of malalignment (varus or valgus). Knee braces are applied with the aim of decreasing pain by reducing the load in one of the compartments of the knee. Moreover, they can improve stability and diminish the risk of falling (Brouwer et al 2005). Knee braces are made of combinations of metal, foam, plastic, elastic material and straps. They are available 'off the shelf' or by manufacture of an individualised brace. As many patients benefit from off-the-shelf knee braces such as sport braces in daily rheumatological practice, the prescription of custom-made braces for knee OA should be carefully considered. It should be noted that their cosmetic aspects, difficulties with putting them on and off, lack of comfort while wearing them, and interference with clothing may affect adherence.

2.3.5 Footwear

Appliances for the rheumatic foot are prescribed to relieve excessive pressure, to reduce shock and shear, to accommodate, correct and support deformities, and to control or limit painful motion of joints (Rao et al 2012).

Prescription footwear is made according to practitioner-prescribed specifications. External shoe modifications may consist of rocker soles, extended steel shanks, stabilisers, wedges or extensions (figure 12). Inserts may comprise soft, semi flexible or rigid insoles or toe wedges. Custom-made in-shoe devices may be moulded or milled from an impression of the foot (eg, a plaster cast or three-dimensional laser scan).

Apart from prescription footwear, off-the-shelf footwear for those with arthritis, to which orthopaedic amendments often can be made, is readily available (figure 13).

Figure 12 Custom-made shoes with a metatarsal bar underneath.



Figure 13 Off-the-shelf footwear with elastic leather upper.



2.4 Electrophysical modalities

Under this designation we include a range of modalities including electrical, thermal, light, sound and magnetic energy, mainly used to promote positive effects upon body functions and structures, but also to facilitate the performance of physical activity and exercise.

2.4.1 Heat and cold therapy

Heat is mainly prescribed for muscle relaxation, to reduce stiffness and to improve local circulation. It may be administered in the form of superficial heat (hot packs, paraffin or wax baths, thermal baths and infrared) or deep heat (electromagnetic wave forms and ultrasound). The main goals of cold therapy are to reduce pain and decrease swelling. It is applied by means of ice packs, ice chips, ice massage, cryowraps, cold air, vapocoolant sprays or whole-body cryotherapy.

Overall, the evidence for the effectiveness of heat and cold therapy in rheumatic diseases is scant. A beneficial effect of heat (paraffin) on ROM, hand function, pain and stiffness has been reported in patients with RA (Robinson et al 2002), whereas cold therapy was found to have a positive effect on ROM, function, strength or swelling in knee OA (Brosseau et al, 2003). Both superficial heat and cold therapy need to be used with caution, as they may cause dermal injury, in particular in patients with reduced sensibility (eg, diabetic neuropathy) or peripheral vascular disease. Moreover, both superficial heat and deep heat are usually advised against in the case of local joint inflammation, as both have been found to increase the intra-articular temperature.

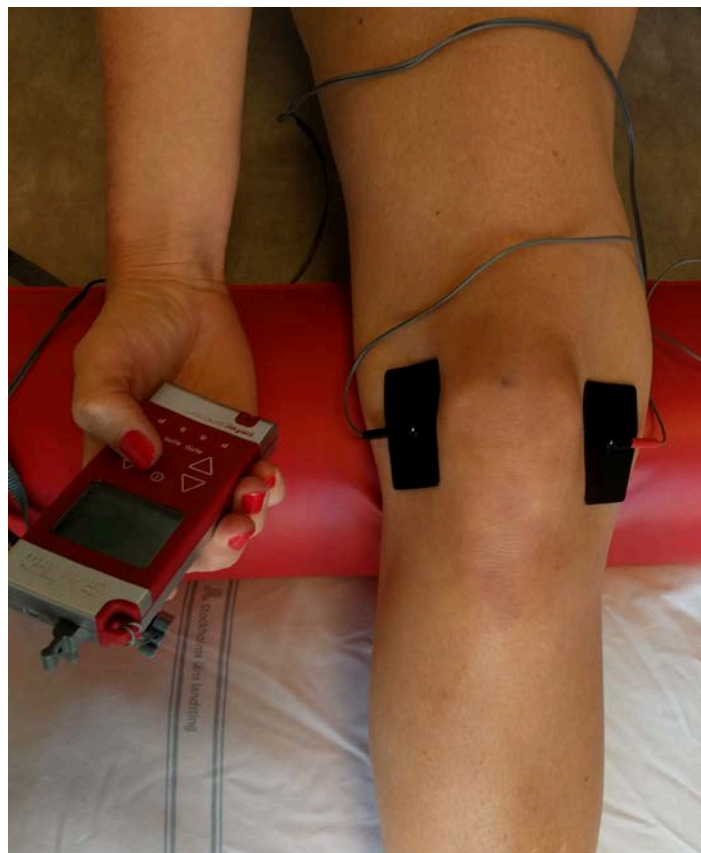
2.4.2 Electrotherapy

Electrotherapy consists of the therapeutic use of different forms of electric currents, mostly applied by surface electrodes. The main clinical indications are pain control and muscle stimulation. The most common form of

therapeutic electrical stimulation used for pain control is transcutaneous electrical nerve stimulation (TENS), which can be applied in case of loco-regional pain. TENS devices are small, portable instruments, producing sharp impulses (0.2 ms) within a frequency range of 1–150 Hz. The patient can activate and control intensity as needed after appropriate instruction (figure 14).

There is low quality evidence for the effectiveness of TENS in RA and moderate quality evidence that TENS reduces pain in knee OA. The electrodes of TENS devices may occasionally cause skin irritation. Moreover, it is recommended that TENS is not applied over the anterolateral aspect of the neck, to avoid vagal stimulation. In addition, people with pacemakers are advised not to use TENS near the heart.

Figure 14 TENS intervention for the knee. Patient consent obtained



2.4.3 Laser therapy

Low level laser therapy was introduced for the treatment of rheumatic diseases in the 1980s. It uses a light source that generates extremely pure light of a single wavelength. Low level laser therapy aims to decrease inflammation, with its mechanism not being thermal but rather related to photochemical reactions in the cell. There is moderate quality evidence that low level laser therapy applied to the hands reduces pain and morning stiffness in patients with RA, and that low level laser therapy applied to the knee reduces pain in patients with knee OA.

2.5 Spa therapy

Bathing in water (spa therapy, balneotherapy or 'passive' hydrotherapy) is still very popular in some parts of the world, including Europe, not only in patients but also among the general population. Water from mineral and thermal springs has been particularly valued, although evidence for the impact of the qualities of the water is scarce. Balneotherapy can include a variety of modalities, such as radon–carbon dioxide baths, carbon dioxide baths, Dead Sea baths or sulphur baths. Balneotherapy is best tolerated with temperatures of around 34°C and a duration of about 20 min (Verhagen et al 2012). The aim of balneotherapy is to improve the range of joint motion and muscle strength, relieve muscle spasm, maintain or improve functional mobility, soothe pain and, as a consequence, relieve patients' suffering and improve their well-being. Balneotherapy is often combined with other treatment modalities, in particular exercise programmes, with comprehensive programmes usually having a duration of 2–3 weeks. Overall, there is low quality evidence for the effectiveness of balneotherapy in RA, OA or AS (Verhagen et al 2003; Verhagen et al 2008; Verhagen et al 2012). As combined spa-exercise programmes are most commonly provided in a health holiday setting, it remains unclear to what extent the setting contributes to their perceived benefit.

2.6 Vocational rehabilitation

The importance of work to patients goes well beyond their economic needs; it may have a decisive impact upon their overall quality of life. The rheumatologist has an important role in identifying working problems by asking patients on a regular basis to what extent and how their rheumatic condition has influenced their work ability and working status. In case of a working problem, the rheumatologist may refer a patient for vocational rehabilitation (VR). VR can be defined as 'a process to overcome the barriers an individual faces when accessing, remaining or returning to work following injury, illness or impairment'. It may encompass a broad range of interventions, beyond medical and non-pharmacological management of the condition: assessment of needs, work adjustment and control measures, staged return-to-work management, disability awareness training, retraining and capacity building, and support for the individual, employer or others (box 1). With respect to referrals for VR, it will depend on the healthcare system and/or social security system in a specific country as to which professional or which service within or outside the healthcare system is most suitable. In some countries occupational therapists provide individual consultations regarding work related problems (Macedo AM et al 2009). A systematic Cochrane review assessing the effects of non-pharmacological interventions aiming to prevent job loss, work absenteeism or improve work functioning in persons with inflammatory arthritis found that there was a potential for positive long term results. These interventions should include an analysis of a person's work activities, work functioning assessment of ergonomic needs and communication at work to identify those features of working life that are placing the person at risk of dropping out of work (Hoving JL et al 2014). Comprehensive work interventions may have positive psychological effects, as well as result in increased work participation (Cignac et al 2012*). Some studies report favourable results in

the early stages of work disability, including the perception of any working problems by the patient while working (work instability) or the occurrence of sick leave (Allaire et al 2003). Currently data are insufficient to identify patients at risk for work disability and to determine the optimum time to intervene (Cignac et al 2012*), but the high personal and socioeconomical cost of sick leave provides a strong argument for early identification of problems, and early interventions.

Box 1 Examples of vocational rehabilitation strategies to enhance job retention

Employee

- Changing medication regimens; good symptom control
- Pacing: taking more rest breaks and microbreaks
- Work simplification, ensuring immediate work area is ergonomically structured
- Using splints, assistive devices and equipment adaptations
- Increased planning of work tasks, changing work tasks
- Informing employer and/or colleagues about disease and functional ability/disability
- Appropriate help-seeking from colleagues
- Altering working hours, decreasing days
- Transport changes
- Changing jobs

Employer

- Providing special equipment, environmental modifications and access to disabled parking
- Job flexibility (flexible working time, task variation, reducing time pressure)
- Better understanding of rheumatic conditions

Employee and employer

- Timely usage of VR services
- Good working relationships between employee/patient, employer and colleagues
- Knowledge of the rights of people with disabilities and employers' responsibilities to such people

Adapted from Hammond, Best Pract Res Clin Rheumatol 2008;22:435–49.

3 Rehabilitation in specific rheumatic conditions

In this section we will provide a short overview of the most common rehabilitation needs and opportunities related to a number of specific rheumatic conditions, underlining the possible role of rheumatologists and the potential contribution of specialised professionals.

3.1 Rheumatoid arthritis (RA)

Similar to the monitoring of disease activity, the rheumatologist plays an important role in the monitoring of the patient's functioning in daily activities and also societal participation during the course of the disease. For standardised monitoring of functional disability, the Health Assessment Questionnaire is often used, including 20 items on physical function and also querying help from another person or use of devices. Although this questionnaire does not address level of participation, including work disability, the HAQ score could be used as a screening tool for assessing the need of comprehensive multidisciplinary assessments of the components of

disability and corresponding interventions (Thyberg et al 2012). Despite the availability of many effective drugs (such as synthetic and non-synthetic disease modifying drugs) for the treatment of RA, limitations in daily activities and/or restrictions in participation are still a consequence of living with RA for many patients. While some patients experience limitations already for performing basic daily activities, more often challenges are related to performing complex actions, including work (paid or unpaid) and leisure activities. Moreover, the prospect of living with a chronic disease and being in need of medication places an emotional burden on patients which is sometimes underestimated. For patients experiencing any limitation in their functioning, there are a number of rehabilitative interventions to be considered as an adjunct to pharmacological therapy.

3.1.1 General rehabilitative management

In general, exercise and patient education are the cornerstones of the rehabilitative treatment of RA patients, and access to a multidisciplinary team is considered to be a part of the standard care for patients with RA in many countries.

With respect to exercise, most research in RA has so far focused on dynamic exercises (exercise with the aim of improving cardiorespiratory fitness and/or muscle strength). It has been consistently demonstrated that in patients with RA dynamic exercises, either supervised and/or home-based, are effective with respect to improvement in aerobic capacity and muscle strength, with no detrimental effects on disease activity or pain, or radiological damage (Hurkmans et al 2009; Swärdh et al 2016). There are also results indicating that physical activity and exercise has significant effect upon self-reported fatigue in RA patients (Rongen-van Dartel et al 2015; Cramp et al 2013), and can improve sleep quality (Durcan 2014). It is important to underline that, contrary to a rather common belief, exercising inflamed joints does not have any deleterious effects.

Given these health benefits, RA patients should be advised to maintain an amount of physical activity that at least equals public health recommendations. If a patient cannot achieve this goal on his or her own—due to, for example, local disease activity or joint damage, comorbidity, inability to modify exercises according to disease fluctuations or movement anxiety, and/or if there are limitations in specific movement patterns or daily activities that need to be addressed—then this is an indication for guidance and supervision by a physical therapist.

In RA, a substantial number of studies have consistently demonstrated small, short-term beneficial effects of a broad range of psycho-educational interventions on health status (pain, functional disability, fatigue, psychological well-being and disease activity) (Iversen et al 2010*; Knittle et al 2010; Knittle et al 2012; Cramp et al 2013). Sustained effects of psycho-educational interventions have been reported in studies where CBT was administered, in particular early in the course of RA or in patients with a psychosocial risk profile (Evers et al 2002). So far, the optimal composition and timing of psycho-educational interventions in RA have not been established, but factors enhancing their effectiveness and/or maintenance include: a duration of at least 6

weeks; explicit use of cognitive behavioural approaches; individualised weekly action plans with progress review; the usage of protocols and participant handbooks; provision by the same trained leaders; and the employment of intervention techniques derived from the self-regulation theory (Iversen et al 2010*; Knittle et al 2010). With respect to educational interventions promoting optimal function in everyday life activities (joint protection) and energy conservation in particular, the literature provides evidence for the effectiveness of structured programmes, mainly delivered by occupational therapists, on functional ability (Steultjens et al 2004). Evidence for the effectiveness of assistive devices was found to be scarce (Tuntland et al 2009). However, daily experience as well as high rates of possession and usage in epidemiological studies suggest their benefit for many RA patients. In case it is not clear which assistive device would be the best solution for a patient's functional limitation, or when there is a need for individually manufactured devices or large adaptations to the home, referral to a rehabilitation specialist, occupational therapist or nurse specialist (depending on the complexity of the situation and the availability of professionals or services) must be considered.

3.1.2 Management of hand problems

Wrist pain is common in RA patients. Hand exercises have been shown to be both effective and cost-effective in RA (Lamb et al 2014). In addition to advice on appropriate assistive devices, wrist splints can be considered. As regards the type of splint, working wrist splints are especially recommended, as the literature suggests that these may improve pain and strength during the performance of activities (Veehof et al 2008), whereas no beneficial effects of resting wrist splints have been documented in RA (Adams et al 2005). In case of swan neck and/or boutonnière deformities, finger splints may be considered with the aim of improving finger stability and correcting the deformity, thereby improving dexterity. Their effectiveness has been established in a number of studies in RA patients (Zijlstra et al 2004; van der Giesen et al 2009). With the prescription of every type of splint, careful advice, including on the aim of the splint, joint position, wearing times and skin care, and an evaluation of the effect should be provided.

3.1.3 Management of foot problems

RA patients' feet and walking ability are often not adequately considered, although foot involvement is present in the majority of patients.

In patients with RA, it was found that extra-depth shoes decrease pain during weight bearing activities such as standing, walking and stair climbing. Furthermore, it was concluded from a systematic review that in patients with RA, custom-made foot orthoses reduce pain and forefoot pressure (Hennessy et al 2012). Foot orthoses may improve pain in patients with RA, but their impact on disability is unclear (Conceição CS et al 2015). Moreover, research in patients with RA and OA with painful hallux valgus found that custom-made foot orthoses reduced foot pain; however, there was no benefit in comparison with surgery.

3.1.4 Management of cervical spine problems

Cervical spine orthoses are predominantly prescribed for patients with RA and atlantoaxial (C1–C2) subluxation. In these cases, the aim of a cervical spine orthosis is to limit motion of the cervical spine, especially flexion, thereby reducing pain, muscle tension and paraesthesias, and the risk of spinal cord injury. There are different types of cervical spine orthoses, varying with respect to their shape, material, extent and localisation of points of support, and comfort. Wearing cervical spine orthoses, in particular hard cervical collars, is considered uncomfortable by many patients, due to problems of heat and difficulties with eating, dressing, washing oneself, and getting the collar on and off.

Concerning the effectiveness of cervical spine orthoses in RA, some studies suggest that flexion of the cervical spine is indeed limited, especially when wearing a stiff cervical collar, whereas in other studies stabilisation of cervical motion was unsatisfactory. An effect of cervical spine orthoses on the progression of C1–C2 subluxation in RA has not been demonstrated. A cervical collar can promote muscle relaxation and may be effective for pain relief in individual patients with non-specific cervical pain syndromes.

3.2 Spondyloarthritis (SpA)

Most of the general recommendations on exercise and patient education in RA patients are applicable to patients with SpA (including ankylosing spondylitis (AS)). There is a growing consensus that an exercise programmes for patients with SpA should be vigorous and include flexibility, strengthening and cardiorespiratory components. Flexibility exercises are particularly aimed at maintaining or improving spinal mobility, chest expansion and the ROM of peripheral joints (hip and shoulder motion) and to decrease symptoms of stiffness. Postural muscles, especially in the thoracic spine, and gluteal and quadriceps muscles should be conditioned. A cardiorespiratory component is needed because of the risk of restrictive pulmonary involvement. In addition to exercises, patients need information and guidance regarding improvement and maintenance of appropriate body positions during work (in or out of the home), leisure, sleeping and driving.

Given the increased risk of fractures, passive mobilisation of the spine of the patient with axial SpA is dangerous and should never be advised or performed.

Changing position and flexibility exercises should be carried out frequently. Patients with SpA should be referred to a physical therapist for postural guidelines and instruction on an exercise regimen that should be performed by the patient on a daily basis. Participation in weekly group or sports activities for patients with SpA should be recommended to enhance adherence.

In patients with AS, a beneficial effect of exercise programmes, including strengthening, cardiorespiratory exercises, hydrotherapy, sports activities and stretching, on spinal movement has been consistently demonstrated (van den Berg et al 2012*; O'Dwyer et al 2014*). The evidence was moderate concerning the

effect on physical function, disease activity and chest expansion, and low-level concerning pain, stiffness, spinal mobility and cardiorespiratory function. Overall slightly more favourable results were seen with supervised exercises than with individualised home exercises (O'Dwyer et al 2014*).

With respect to education, the patient with AS is advised to comply with a number of recommendations, including medication use, exercise, and modification of working methods or of the environment. When the evidence on the effectiveness of education in this patient group was considered, it was found that energy conservation and educational interventions promoting optimal function in everyday life activities (joint protection programme) as an adjunct to treatment with anti-tumour necrosis factor α (anti-TNF α) agents was beneficial, with synergistic effects on pain, function and disability (Spadaro et al 2008).

Techniques and devices may be needed to compensate for the lack of spinal, cervical, hip or shoulder movement. Devices considered very useful in this patient group include long-handled dressing aids, reading stands, elongated rear view mirrors and lumbar back supports. Patients should use as few pillows as possible, but at least one is needed to support the head and cervical lordosis. In AS, common sites for enthesitis are under the heel, where the plantar fascia attaches, and behind the heel at the Achilles tendon insertion. Shoe inserts that relieve localised pressure under the heel or raise the hind foot can relieve pain in these cases.

Inpatient rehabilitation has also proven to be efficient for increased function and reduced pain (van den Berg et al 2012*).

3.3 Osteoarthritis (OA)

The main components of non-pharmacological treatment in OA are education, exercise and weight reduction (Hochberg et al 2012). The provision of oral and written information about the disease, its course and pharmacological treatment is important. Patients should also be informed about the use of adaptive devices and orthoses, 'pacing' of activities, and a healthy lifestyle (physical activity, reducing overweight). Moreover, the limited potential benefits and side effects of thermotherapy or TENS in addition to these interventions should be highlighted (Palmer et al 2014). Education on all of these topics is the starting point for any self-management intervention for OA in one or more joints. Exercise should, apart from general improvement of cardiorespiratory fitness and muscle strength, focus on the reduction of local joints impairment (eg, local muscle weakness, limited ROM) in order to improve the performance of daily activities.

3.3.1 OA of the hip and/or knee

OA of the hip and/or knee is likely to be associated with reduced muscle strength, reduced knee joint proprioception, impaired balance and an increased risk of falls. In addition to the advice of attaining and maintaining an active lifestyle by meeting public health recommendations on physical activity, cardiorespiratory exercises and muscle strengthening exercises (gluteal and quadriceps muscles), in

combination with flexibility and walking exercises, are recommended for OA of the hip and/or knee. In patients with both knee and hip OA, a positive effect of land-based exercise programmes on pain and function has been consistently demonstrated. Additional 'booster' sessions provided after the treatment period appear to positively influence the duration of the effect (Pisters et al 2007; Hernandez-Molina et al 2008).

In overweight or obese patients, advice or counselling on weight reduction may contribute to a decrease in the mechanical load on joints, thereby lessening pain and improving function.

The use of walking aids may reduce pain in patients with hip and knee OA. Moreover, based on expert opinion, patients with hip and knee OA are generally advised to wear shoes with thick but soft soles, and no raised heels. Laterally or medially wedged insoles are sometimes recommended in patients with medial or lateral tibiofemoral OA, respectively. In patients with knee OA and instability and/or malalignment, a knee brace can be considered, with the aim of reducing pain, improving stability and reducing the risk of falling. Taping of the patella (ie, applying adhesive, rigid, strapping tape to glide, tilt and/or rotate the patella to pull it medially) can be used to modify patella position. This intervention might be considered in chronic knee pain resulting from either anterior knee pain or patellofemoral OA. Although positive effects of taping the patella in chronic knee pain are reported, no firm conclusions can be made with respect to the optimal direction (medially or laterally) (Warden et al 2008). Self-care activities may be facilitated by the use of assistive devices such as raised toilet seats or chairs, grab bars or shower seats. In the case of complex problems or OA in multiple sites, consultation with a rehabilitation specialist or occupational therapist is likely to be beneficial.

3.3.2 Hand OA

As part of the management of hand OA, a patient should be advised on pacing of hand use, and to avoid repetitive power grip, pinch and twisting movements. Education combined with exercises have been found to improve functional outcomes in hand OA more than information alone (Hennig et al 2014). A Cochrane review evaluating the effect of hand exercise in hand OA concludes that exercise has small beneficial effects on hand pain, function and joint stiffness (Østerås et al 2016).

Instability and pain of the first carpometacarpal joint, particularly during activities in which force is exerted by the thumb, can be counterbalanced by a thumb splint (Ye et al 2011*). In addition, numerous assistive devices, including, for example, enlarged grips on pens and cutlery, and electric can openers can be very useful.

3.4 Regional musculoskeletal pain syndromes

Under this heading we refer to a number of conditions including tendinitis, tenosynovitis, bursitis, and ligament strains (Speed and Hunter 2007). Space does not allow a detailed description of rehabilitative methods applicable to the different conditions. However, a few basic principles can help the rheumatologist to achieve good results in these common conditions.

With musculoskeletal pain syndromes, the key to successful rehabilitative management includes ensuring that the patient has a full understanding of the disorder and of precipitating and aggravating factors, such as repetitive activities that irritate the involved structures or prolonged, static strain. Avoidance of these factors may include modification of the work environment. For many soft tissue conditions, it should also be explained that the process of recovery may be lengthy. Relief of pain is another important principle. In addition to pharmacotherapy, TENS may be helpful in the management of local pain. Lack of exercise and improper use of muscles or poor posture often contribute to the development or persistence of soft tissue conditions. Rehabilitation therefore includes exercises in most soft tissue conditions, preferably designed and supervised by a physical therapist. An exercise programme should in general consist of graded flexibility and muscle conditioning exercises, as well as cardiorespiratory exercises. Evidence for the effectiveness of electrophysical treatment modalities other than TENS, such as low level laser therapy, ultrasound and thermotherapy, is scarce. Low level laser therapy and ice may be effective in lateral epicondylitis. Cryotherapy can also be applied in Achilles tendinopathies. Depending on the nature and site of involvement, various adaptive devices and orthoses, aiming to reduce strain or excessive movement, can be prescribed, such as heel raises in Achilles tendinopathy and wrist splints in carpal tunnel syndrome.

3.5 Low back pain

Low back pain is a common condition, with the majority of adults having low back pain at some time in their lives.. Most patients have ‘non-specific low back pain’ with, in general, a favourable prognosis. A minority of these patients will develop chronic low back pain, with symptoms persisting beyond 3 months. This group may be seen by the rheumatologist for treatment and/or to exclude low back pain resulting from inflammatory rheumatic conditions, in particular spondyloarthropathies.

With respect to rehabilitation in chronic low back pain (van Middelkoop et al 2011*), all patients should be instructed in self-care techniques. Any advice should stress the importance of maintaining activity as tolerated, with bed rest found not to improve either function or pain. Self-care education books based on evidence based guidelines are an efficient method to support the verbal information and advice provided by the clinician. There is no compelling evidence that lumbar supports are effective in patients with chronic low back pain. Home-based and supervised exercise programmes including muscle strengthening, spinal mobility, cardiorespiratory and mind-body exercises are effective and safe in patients with chronic low back pain. Back schools consist of an education and skills programme, including exercise therapy. Overall, the evidence for their effectiveness is inconsistent; they seem effective in an occupational but not in a primary healthcare setting. Referral to an interdisciplinary rehabilitation programme can be considered for patients with severe limitations of daily activities and societal participation (in particular paid work), in whom monodisciplinary treatment has failed.

Overall, there are no trials evaluating the optimal sequencing of non-pharmacological and non-surgical therapies, and there is no evidence to support the superiority of provision of care by specific clinicians. In general, clinicians should avoid prescribing interventions not proven to be effective. Factors to consider in advising a treatment regimen include cost, convenience, availability of skilled providers, and patient preference.

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SUMMARY POINTS

- Rheumatology rehabilitation aims to enable people with rheumatic conditions to achieve and maintain optimal functioning in their lives.
- Rehabilitation interventions are a core part of the management programme for most rheumatic patients, as they contribute to the reduction of pain and maintenance of function and social interaction, with a decisive impact upon quality of life.
- Exercises and education are the cornerstones of rehabilitation in rheumatic conditions. In addition, aids and devices and orthoses and, to a lesser extent, (electro)physical treatment modalities may play a role in the rehabilitative management of rheumatic conditions.
- Complex multidisciplinary rehabilitation programmes require a high degree of patient involvement, and a structured plan for goal setting and rehabilitation.
- The rheumatologist can safely use and prescribe a variety of rehabilitation modalities to his or her patient's benefit, with emphasis on education and other self-management dimensions, exercise, activity pacing, common orthoses, and footwear.
- The rheumatologist is an important ally of the patient in finding the most appropriate rehabilitation resources and evaluating their efficacy.

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A previous version was co-authored by Mari Klokkeud, Till Uhlig, Cornelia van den Ende

IN-DEPTH DISCUSSION I

Fibromyalgia

Fibromyalgia is defined by subjective symptoms with widespread pain as its central feature. Widespread pain is typically accompanied by several other symptoms, with emphasis on fatigue and unrefreshed waking. Fibromyalgia is currently attributed to a derangement of central pain modulation: patients have lowered mechanical and thermal pain thresholds, high pain ratings for noxious stimuli, altered temporal summation of pain stimuli and ineffective inhibitory descending pathways. [Goldenberg et al, 2004].

Assessment of starting points for rehabilitation

Full understanding of fibromyalgia requires a comprehensive assessment of pain, physical functioning, emotional and social functioning, pain cognitions and maladaptive pain behaviour [Carville et al, 2008]. The health consequences for the individual diagnosed with fibromyalgia may vary from tolerable nuisance caused by pain interfering with daily activities to severely limited activities and restrictions in participation due to the multiple symptoms associated with this condition. The goal of all rehabilitation interventions for patients with fibromyalgia should be to reduce the activity- and participation restrictions caused by symptoms such as pain and fatigue.

Initial assessment should include a thorough understanding of the patient's resources and barriers in all domains in the ICF, including body function-/structure, activity and participation. Patients should be asked about their goals for improvement, beliefs and behaviour with respect to the symptoms, possible barriers and obstacles towards recovery and increasing activity levels [Goldenberg et al, 2004]. Illness perceptions and beliefs might be of particular importance, though evidence is still lacking. For instance, beliefs that rest is the best therapy that physical activities increase pain and that pain is harmful are common among patients with fibromyalgia, thus inducing physical inactivity.

Non-pharmacological treatment

Two important starting points of treatment are the acknowledgment of patient's symptoms by the rheumatologist and the patient's motivation to actively participate in treatment. Education with reassurance regarding "no harm" caused by physical activity should be the focal point of treatment [Fitzcharles et al, 2012]. Confirming the diagnosis and describing its clinical picture [Table 1] can have a positive impact on patients with fibromyalgia, in particular giving them validation and reassurance [Arnold et al, 2012]. Optimal treatment of fibromyalgia requires a combination of pharmacological and non-pharmacological treatment modalities. Core elements of non-pharmacological treatment of fibromyalgia are education, exercise therapy and cognitive behavioural therapy (Nuesch et al 2013, Bernardy et al 2013, Häuser et al 2010). Treatment should be tailored to individual needs.

A stepped care approach may be a valuable tool to guide non-pharmacological management of fibromyalgia [Goldenberg et al, 2004], implying that simple measures and interventions such as education should be tried

initially and offered to all patients, while interventions in later steps are reserved for those whose condition was not controlled by lower step treatment options. If education is not sufficiently effective, patients may be referred to an exercise program utilizing a graded approach in case of physical inactivity or to a cognitive behavioural treatment delivered by a psychologist if maladaptive cognitions and pain behaviour are pronounced. For patients with persistent complaints or suffering with a relatively high level of psychological distress a multimodal approach combining exercise with cognitive behavioural therapy is warranted [Häuser et al, 2008; Van Koulil et al, 2010]. In general, prescription for assistive devices and adaptation of the physical environment is not recommended, as these might uphold undesirable pain behaviour and increase physical inactivity. Evidence about the effectiveness of dietary interventions and complementary therapies, including acupuncture and homeopathic remedies is inconclusive, but these may be of benefit to individual patients.

Education

Education may be provided on an individual basis by a rheumatologist or a specialized nurse for patients with limited complaints. Patients should be informed about the benign nature of the disease and the beneficial effects of activity pacing, physical activity and sleep hygiene. Patients should be encouraged to find the optimal balance between different types of exertion and rest periods and to establish consistent patterns of alternating periods of rest and relaxation with periods of activity. Sleep hygiene measures include, amongst others, a fixed routine of getting to bed and rising, a daily exposure to daylight and the avoidance of reading and watching television in bed. For patients with a wide range of complaints interfering with multiple domains of daily functioning, referral to a specialised nurse or, if available, an educational group is warranted. A structured educational program has beneficial effects on pain, sleep, fatigue and quality of life [Goldenberg et al, 2004].

Educational programmes should be tailored to individual informational needs. Beliefs and misunderstandings about the aetiology and the chronicity of pain should be explored and discussed. Pain education focuses on explaining basic pain physiology and the contrast between acute versus benign chronic pain. “Pain depends on where your brain thinks a problem is, not necessarily where it really is” and “Acceptance that chronic pain cannot be cured reduces its impact” could be useful key concepts to explain. Components of educational programmes should also include strategies to cope with symptoms such as fatigue, pain or sleep disturbances. To accomplish sustained behavioural changes the use of techniques enhancing a patient’s motivation, such as motivational interviewing, is advocated. Education is a continuous process and can be integrated with exercise and/or cognitive behavioural therapy.

Exercise

Aerobic exercise reduces pain, fatigue and depressed mood, and improves health related quality of life and physical fitness, at post treatment. Any type and intensity of aerobic exercise such as (brisk) walking, biking or swimming is suitable, if tailored to patient's preferences regarding physical activities. [Häuser et al, 2010]

Patients should be advised that exercise is not harmful; it does not cause any damage to the body. However, it should be noted that exercise might temporarily increase pain after each exercise session at the start of the programme. In contrast to healthy people, patients with fibromyalgia might experience a reduced threshold for pain immediately after exercise [Nijs et al, 2012]. As a result, the early stages of exercise therapy programmes are typically prone to dropouts. Therefore, a graded-activity approach is generally advocated [Häuser et al, 2010]. Graded activity is directed at increasing exercise tolerance by increasing the level of activities in a time-contingent way; that is, the gradual increase of intensity of exercises is not symptom-driven but time-scheduled following a pre-set scheme. The ultimate goal of graded exercise is to integrate these activities in the daily living of patients to ensure long-term compliance. Goals and the gradual increase of physical activities are determined and agreed upon for every individual patient. Because the experience of pain is assumed to lead to limited progress, the intensity of exercise and activities at the start of the treatment period is set below the patient's usual activity level, making it likely that the patient can complete the activities successfully.

Picture 1 Patients with fibromyalgia should be advised that exercise is not harmful, but a graded activity approach is advocated (Photo: National Advisory Unit on Rehabilitation in Rheumatology)



Continuation of exercise is necessary to maintain positive effects on pain [Nijs et al, 2012]. Therefore, education on strategies to integrate physical activity in daily life should be given. In addition, mind-body interventions such as relaxation exercises and Tai Chi exercises [Wang et al, 2010] to improve awareness and reduction of muscle tension may complement aerobic exercise.

Cognitive behavioural therapy (CBT)

Cognitive behavioural therapy is built upon the assumption that cognitions influence emotions and behaviour and vice versa. CBT aims to solve problems concerning dysfunctional emotions, behaviours and cognitions through a goal-oriented, systematic procedure. Cognitive behavioural therapy should be provided by skilled health professionals such as psychologists or health professionals with CBT education.

Several randomised clinical trials have explored the usefulness of cognitive behavioural therapy for managing fibromyalgia [Nuesch et al, 2013]. CBT interventions typically include three elements: (1) an educational phase—in which patients are familiarized with a model for understanding their pain, (2) a skills training phase—in which training is provided in a variety of cognitive and behavioural pain-coping skills (e.g. cognitive restructuring techniques, activity pacing, pleasant activity scheduling, problem-solving, sleep hygiene), and (3) an application phase—in which patients learn to apply their skills in progressively more challenging real-life situations [Williams et al, 2003]. Real-life situations include work, leisure and social relationships. CBT has shown small incremental benefits over control interventions in reducing pain, negative mood and disability at the end of treatment and at long-term follow-up [Bernardy et al, 2013]

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IN-DEPTH DISCUSSION II

Footwear in rheumatic diseases

This in-depth discussion will address two different instances where the rheumatologist should take a professional interest in footwear:

1. Foot problems in rheumatic diseases, which can be ameliorated by appropriate footwear
2. The use of footwear to improve rheumatic conditions in anatomical regions other than the feet.

MANAGEMENT OF FOOT PROBLEMS IN RHEUMATIC DISEASES

Foot problems in rheumatic diseases

Foot involvement is common in a number of rheumatic diseases and tends to have a considerable impact upon patients' quality of life, due to direct interference with mobility and societal participation.

Approximately 80-90% of individuals with rheumatoid arthritis (RA) are reported to have symptoms in the feet [Grondal et al, 2008]. The most frequent foot problems in RA include pain on the soles of the feet, particularly in the metatarsal areas. This may be due to a number of reasons. In the early phases of the disease it is most usually be due to synovitis of the metatarsophalangeal (MTP) joints. In later phases, dorsal subluxation of the proximal phalanges with anterior displacement of the fat pad, together with collapse of the transverse arch of the forefoot may lead to bursitis, callosities and skin breakdown, causing pain and difficulty in walking. Hallux valgus and cock-up deformities or claw toes of the lesser rays associated with plantar plate and structural joint damage may produce pressure against the shoe (Figure 1). In the hindfoot and midfoot, a complex deformity observed in advanced RA or psoriatic arthritis seems to start with subluxation of the talo-navicular joint, which causes a flattened medial arch with subsequent pronated midfoot and lateral deviation of the forefoot. In extreme cases the foot comes to rest medially, on the subluxed the talonavicular joint (Figure 2), with pain as an inevitable consequence. Another common deformity in late stages of the disease is hind foot valgus due to subtalar joint involvement (Figure 3). Apart from complaints associated with deformities, patients with RA may have foot problems related to the skin (ulceration), nails (infection), vascular (vasculitis) and/or neurological symptoms (sensory loss), which may also contribute to limitations of foot function and gait [Williams et al, 2011].

The most common site of involvement in the osteoarthritic foot is the first MTP joint. Examination reveals restricted mobility of the joint, particularly in extension (hallux rigidus). A hallux valgus with bunion formation is also frequently seen in OA. There has been increasing interest in osteoarthritis of the midfoot, which has been shown recently to be far more common than thought previously, and is linked to trauma, inflammatory arthropathy, mechanical stress and idiopathic osteoarthritis [Roddy et al 2013].

Figure 1



Figure 2



Figure 3



In ankylosing spondylitis, two common sites for enthesitis are under the heel where the plantar fascia attaches and behind the heel at the Achilles tendon insertion [Clark, 1996].

Hallux valgus, flat feet, pes cavus and plantar fasciitis can present in connection with rheumatic conditions or as independent disorders.

Management of the rheumatic foot

Any foot management strategy starts with an appropriate assessment [Williams et al, 2011; Clark, 1996; Helliwell et al, 2011; Helliwell, 2003; Rao et al, 2012], which should take not more than 1 minute [Helliwell et al, 2011]. History taking should include an evaluation of the rheumatic condition and general health, foot symptoms, activities of daily living and lifestyle [Williams et al, 2011]. The physical examination starts with a simple, but systematic observation of the overall foot shape and palpation of the relevant joint margins, soft tissue structures and insertions, to identify inflamed or damaged tissues and a careful inspection of the skin and nails. Next, active movement of the foot is evaluated, assessing the direction, range and quality of motion and any related pain. In addition, clinician mediated passive motions of ankle, subtalar, midfoot and forefoot joints, noting pain and again the direction, range and quality of movement and gait are performed [Williams et al, 2011; Helliwell et al, 2011]. The assessment is completed with an inspection of the patient's footwear. Foot-specific questionnaires can also be used to quantify the severity of pain and functional disability [Rao et al, 2012].

When considering adaptations of footwear or appliances for the rheumatic foot it is important to consider the potential mechanisms through which they can help:

- relieve excessive pressure
- reduce shock and shear
- accommodate, correct or support deformities
- control or limit painful motion of joints [Clark, 1996].

Table 1 summarizes the possible functions of special shoes and foot orthoses. Table 2 gives examples of common rheumatic foot problems and possible solutions [Beardmore, 2001].

The effects of adapted footwear, insoles and inlays in rheumatic diseases have been assessed in several systematic reviews [Riskowski et al, 2011; Hennessy et al, 2012; Clark et al, 2006; Hawke et al, 2008], which included, however, a limited number of high quality randomized controlled trials.

For most patients, the use of “off-the-shelf” or stock footwear will be sufficient to suit their needs, whereas a limited number of patients are in need of custom-made or bespoke shoes. Patients may benefit with advice regarding the selection of shoes from very early on in their disease course, even before deformity makes the need obvious.

Generally desirable features of shoes for patients with rheumatic conditions are:

- a deep and wide toe box to accommodate toes that are flexed up,
- sufficient width to accommodate the splayed forefoot,
- sufficient plantar support, in particular a supportive medial arch,
- thick, soft sole with the ability to absorb and distribute pressures (e.g. by means of air or synthetic foams) and
- non-raised and broad-based heel, maximum height 2-3 cm,
- the shoe should be laced or otherwise fastened securely on the foot and has enough room to place devices in it,
- the shoes should be comfortable and keep dry inside.

Table 1. Function of special shoes and foot orthoses

1. To accommodate deformities and relieve pressure
2. To support the biomechanical mal-alignment and reduce associated abnormal compensatory movements.
3. To provide cushioning and shock absorption.
4. To redistribute weight bearing to a more normal pattern throughout the gait circle.
5. To support the hindfoot and the longitudinal arch in order to reduce excessive pronation.
6. To support the transverse arch and provide lift to the metatarsophalangeal joints, reducing weight bearing on these joints.
7. To decrease excessive and/or aggravating articular movement during weight bearing.

Adapted from: Clark BM. Foot management and ambulatory aids. In: Wegener ST, Belza BL, Gall EP (eds). Clinical care in the rheumatic diseases. American College of Rheumatology, Atlanta, 1996.

Table 2. Shoe specifics for common rheumatic foot problems

Condition	Clinical Problem	Solution
RA / OA	Hallux valgus with bunion	Wide, soft, deep toe box, stretch medial leather
RA	Cock-up toes	Deep toebox, soft leather upper, stretch upper, donut pads, sandals
RA	Valgus hindfoot	Medial wedge/medial arch support, lace-up canvas ankle support, ankle-hindfoot orthosis
RA	MTP subluxation with callosities	Metatarsal bar, metatarsal pad or sole inserts aiming to redistribute pressure under the foot and/or limit intersegmental motion
OA	Hallux rigidus	Metatarsal bar, rigid sole, rocker-bottom sole to limit stress and motion through the first metatarsophalangeal joint
AS	Heel pain	Rubber or plastic heel cups, sponge inserts with a hole cut

Adapted from: Beardmore T. Rehabilitation. In: Klippel JH, Crofford LJ, Stone JH, Weyand CM (eds). Primer on the rheumatic diseases. 12th edition. Arthritis Foundation, Atlanta, Georgia, 2001.

Please note that commonly available sports shoes, walking shoes or off-the-shelf shoes for people with foot problems are frequently enough to fulfil these requirements (Figure 4). Sometimes individually-tailored shoe modifications are necessary.

In RA, extra-depth shoes or insoles can, in general, be expected to offer benefit upon pain and functional ability. External shoe modifications may consist of rocker soles, extended steel shanks, stabilizers, wedges or extensions. A toe rocker-soled shoe is thought to reduce pain by decreasing forefoot loading and promoting a normal heel-toe motion during gait (Figure 5). With disease progression, patients with RA move from a heel-toe rolling gait to a more shuffled step with a delayed heel lift and the toe rocker-soled shoe may slow this progression [Riskowski et al, 2011].

Figure 4



Figure 5



Insoles may be designed to provide cushioning and shock absorption, to relieve pressure and redistribute weight bearing and to relieve pain and swelling. Insoles can either be commercially available devices or may be custom made. They may be made of soft, compressible material, or more rigid material, requiring the making of a cast of the foot first (Figure 6). Metatarsalgia and medial arch collapse are the most common indications for insoles in patients with RA. There is some evidence that rigid orthoses used in fairly early disease slow progression of deformity, reduce pain and functional limitation [Woodburn, 2002]. Overall, the recommendation is that foot orthotics should be custom-designed to meet the individual's unique needs to reduce pain [Hennessy et al, 2012].

Callus over the plantar metatarsal area should be removed with caution, as it may have a protective role [Williams et al, 2011]. If a debridement is considered, pressure-relieving insoles should be provided in order to protect the foot from the risk of ulceration [Williams et al, 2011]. The effect of debridement is although not clear [Siddle et al, 2013].

The hindfoot valgus deformity in RA with pronation in the midfoot needs special attention. As long as this deformity is correctable, patients may have some benefit from a medial arch support [Woodburn, 2002]. However, when there is a fixed valgus deformity of the hindfoot, which is the case in most RA patients, such a device is not able to correct the deformity, and will increase the risk of pressure sores of the skin under the medial arch.

Apart from insoles, patients may benefit from small inserts such as foam rubber spacers and doughnut hole pads, dealing with overlapping toes and pressure points. Custom made shoes are needed in case of severe foot deformities (Figure 7). As “ready-made” orthopaedic shoes will most likely not meet individual requirements, they should not be advised in these cases.

Figure 6



Figure 7



FOOTWEAR FOR RHEUMATIC CONDITIONS IN OTHER ANATOMICAL SITES THAN THE FEET

Overall, the literature suggests that in patients with knee OA, footwear can affect knee joint loads, whereas in hip OA the evidence is scanty [8]. Nevertheless, based on expert opinion, it is recommended that, in both hip and knee OA, clinicians should evaluate the patient's feet and shoes when exploring treatment strategies. In general, patients with hip and knee OA should be advised to wear shoes with thick but soft soles, and minimally raised heels. In patients with medial tibiofemoral knee OA with varus deformity, full-length lateral wedged insoles could be considered [Brouwer et al; 2005] although many patients do not tolerate valgus

wedges well. In patients with lateral tibiofemoral OA with valgus deformity or patients with RA and knee involvement, where valgus deformity is more common than varus deformity, medial wedged insoles can be recommended.

Shoe lifts by means of an internal or external pad (or both) may be used to correct leg length discrepancy, especially if this has developed later in life, e.g. after surgery or a fracture. In adults, minor length discrepancy (asymmetries between 0.75 and 2.50 cm) can be corrected, with a generally accepted extent of 50% of the discrepancy. Shoe lifts are inexpensive and can be removed if they are not effective.

PRESCRIBING FOOTWEAR

Patients with rheumatic conditions and foot problems or other symptoms which could benefit from appropriate footwear should be referred to a podiatrist or orthopaedic shoemaker in an appliance department where stock or bespoke footwear with insoles are provided. Specialist rheumatology podiatry and multidisciplinary approaches to foot problems are only available in a limited number of places [Helliwell, 2003]. From the literature it is known that much therapeutic footwear will end up as “shoes in the cupboard” [Brouwer et al, 2005; de Boer et al, 2009]. Reasons for not using orthopaedic footwear include a negative evaluation (ease of use, dislike of appearance, not fitting well and lack of comfort) [De Boer et al, 2009] or a lesser need [Van der Esch et al, 2003]. Specialist therapeutic footwear impacts more on the patients’ body image and emotions than previously acknowledged [Williams et al, 2007a]. Therefore, patients must be effectively engaged and empowered in the choice of footwear as an acceptable intervention for their foot problems [Williams et al, 2007b]. To ensure that the patient is satisfied with the result of the intervention, multiple visits may be necessary.

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Glucocorticoids

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LEARNING OBJECTIVES

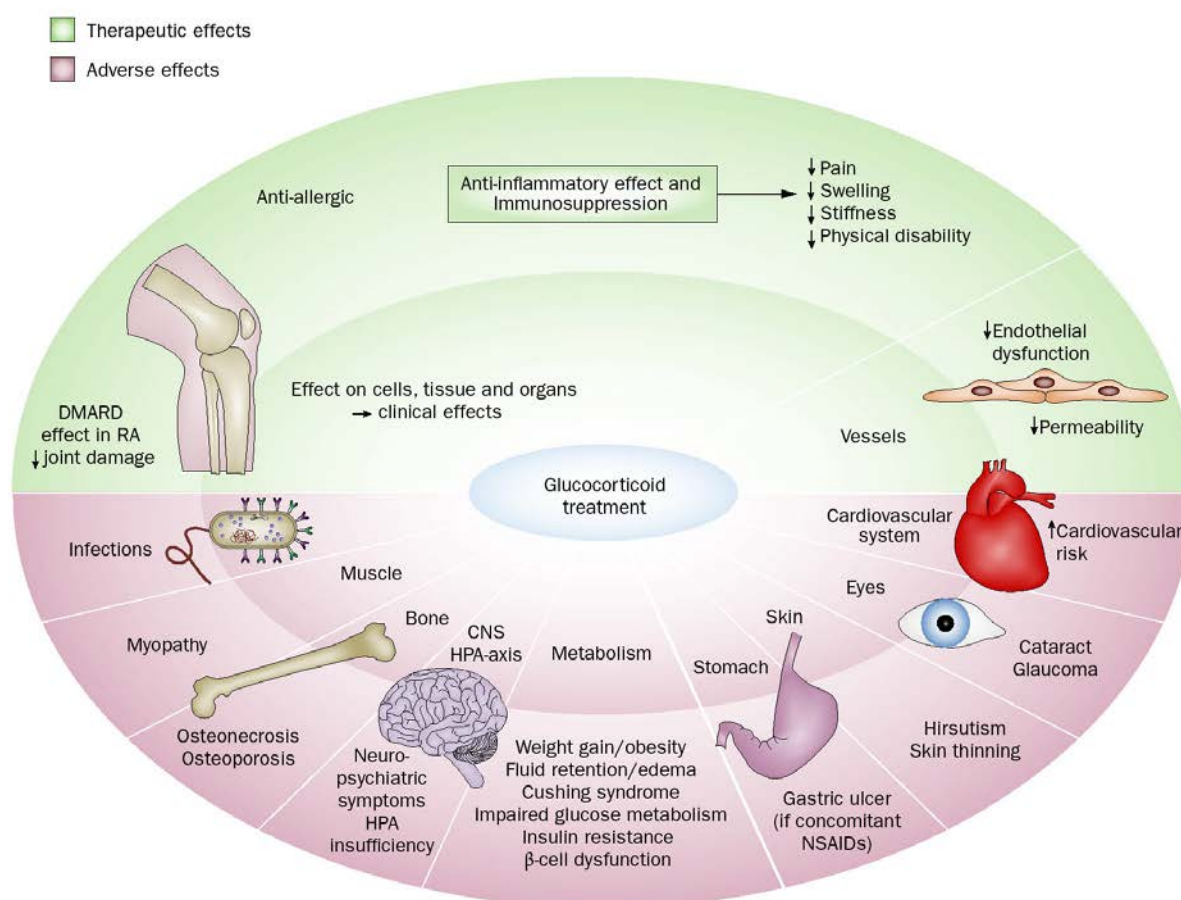
- ➔ Describe the pharmacologic characteristics of glucocorticoids
- ➔ Explain the different mechanisms of glucocorticoid actions
- ➔ Evaluate the therapeutic effects of glucocorticoids
- ➔ Clarify the appropriate terminology for glucocorticoid treatment
- ➔ Give examples of treatment regimens for specific clinical situations
- ➔ Describe the adverse effects of glucocorticoid therapy
- ➔ Evaluate the need for protective measures and monitoring
- ➔ Outline approaches to the development of new glucocorticoids

1 Introduction

Glucocorticoids have become the most important and frequently used class of anti-inflammatory drugs since their introduction into clinical practice in 1948. The estimated prevalence of the use of glucocorticoids in the general adult population ranges from 0.5–1.2% (Overman et al, 2013). The 1.2% prevalence is an estimate from the USA, corresponding to 2,513,259 individuals, mostly chronic glucocorticoid users, with a non-significant downward trend of glucocorticoid use from 1999 to 2008 (Overman et al, 2013). For patients with rheumatoid arthritis (RA), worldwide estimates of the percentages on treatment with glucocorticoids range from 15% to 90% (Sokka et al, 2009). Glucocorticoids are relatively inexpensive drugs, but due to the great volume prescribed, the total financial market size is huge.

The major reasons for the widespread use of these drugs are—next to low cost—their versatility and effectiveness, although, especially if applied at higher dosages and/or for longer treatment durations, glucocorticoids have a wide range of adverse effects (figure 1).

Figure 1 Broad spectrum of effects of glucocorticoids. CNS, central nervous system; DMARD, disease-modifying antirheumatic drug; HPA, hypothalamic–pituitary–adrenal; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis. (Reproduced with permission from Hoes et al. *Nat Rev Rheumatol* 2010;6:693–702.)



There have been important developments in the past decades. Joint sparing capacities of glucocorticoids in early RA have been recognised. The increased understanding of basic inflammatory mechanisms provides a basis for the development of new drugs. New applications have been introduced and international guidelines on therapy and management have been created, enabling safer use of these drugs. In this chapter, we focus on the characteristics of glucocorticoids and the therapeutic effects and adverse effects which are frequently seen in clinical practice.

2 Characteristics of glucocorticoids

2.1 Structure

Cholesterol is the precursor of all steroid hormones, such as sex hormones, mineralocorticoids and glucocorticoids. The term 'steroid' refers to the basic sterol skeleton. Sex hormones are predominantly produced in the gonads, but also in the adrenal cortex. Mineralocorticoids, of which aldosterone is the main natural hormone are synthesised in the adrenocortical zona glomerulosa. Cortisol (hydrocortisone), the major endogenous glucocorticoid is produced in the adrenocortical zona fasciculata.

2.2 Classifications

Classification of steroids into mineralocorticoids and glucocorticoids is not completely accurate, because the groups slightly overlap (eg, endogenous glucocorticoids also have some mineralocorticoid effects). However, synthetic (exogenous) glucocorticoid drugs are more restricted to glucocorticoid effects only; therefore it is considered appropriate to use the term 'glucocorticoids' when referring to glucocorticoid drugs (Buttgereit et al, 2002*).

Glucocorticoids can also be classed according the duration of their effect or their solubility in water and other characteristics (table 1). Even though experimental and clinical evidence for the preciseness of their relative potencies is weak, and although at high and very high dosages non-genomic effects also occur which may change the relative potencies of the different glucocorticoids, these estimated potencies are useful in daily clinical practice as a general therapeutic guideline.

Imprecise semi-quantitative textual labelling of glucocorticoid doses warranted a standardised dose classification (table 2) (Buttgereit et al, 2002*); it is based on the extent of cytosolic glucocorticoid receptor (GR) occupation of glucocorticoids and genomic and non-genomic effects at different dosages. Precise description of glucocorticoid therapy should not only include the dosage and type of drug, but also the route of administration, the timing of administration during the day, the proposed duration of the therapy, and the cumulative dosage, where appropriate.

Table 1: Classification according pharmacodynamics of glucocorticoids used in rheumatology

	Equivalent glucocorticoid dose (mg)	Relative glucocorticoid activity	Relative mineralocorticoid activity ¹	Protein binding ²	Half-life (hr) in plasma	Biological half-life (hr)
<i>Short-acting</i>						
Cortisone	25	0.8	0.8	-	0.5	8-12
Cortisol	20	1	1	+++	1.5 - 2	8-12
<i>Intermediate-acting</i>						
Methylprednisolone	4	5	0.5	-	> 3.5	18-36
Prednisolone	5	4	0.6	+	2.1 - 3.5	18-36
Prednisone	5	4	0.6	++	3.4-3.8	18-36
Triamcinolone	4	5	0	+	2 - >5	18-36
<i>Long-acting</i>						
Dexamethasone	0.75	20-30	0	+	3 - 4.5	36-54
Betamethasone	0.6	20-30	0	+	3 - 5	36-54

¹ clinical signs: sodium and water retention, potassium depletion

² symbols: -= none; += high; ++= high to very high; +++= very high

Table 2: Classification of glucocorticoid dosages

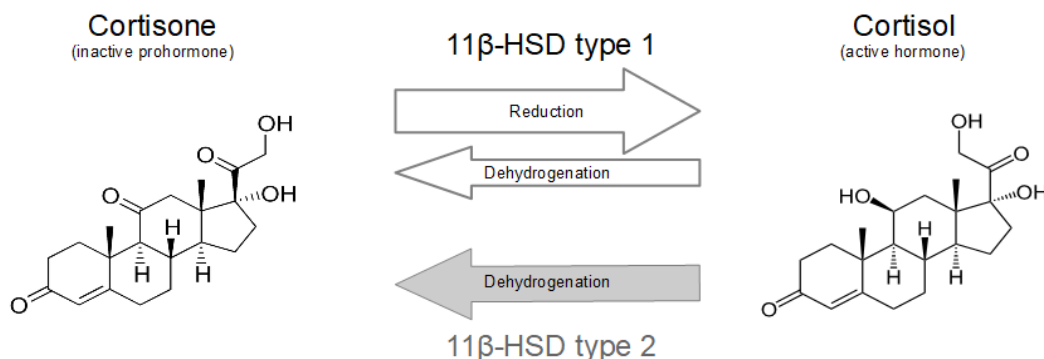
Low dose	≤ 7.5 mg prednisone equivalent per day
Medium dose	> 7.5 mg and ≤ 30 mg prednisone equivalent per day
High dose	> 30 mg and ≤ 100 mg prednisone equivalent per day
Very high dose	> 100 mg prednisone equivalent per day
Pulse therapy	≥ 250 mg prednisone equivalent per day for one or a few days

2.3 Conversion into active hormones and vice versa

Cortisone and prednisone are inactive prohormones. They are chemically reduced in the liver into their active forms cortisol and prednisolone, which have high affinity for the GR. This generation of biologically active glucocorticoids from their inactive forms is promoted by the reductase action of the intracellular enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD) type 1.

The same enzyme can, by dehydrogenation, also promote the reverse reaction, leading to inactivation of active glucocorticoids. In contrast, 11 β -HSD type 2 has dehydrogenase activity only, so it only catalyses the conversion of active glucocorticoids to their inactive forms (Box 1).

Box 1 Reduction of the inactive prohormone cortisone to the active hormone cortisol by the enzyme 11 β -HSD type 1. An inactivation of cortisol is catalysed by the dehydrogenase activity of 11 β -HSD type 1 and type 2.



In different tissues, local balance between the intracellular enzymes 11 β -HSD type 1 and type 2 might modulate intracellular glucocorticoid concentrations and thus tissue sensitivity for glucocorticoids (Buttgereit et al, 2008b). Synovial tissue metabolises glucocorticoids via the two 11 β -HSD enzymes, with the net effect being glucocorticoid activation; this increases with inflammation. This endogenous glucocorticoid activation in the joint is likely to have an impact on local inflammation and on bone of the joint (Hardy et al, 2008).

In the case of serious liver insufficiency this conversion is less efficient, and the active glucocorticoids should be prescribed instead of the prohormones.

2.4 Water and lipid solubility

Glucocorticoids in free form (as alcohol) are insoluble in water and can be used in tablets. Absorption occurs presumably within 30 min and the bioavailability of prednisone and prednisolone is high. Glucocorticoid esters also have limited water solubility but are lipid soluble and therefore are suitable for intramuscular, intralesional and intra-articular use. Glucocorticoid salts are water soluble and thus can also be administered intravenously. For local (intra-articular or intralesional) treatment, less water soluble preparations are to be preferred, since the less water soluble they are, the longer the duration of the effect.

2.5 Protein binding

Only 5–10% of the natural glucocorticoids circulate in free form and are biologically active. The remaining are bound to proteins, primarily transcortin (also called glucocorticoid-binding globulin) and albumin. The half-life is dependent on protein binding, distribution to different body compartments which also depends on protein binding, affinity for the cytosolic GR (which is higher in synthetic glucocorticoids), and the rate of metabolism. Patients with low levels of plasma proteins, which can be caused by liver diseases or chronic active

inflammatory diseases, are therefore more susceptible to effects and adverse effects, and dose reduction should be considered.

2.6 Metabolism and drug interactions

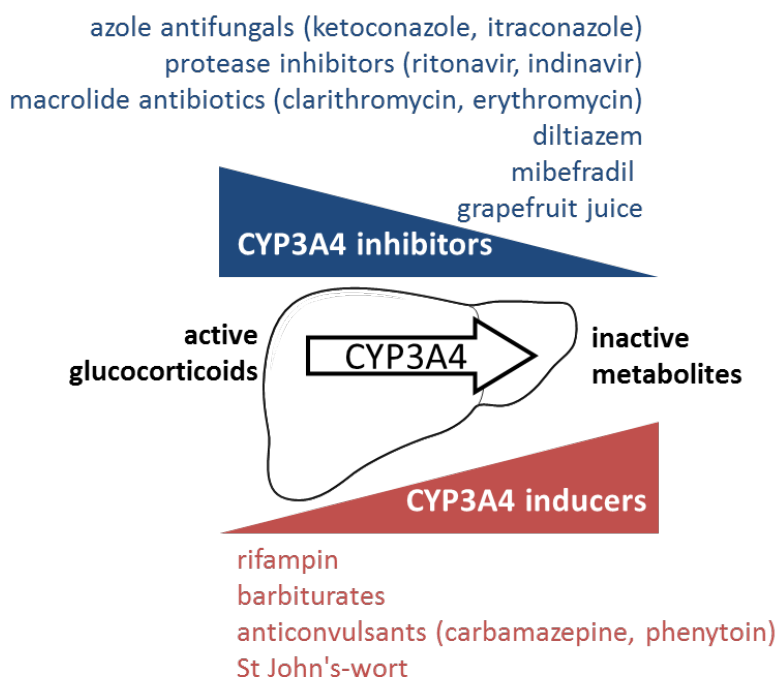
Pharmacologically active glucocorticoids are metabolised by isozymes of the cytochrome P450 (CYP) in the liver into inactive metabolites, which are excreted in the urine. As a consequence, patients with renal or liver disease may have increased half-lives of active glucocorticoids, resulting in increased effects at a given dose, but in general patients with renal insufficiency do not require dosage adjustment. Prednisolone is partially removed by haemodialysis.

Drug interactions are based on induction or inhibition of CYP enzymes. CYP3A4 inducers like rifampin increase the breakdown of glucocorticoids, diminishing their effects to a clinically relevant extent (Schulte et al, 1987). . On the other hand, concomitant therapy with inhibitors of CYP3A4 might result in an increased risk of (adverse) effects (Varis et al, 2000a; Varis et al, 2000b) (Figure 2). To complicate matters, ketoconazole in doses of 400–800 mg per day inhibits the synthesis of cortisol induced by adrenocorticotrophic hormone (ACTH) and is used to treat Cushing disease (the pituitary-dependent cause of Cushing syndrome). However, several CYP3A4 inhibitors are probably not that important for prednisone and prednisolone metabolism; also the effect of grapefruit juice intake is likely to be of limited clinical significance (Varis et al, 2000c).

Concomitant therapy with prednisolone and cyclosporine may result in higher plasma prednisolone concentrations, whereas concomitant therapy with methylprednisolone and cyclosporine may result in increased cyclosporine concentrations. This is probably caused by competitive inhibition of microsomal liver enzymes. Sulphasalazine has been reported to increase the sensitivity of immune cells for glucocorticoids (Oerlemans et al, 2007), which could be beneficial, but the clinical relevance of this finding has yet to be confirmed.

2.7 Sensitivity and resistance to glucocorticoids

The several potential mechanisms involved in the variability of glucocorticoid sensitivity have not all been fully elucidated (Barnes and Adcock, 2009). Modulation of these mechanisms could potentially reduce the proportion of patients who fail or react less favourably as expected on these drugs. Also, more research on hereditary glucocorticoid resistance (rare) and the antagonising actions of cytokines is warranted.

Figure 2 Drug interactions based on induction and inhibition of CYP3A4

Summary : The major endogenous glucocorticoid cortisol is produced in the adrenocortical zona fasciculata from the steroid precursor cholesterol. Two different types of the enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD) are responsible for the inactivation of cortisol to cortisone and/or vice versa. Pharmacologically glucocorticoids are classified based on their duration of action. Other relevant pharmacodynamic features are mineralocorticoid activity, protein binding, half-life and solubility. Drug inactivation by members of the cytochrome P450 superfamily takes place in the liver.

3 Basic mechanisms of glucocorticoids

Glucocorticoids influence the transcription of about 1% of the entire genome. This results in a very broad spectrum of effects induced by a single class of endogenous hormones and hormonal drugs.

3.1 Genomic and non-genomic mechanisms

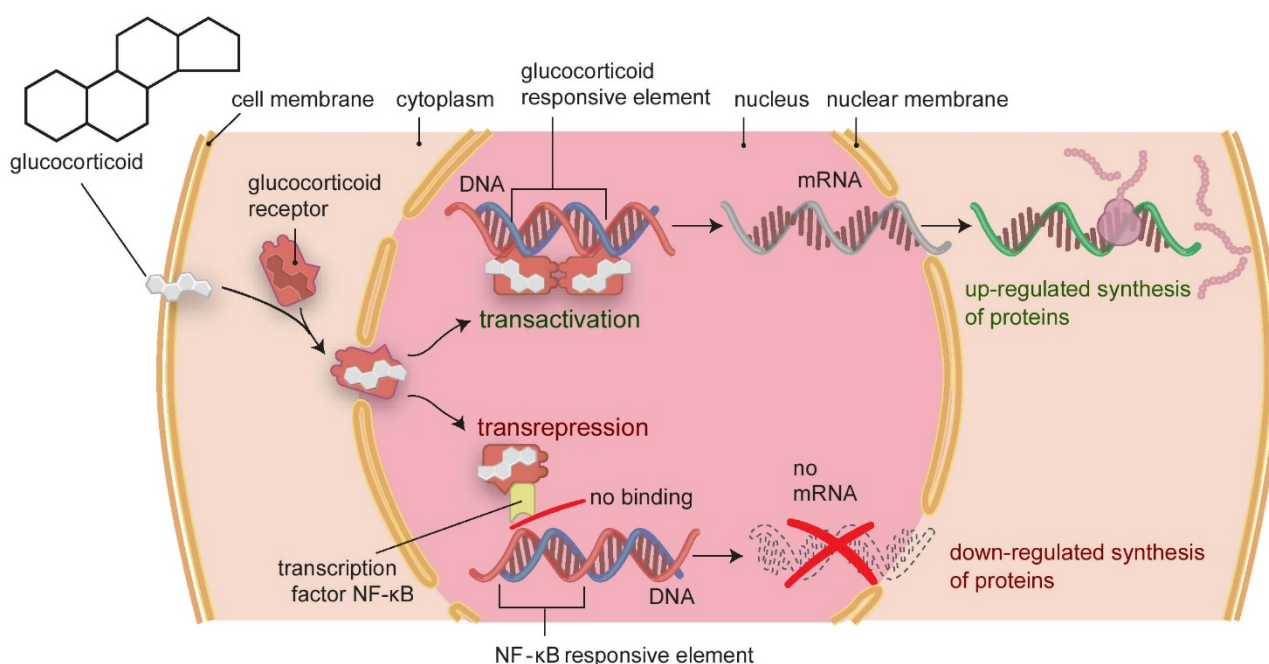
Effects of glucocorticoids are mediated via classic genomic mechanisms and via non-genomic mechanisms.

3.1.1 Genomic mechanisms

Anti-inflammatory and immunomodulatory effects of glucocorticoids are predominantly based on genomic mechanisms (Buttgereit et al, 2004) (figure 2). Unbound glucocorticoid molecules can cross the cell membrane, because of their lipophilic structure and low molecular weight. They bind to the α isoform of cytosolic GCRs, which is present in almost all tissues; the β isoform is not capable of binding to glucocorticoids.

The cytosolic GCR is a multiprotein complex with several heat shock proteins attached as chaperones, which are shed after binding of the glucocorticoid. A receptor–glucocorticoid complex is formed and rapidly translocated into the nucleus. In the nucleus, this GCR–glucocorticoid complex can influence gene expression via binding as a dimer to specific consensus sites in the DNA, resulting in induction of regulatory protein synthesis. This effect is called transactivation. GCR–glucocorticoid complexes as monomers also interact with transcriptional factors (such as activator protein-1, interferon regulatory factor-3 and nuclear factor kappa B), leading to inhibition of binding of these transcriptional factors to their consensus sites in the DNA. This process results in down-regulation of predominantly pro-inflammatory protein synthesis and is called transrepression.

Figure 3 Genomic actions of glucocorticoids. *Glucocorticoid binds to the glucocorticoid receptor (GR) in the cytoplasm. This complex migrates into the nucleus. Activation of transcription (transactivation) by binding of GR–glucocorticoid complex dimers to glucocorticoid-responsive elements of DNA up-regulates synthesis of regulatory proteins, thought to be responsible for metabolic effects and also some anti-inflammatory/immunosuppressive effects. Interaction of GR–glucocorticoid complex monomers with pro-inflammatory transcription factors, such as activator protein-1, interferon regulatory factor-3, and nuclear factor-kappa B (NF-κB) leads to inhibition of binding of these transcriptional factors to their DNA consensus sites (for NF-κB: NF-κB-responsive elements). Thus the transcription of these pro-inflammatory transcription factors is repressed. This is called ‘transrepression’ and down-regulates synthesis of predominantly inflammatory/immunosuppressive proteins. (Adapted from Jacobs JWG, Bijlsma JWI. Glucocorticoid therapy. In: Firestein CS, et al, eds. Kelley and Firestein’s textbook of rheumatology. 10th edn. Philadelphia: Saunders Elsevier, 2017:932–57.)*



Genomic mechanisms occur with all dosages of glucocorticoid therapy, even at very low ones. Genomic effects are relatively slow, and significant changes in regulatory proteins are seen after at least 30 min. Although between 10 and 100 genes per cell are directly regulated by glucocorticoids, many genes are regulated indirectly through interaction with transcription factors and co-activators. Therefore, it may take hours or up to days to realise maximal therapeutic effects.

Glucocorticoids also act through post-transcriptional and post-translational mechanisms. They decrease the stability of messenger RNA through the induction of ribonucleases. This mechanism could be an explanation for the inhibition by glucocorticoids of synthesis of interleukin (IL)-1, IL-6, granulocyte-macrophage colony-stimulating factor, and inducible cyclo-oxygenase (COX) (Ristimäki et al, 1996)—that is, COX-2.

It has been suggested that transrepression is responsible for several desirable anti-inflammatory and immunomodulating effects, whereas transactivation is associated with frequently occurring side effects as well as with some immunosuppressive activities. If this hypothesis is true, selective GR agonists (SEGRAs) exerting almost exclusively transrepression and no or very limited transactivation would show glucocorticoid therapeutic activity and fewer side effects. However, a study in a mouse strain with a deficiency to form dimer GR–glucocorticoid complexes, and thus with a transactivation deficiency, showed—along with a failure of glucocorticoids to exert a full anti-inflammatory response—classic side effects in these mice, such as osteoporosis (Vandevyver et al, 2013). Furthermore, in an asthma trial the effect of a SEGRA was disappointing (Bareille et al, 2013). Several clinical trials to investigate the efficacy and safety of different SEGRA formulations are ongoing or completed, but due to the lack of publications of the study results, clinical evidence is still missing.

3.1.2 Non-genomic mechanisms

Although clinically the effects of non-genomic mechanisms cannot be discriminated from effects of genomic mechanisms, effects of non-genomic mechanisms occur more rapidly, even within seconds or minutes. Today, non-genomic mechanisms are classified into 3 groups

- mechanisms caused by the release of proteins from the cytosolic GR multi-protein complex after GC binding
- interaction with membrane-bound GC receptors which are present on peripheral blood mononuclear cells (Buttgereit et al, 2011)
- non-specific GC effects resulting from the interaction of GC - especially at very high concentrations - with cellular membranes.

Most non-genomic mechanisms still need to be unravelled; hopefully this will yield therapeutic targets for development of new drugs.

Clinical evidence of the existence of non-genomic effects includes the spontaneous improvement of clinical symptoms after the application of high doses, immediate onset of action in the treatment of anaphylaxis and rapid effects following topical application (Buttgereit and Scheffold, 2002).

3.2 Immunosuppressive and immunomodulatory actions

Glucocorticoids reduce activation, proliferation, differentiation, and survival of different inflammatory cells, such as different types of leucocytes, endothelial cells and fibroblasts via manifold mechanisms (Coutinho and Chapman, 2011). This is the main glucocorticoid therapeutic action in most rheumatic diseases. In general, the higher the dose of glucocorticoids, the stronger the effect. Therefore, low doses can be effective in inhibiting signs and symptoms of joint inflammation in RA, but high doses and pulses of glucocorticoids are needed to treat life-threatening vasculitis or other very serious situations.

The absolute numbers of most inflammatory cell types in the body decrease with glucocorticoid administration. There are less circulating monocytes/macrophages and their synthesis of pro-inflammatory cytokines and prostaglandins as well as their expression of MHC class II molecules and Fc receptors are reduced. The number of circulating T-cells and their production and action of different cytokines (e.g. IL2) are diminished. The numbers of eosinophil and basophil granulocytes are reduced, whereas the number of circulating neutrophils is increased. This is the result of down-regulation of adhesion molecules by glucocorticoids, thereby preventing migration of neutrophil granulocytes from the circulation to inflammatory sites. The number of B cells and immunoglobulin production are hardly affected by glucocorticoid treatment, but the actions of glucocorticoids on B cells are not well understood (Baschant et al, 2012).

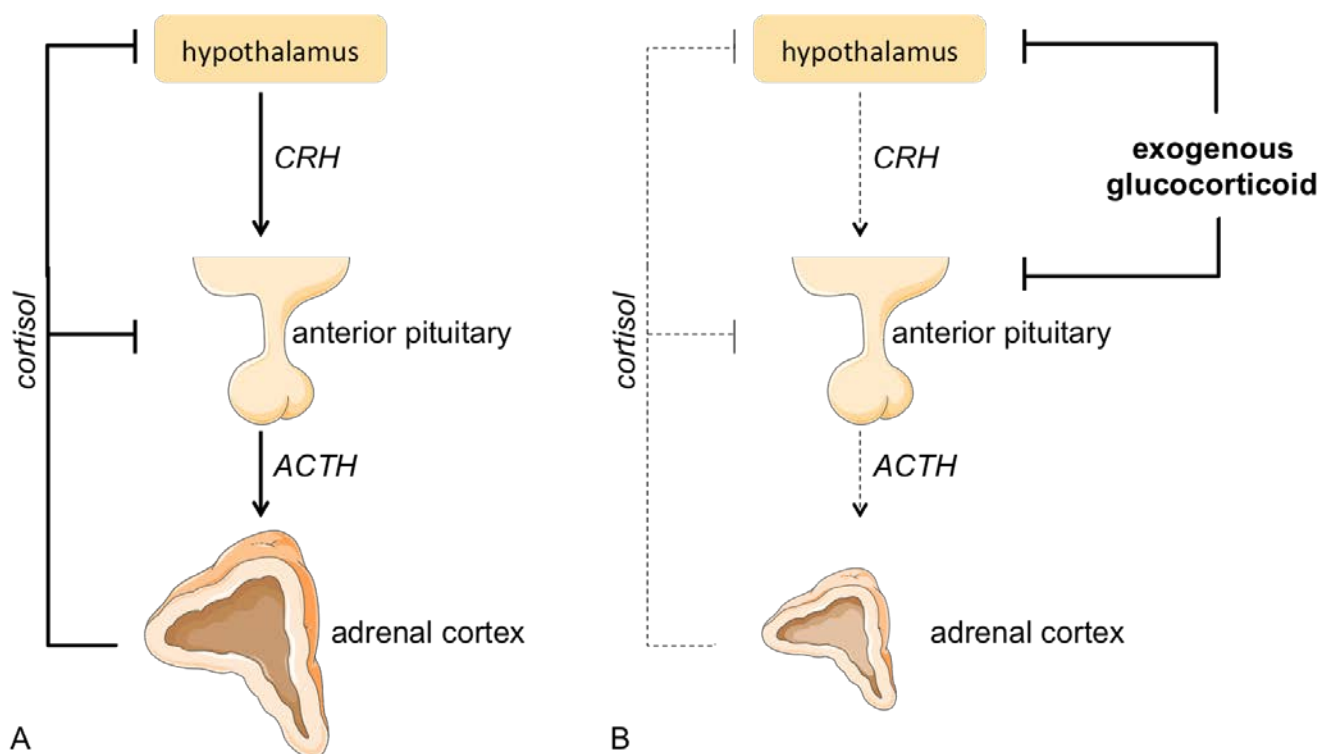
The effects of glucocorticoids on cytokine production and levels are complex. Especially in higher doses, glucocorticoids inhibit synthesis of most of the pro-inflammatory cytokines which play important roles in the development of synovitis, cartilage degradation and bone erosions, such as IL-1 β , IL-2, IL-3, IL-6, tumour necrosis factor α (TNF α), interferon- γ (a typical T helper (Th)1 cytokine), and IL-17 (a Th17 cytokine). Glucocorticoids stimulate or do not affect production of Th2 and regulatory cytokines such as IL-4 (a typical Th2 cytokine), IL-10 and IL-13, which are related to B cell activation and extra-articular features of RA. In macrophages, glucocorticoids at low concentrations enhance secretion of nitric oxide—via the cytokine-inducible form of nitric oxide synthase—and expression of pro-inflammatory cytokines, but glucocorticoids at high concentrations inhibit these (Lim et al, 2007). Glucocorticoids also inhibit the expression of adhesion molecules, such as intercellular adhesion molecule-1 and E-selectin, and chemotactic cytokines such as IL-8 and macrophage chemo-attractant proteins. Glucocorticoids inhibit COX-2 in arachidonic acid metabolism, decreasing levels of inflammatory prostaglandins and destructive proteinases.

3.3 Suppression of hypothalamic–pituitary–adrenal axis

Administration of glucocorticoids leads to negative feedback on the hypothalamus and pituitary glands, resulting in less secretion of corticotropin-releasing hormone (CRH) and ACTH, respectively. As a result, the cortisol secretory capacity of the fasciculate-reticularis zone of the adrenal cortex may decrease, since this inner cortical zone producing cortisol is dependent on ACTH for structure and function. Chronic suppressed

cortisol production leads to atrophy of the fasciculate-reticularis zone and clinically to adrenal insufficiency (figure 4), referred to as tertiary adrenal insufficiency, due to the inhibition of CRH release (Charmandari et al, 2014). When ending glucocorticoid therapy or in case acute stress or injury it is important to bear this in mind to prevent an adrenal crisis (also known as Addisonian crisis) (see also 5.8). The outer glomerulosa zone is not dependent on ACTH and therefore its ability to produce mineralocorticoids is not impaired, in contrast to when there is primary adrenal insufficiency, for example, by autoimmune adrenal damage (morbus Addison). However, hyponatraemia can be a symptom of tertiary adrenal insufficiency resulting from increased ADH release (Grammatiki et al, 2016).

Figure 4 *Suppression of the hypothalamic-pituitary-adrenocortical axis. In healthy individuals (A) CRH (corticotropin-releasing hormone) from the hypothalamus increases ACTH (adrenocorticotrophic hormone) secretion from the anterior pituitary gland, stimulating the adrenocortical fasciculate-reticularis zone. Cortisol is released and leads to a suppression of CRH and ACTH secretion by negative feedback. During therapy (B) the exogenous glucocorticoid has the same effect causing atrophy of the adrenocortical fasciculate-reticularis zone.*



Summary : Glucocorticoids mediate their strong anti-inflammatory and immunosuppressive effects via genomic and non-genomic mechanisms. Genomic mechanisms of glucocorticoid actions are mediated by the cytosolic glucocorticoid receptor resulting in an increased transcription of regulatory proteins (transactivation) and/or a suppressed transcription of pro-inflammatory proteins (transrepression). Non-genomic mechanisms are responsible for very rapid glucocorticoid effects. Glucocorticoids have a strong influence on most immune cells and thereby on the production of different cytokines. Glucocorticoid treatment leads to a suppression of the HPA axis causing a decreased cortisol secretion in consequence of adrenal atrophy. To prevent clinically manifest adrenal insufficiency, glucocorticoids have to be tapered carefully after chronic use and patients should be informed about possible complications.

4 Applications in rheumatology

Glucocorticoids have multiple therapeutic effects, ranging from pain relief and disease modifying results to strong immunosuppressive actions. Depending on the underlying disease and the desired therapeutic aim (table 3), the route, type of glucocorticoid, dose and duration of glucocorticoid therapy are chosen. These not only determine the magnitude of clinical effect and speed of action, but also the risk of developing adverse effects. Here we discuss the administration of glucocorticoid therapy, with emphasis on use in RA, because the therapeutic roles of glucocorticoids in the management of other rheumatic diseases will be discussed in more detail elsewhere.

Table 3: General use of glucocorticoids in rheumatology, initial doses*

	oral			intravenous
	low*	medium*	high*	very high dose/pulse
Arthritides				
gouty arthritis, acute	-	2	2	-
juvenile idiopathic arthritis	-	1	1	-
osteoarthritis	-	-	-	-
acute CPP crystal arthritis	-	-	-	-
psoriatic arthritis	-	1	-	-
reactive arthritis	-	-	-	-
rheumatic fever	-	1	1	-
rheumatoid arthritis	2	2	1	1
Collagen disorders				
dermatomyositis, polymyositis	-	-	3	1
mixed connective tissue disease	-	1	-	1
polymyalgia rheumatica	-	3	-	1
Sjögren's syndrome, primary	-	-	1	-
systemic lupus erythematosus	-	2	1	1
systemic sclerosis	-	1	-	-
Systemic vasculitides				
in general	-	-	3	1

**Initial dose: dose at the start of therapy, will often be decreased in time depending on disease activity; doses in prednisone equivalents a day: low: ≤ 7.5 mg; medium: > 7.5 mg but ≤ 30 mg; high: > 30 mg but ≤ 100 mg; very high: > 100 mg.*

–: rare use; 1: infrequent use, for therapy resistant disease, complications, severe flare, major exacerbation, and for bridging the lag-time of recently started therapy; 2: frequently added to/used as the basic therapeutic strategy; 3: basic part of the therapeutic strategy.

CPP, calcium pyrophosphate.

4.1 Main therapeutic aims

4.1.1 Immunosuppression, symptomatic effect

Apart from immunosuppression in collagen diseases and vasculitides, in which glucocorticoids are anchor drugs, glucocorticoids as adjunctive therapy are effective in relieving symptoms (pain, stiffness, functional limitation) in RA and many other types of arthritis. A review provided evidence of short-term benefit in RA, with a large effect size on pain. However, long-term benefit is less impressive: a review of seven studies (253 patients in total) evaluating the symptomatic effect of glucocorticoids in RA concluded that, when administered for a period of about 6 months, they had a moderate effect size (standardised mean difference) for pain of 0.43 (Criswell et al, 2000). Improvement has also been documented regarding several other clinical parameters, including joint scores, morning stiffness and fatigue, but also regarding acute phase reactants, such as erythrocyte sedimentation rate and C reactive protein. Although after 6 months of therapy the clinically beneficial effects of glucocorticoids in general seem to diminish, many clinicians report that if this therapy is then tapered off or stopped, patients may experience aggravation of symptoms. This may indicate suppression of the hypothalamic–pituitary–adrenal axis, but also that the glucocorticoid still was clinically effective after all.

In intensive (tight-control, treat-to-target) treatment strategies in early RA, glucocorticoids are used for rapid disease control, with fast symptomatic improvement besides possible slowing of joint damage for some schemes (see next paragraph). There is reluctance to prescribe the COBRA (Combination therapy for Rheumatoid Arthritis) approach because of high initial doses of glucocorticoids (van Tuyl et al, 2008). However, also the use of lower initial doses of glucocorticoids as in COBRA-light (den Uyl et al, 2014; Ter Wee et al, 2014) and COBRA-slim (Verschuieren et al, 2017), the application of oral short-term medium dose glucocorticoids (start 30 mg prednisone equivalent daily, tapering to zero in 10 or 34 weeks, respectively) or one intramuscular 120 mg methylprednisolone injection (de Jong et al, 2014), and intra-articular glucocorticoid injections into inflamed joints (Axelsen et al, 2014) all showed benefit in treat-to-target approaches in early RA.

4.1.2 Joint sparing effect in early RA

Although glucocorticoids are associated with generalised increased bone loss and increased risk of osteoporotic fractures, they have positive effects on periarticular bone in early RA, as joint-sparing agents. In 2007, a meta-analysis including 15 studies and 1414 patients with early RA showed convincing evidence that glucocorticoids, given in addition to standard disease-modifying antirheumatic drug (DMARD) therapy in dosages of 5–10 mg prednisone equivalents daily for 1–2 years, can substantially reduce the rate of progression of erosive joint damage (Kirwan et al, 2007*). Even if added to a tight-control, treat-to-target methotrexate-based strategy aiming for remission, prednisone still has a joint-sparing, disease-modifying effect, as shown in the second Computer Assisted Management in Early Rheumatoid Arthritis trial (CAMERA-II) (Bakker et al, 2012*). The advantage regarding joint damage in patients who used glucocorticoids during the first years of their disease still is detectable during the following years (Landewé et al, 2002; Jacobs et al, 2006). However, it has not yet been established whether glucocorticoids can also inhibit progression of erosions when started in RA of longer duration, or whether use for longer than 2 years in early RA has additional joint sparing effects compared to use for 1–2 years. . A recent update of the EULAR guidelines to treat RA states that ‘short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible’ (Smolen et al, 2017). The added efficacy of GC when combined with csDMARDs is well established. In the previous EULAR guidelines, glucocorticoids were also dealt with in a recommendation, but the wording was different: ‘low-dose GC should be considered as part of the initial treatment strategy for up to 6 months, but should be tapered as rapidly as clinically feasible’. So ‘low-dose’ was, after a critical discussion and evaluation of the recent literature, changed into ‘short-term’.

4.2 Specific glucocorticoid applications

4.2.1 Pulse therapy

At high and very high dosages, non-genomic effects also come into play, with possible changes in the relative potencies of the different glucocorticoids. For example, methylprednisolone and prednisolone have similar potency in low and medium dosages, but in high dose and pulse therapy the non-specific non-genomic effect of methylprednisolone is more than threefold stronger (Lipworth, 2000). This may explain the empirical clinical preference for methylprednisolone for pulse therapy. This treatment is usually given intravenously and applied for a short period of time (1–5 days). Flares or severe disease activity or complications of rheumatic diseases such as systemic lupus erythematosus (SLE), vasculitis, polymyositis and RA are indications for this therapy. The duration of the effect of pulse therapy for RA flares shows large variation among individuals, but beneficial effects generally last for about 6 weeks. In RA in particular, one should differentiate between actual pulse therapy and short-term use of medium to high doses. The former, defined as doses ≥ 250 mg per day, is mainly

applied in case of severe refractory disease and life-threatening exacerbations whereas doses from 30-60 mg per day with subsequent tapering according to the COBRA scheme are often sufficient when treating non-complicated flares. To maintain the beneficial effect for a longer time, it is sensible to intensify the long-term therapeutic strategy for RA. If this is done when pulse therapy is applied, the glucocorticoid pulse bridges the lag-time of the intensified strategy with DMARD, before its clinical effect becomes apparent. A mitigated form of pulse therapy is the monthly intramuscular use of 120 mg depot methylprednisolone acetate. However, in contrast to oral glucocorticoids, this treatment showed only a small effect on joint erosion progression at the cost of a significant increase in adverse events (Choy et al, 2005).

The incidence of adverse effects of incidental pulse therapy is relatively low and is related to the underlying disease. Osteonecrosis and psychosis as adverse effects are more frequently seen in SLE than in RA, so these complications might (also) be attributable to active SLE, or active SLE could be an additional risk factor for development of these adverse effects.

4.2.2 Intra-articular and intralesional injections

Local injections of glucocorticoids are often used in sterile arthritis, bursitis and tenosynovitis. The effect in sterile arthritis depends on arthritis type—that is, diagnosis, local arthritis activity, the joint treated (size, weight bearing or non-weight bearing), application and efficacy of synovial fluid aspiration before injection (Weitoft and Uddenfeldt, 2000), type and dose of the glucocorticoid preparation, injection technique, and possibly application of rest to the injected joint (Gaffney et al, 1995). However, it is difficult to predict precisely the effect of a local injection in an individual.

The effect of intra-articular injections in osteoarthritis seems to be less consistent compared to that in RA (Hirsch et al, 2013); in RA, almost always a good—albeit temporary—effect is noted. However, in an older, retrospective study among RA patients in whom several different joints were injected, knee joints in particular required at least one additional injection (McCarty et al, 1995). Soluble glucocorticoids compared to insoluble glucocorticoids have a more rapid onset of action with probably less risk of atrophy of the subcutis and depigmentation of the skin, especially when given in superficial structures with tight skin, compared to insoluble glucocorticoids. However, insoluble glucocorticoids like triamcinolone hexacetonide are longer acting (Blyth et al, 1994); they can be applied safely into deep sites. Short-acting soluble glucocorticoids can be mixed with long-acting insoluble ones to combine rapid onset with long duration of effect. Injection of a local anaesthetic concurrently with a glucocorticoid may provide immediate relief of pain and can also be applied to dilute the glucocorticoid concentration to avoid local skin atrophy and to increase the volume for better distribution in larger joints. Accuracy of steroid placement probably influences the clinical outcome of glucocorticoid injections in the shoulder and probably also other joints (Eustace et al, 1997); it has been reported that over half of shoulder injections are inaccurately placed. Ultrasound-guided injection may

improve accuracy and effectiveness of injection therapy (Chen et al, 2006). The effect of post-injection rest on the injected joint is debated. In a randomised controlled study, bed rest for 24 h following injection of a knee joint in patients with arthritis resulted in prolonged duration of the clinical response and reduced the need for additional injections, compared to a control group not receiving bed rest (Chakravarty et al, 1994). Favourable effects of resting the injected joints (eg, by splinting in a cast or plaster) for 3 weeks in case of a non-weight bearing (upper extremity) joint and 6 weeks for a weight bearing (lower extremity) joint have also been described (Blyth et al, 1994), but there are negative study results too. Based on the literature, no definite evidence-based recommendation can be made, but it seems prudent to rest and certainly not to overuse the injected joint during several days after injection, even if pain is relieved.

It is recommended that intra-articular glucocorticoid injections in an individual joint should not be given more frequently than 3–4 times a year, especially if it is a weight bearing joint, to prevent glucocorticoid-induced joint damage. This recommendation seems sensible, but there is no definite clinical evidence to support it.

Local adverse effects of local glucocorticoid injections include subcutaneous fat tissue atrophy, especially after improper local injection, local depigmentation of the skin, tendon slip and tendon rupture, lesions to local structures such as nerves, and microbial infections. The reported infection rate of joints following local injections with glucocorticoids is low and ranges from one case in 13 900 to one case in 77 300 injections (Seror et al, 1999; Gray et al, 1981). Of 214 joints affected by bacterial arthritis (including 58 joints with a prosthesis or osteosynthetic material) in 186 patients in a prospective study over 3 years among a population of more than 1 million, only three joint infections were attributed to an intra-articular injection (Kaandorp et al, 1997*).

Systemic adverse-effects of local glucocorticoid injections include disturbance of the menstrual pattern, hot flush-like symptoms during the day of the injection or the day after, and hyperglycaemia, especially in diabetes mellitus.

4.2.3 Modified-release oral therapy

Circadian rhythms of cortisol are different in patients with inflammatory rheumatic diseases compared to healthy individuals. In RA patients, serum cortisol rises earlier in the night and reaches higher levels (Bijlsma and Jacobs, 2008). These changes are driven by pro-inflammatory cytokines. It may be important to time glucocorticoid therapy according to the circadian rhythm of pro-inflammatory cytokines, which are responsible for signs and symptoms early in the morning at the time of awakening. The efficacy and safety of a modified-release prednisone tablet was studied in patients with active RA, who were randomly allocated to standard prednisone tablets taken in the morning or modified-release prednisone tablets taken at bedtime, which release prednisone after a delay of about 4 h. This modified release is aimed at suppressing the rise of pro-inflammatory cytokines in the night. The modified-release prednisone reduced morning joint stiffness better than standard

prednisone taken in the morning (Buttgereit et al, 2008a). Compared to prednisone, the safety profile seemed similar and there was no statistical difference found in hypothalamus–pituitary–adrenal axis function (Alten et al, 2010). In another open study involving patients with active RA treated with conventional DMARDs and prednisone or 6-methyl-prednisolone, better suppression of disease activity was found after 4 months when switching the glucocorticoid taken in the morning to modified-release prednisone taken at bedtime (Cutolo et al, 2013). Further research is needed, for example, to find out whether this preparation is also effective in other diseases, what the difference is in effect compared to prednisone taken at bedtime, and whether the new preparation also has DMARD properties in early RA, which would be expected.

Summary : Due to the various therapeutic effects of glucocorticoid drugs, administration regimes vary depending on the treated disease. Strong immunosuppressive effects are achieved by applying high doses and pulse therapy for immediate disease control in life-threatening conditions. In contrast, even low doses suffice to improve symptoms and prevent joint destruction in early RA. Modified-release prednisone represents a promising approach to relieve symptoms like morning stiffness that are caused by the circadian rhythm of pro-inflammatory cytokines.

5 Adverse effects

Most published studies on glucocorticoid toxicity are retrospective and observational. The inability to differentiate unfavourable outcomes attributable to glucocorticoids from those occurring as a complication of the disease being treated or comorbidities (Au et al, 2011) severely confounds the picture (figure 5). Furthermore, there is strong bias for glucocorticoid use as physicians are inclined to treat patients with more severe disease with glucocorticoids (allocation or channelling bias). Some information on adverse effects can be extracted from randomised clinical trials, in which selection bias can be ruled out and occurrence of adverse effects in glucocorticoid users can be compared with that of controls. However, most of these studies are focused on therapeutic effects of glucocorticoids with limited reporting of adverse effects.

Compared with other antirheumatic agents, glucocorticoids have a low incidence of short-term symptomatic toxicity and it is uncommon for patients to discontinue therapy for this reason. Despite over 60 years of use, robust data on toxicities of long-term glucocorticoid therapy are sorely lacking. Basically, the risk and spectrum of adverse effects of glucocorticoids seem to depend on the dose and duration of therapy (Huscher et al, 2009; Listing et al, 2013; Widdifield et al, 2013) and patient-specific characteristics (protective but also risk factors) (Strehl et al, 2016). An overview on the most common glucocorticoid adverse effects is provided below (da Silva et al, 2006) (table 4).

Figure 3 Interplay of effects of glucocorticoids and negative disease features. Inflammatory diseases have been proven to exert negative effects on bone mass, lipids, endothelium, glucose metabolism and insulin tolerance, infection risk, and pregnancy outcome. These negative effects are also attributed to (especially medium and high dose) glucocorticoids. Glucocorticoids suppress the inflammatory disease and thus also these negative disease-related effects.

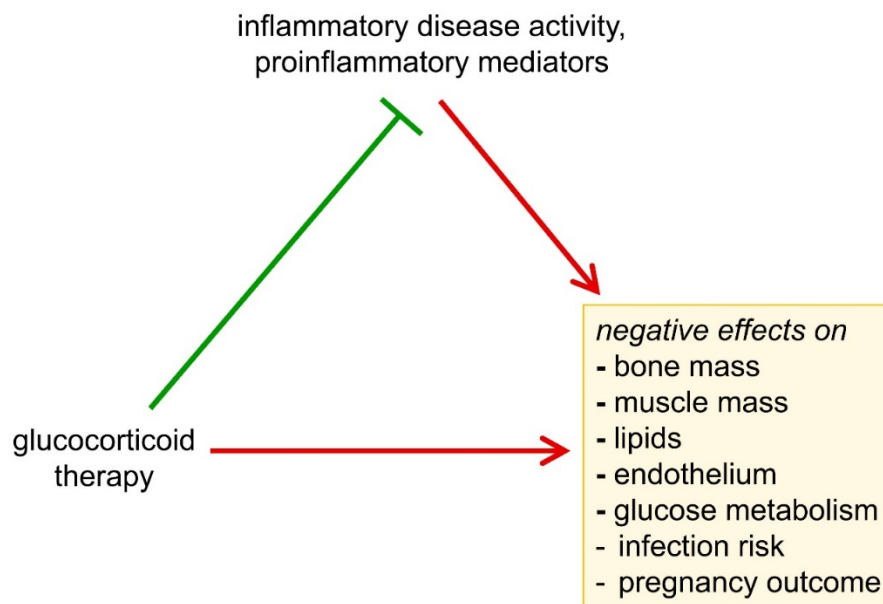


Table 4 Reported adverse effects in glucocorticoid-treated patients with rheumatic diseases

Type of adverse effect	Median (25–75th centiles) number of adverse effects per 100 patient-years of treatment
Cardiovascular (dyslipidaemia, water and electrolyte imbalance, oedema, renal and heart dysfunction, hypertension)	(28–3) 15
Infectious (viral, bacterial, skin infections)	(15–3) 15
Gastro-intestinal (peptic ulcer disease)	(20–4) 10
Psychological and behavioural (mood disturbances)	(236–2) 9
Endocrine and metabolic (glucose intolerance and diabetes, fat redistribution, interference with hormone secretion)	(34–3) 7
Dermatological (skin atrophy, acne, hirsutism, alopecia)	(80–2) 5
Musculoskeletal (osteoporosis, osteonecrosis, myopathy)	(9–3) 4
Ophthalmological (glaucoma, cataract)	(5–0) 4

Summed reported adverse effects (AEs) in 18 studies among patients using glucocorticoids (n = 963) for a rheumatic disease. Data only of studies with patients using glucocorticoids in doses of maximally 30 mg prednisolone equivalent per day and reporting dichotomous adverse effects outcomes were used. Raw data, not corrected for disease activity, comorbidity and the frequency of AEs in the control group (if present) are shown. So, not all negative effects can be specifically attributed to the use of glucocorticoids; common events may be overestimated and less common ones underestimated. AEs were classified into groups and per group expressed as incidence per 100 patient-years (by dividing the number of AEs in a group by the duration of follow-up in years and multiplying by 100). The mean daily dose was 8 mg prednisone equivalent, and the mean duration of the studies was 20 months

Interestingly, the assessment of severity of these adverse effects differs between rheumatologists and patients. In an exercise adverse events were ranked for their importance by both groups. While osteoporosis, diabetes mellitus and cardiovascular effects were ranked within the five most worrisome adverse effects by patients and rheumatologists, the ranking revealed remarkable differences for other adverse effects. For example renal dysfunction, fatigue, palpitations and dyspnoea were ranked as more worrisome by patients compared to rheumatologists (van der Goes et al, 2010a). This exercise reflected concerns about glucocorticoids in both groups, clearly demonstrating that detailed information on the benefits but also risks of glucocorticoids is necessary before start of therapy.

5.1 Cardiovascular adverse effects and events

The development of (premature) atherosclerotic vascular disease as a potential adverse outcome of glucocorticoids is more difficult to study than effects on risk factors for cardiovascular disease. Hypertension is observed in about 20% of patients exposed to exogenous glucocorticoids, but it is related to the dose prescribed and might be less likely with low or medium dose therapy. In patients receiving glucocorticoids in dosages up to 10 mg prednisone equivalent daily, age and elevated pre-treatment blood pressure may better explain significant hypertension than the use of glucocorticoids. Individual variation in susceptibility and other factors, such as the level of starting blood pressure, dietary salt intake, renal function, associated and comorbid diseases, and concomitant drug therapy, are also likely to play a role. While on medium to high doses of glucocorticoid therapy, patients with hypertension require close surveillance of their blood pressure and may need modification of their antihypertensive regimens.

Observational studies on lipids of patients on long-term treatment with medium to high doses of glucocorticoids for renal or cardiac transplants and asthma generally demonstrate elevations in total plasma cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides. However, the effects of glucocorticoids on lipids seem to be dose-dependent; in two studies in SLE patients, significant changes in lipid levels were seen only at prednisone doses above 10 mg daily. Studies have even suggested that low-dose glucocorticoids may reverse unfavourable lipid changes induced by the inflammatory disease and may decrease the negative effects of chronic inflammation on the vascular endothelium (Garcia-Gomez et al, 2008).

Accelerated atherosclerosis and elevated cardiovascular risk have been reported in patients with SLE and in patients with RA (Peters et al, 2010). Glucocorticoids may increase cardiovascular risk further via their potentially deleterious effects on lipids (Wei et al, 2004), glucose tolerance, insulin production and resistance, blood pressure, and obesity (Peters et al, 2010). However, the development of atherosclerotic vascular disease in RA patients on glucocorticoids has been explored in several studies with inconclusive results. In these studies there could be considerable channelling bias; glucocorticoid doses and other confounding factors such

as disease severity and comorbidity and concomitant drug therapy were not always reported. In a QUEST-RA study, glucocorticoid use was associated with a decreased risk of cardiovascular morbidity (hazard ratio 0.95, 95% confidence interval (CI) 0.92 to 0.98), but this beneficial effect was smaller than that of other DMARDs (Naranjo et al, 2008). In another study in RA, carotid plaque and arterial incompressibility was associated with glucocorticoid exposure, independent of cardiovascular risk factors and RA clinical manifestations (Zampeli et al, 2012). A literature review showed only a trend of an association in RA patients between exposure to less than 10 mg/day of prednisone and the risk of major cardiovascular events (Ruyssen-Witrand et al, 2011). In another study, among glucocorticoid users the risk of cardiovascular diseases was increased in those using at least 7.5 mg prednisolone equivalent daily, but not in those using lower dosages (Wei et al, 2004). In an RA cohort with prospective yearly data assessments, including 779 patients with a total of 7203 patient-years of observation, during which 237 patients died, Cox proportional hazards regression adjusted for potential confounders and for the propensity to receive glucocorticoids was used to assess the hazard ratio of glucocorticoid use for cardiovascular mortality (del Rincon et al, 2014*). Compared to no glucocorticoid use, daily doses up to 7 mg prednisolone equivalent were not associated with a statistically increased hazard rate; the hazard rate at 8–15 mg was 2.3 (95% CI 1.4 to 3.8) and at ≥ 15 mg it was 3.2 (95% CI 1.1 to 9.0). Compared to no glucocorticoid use, cumulative doses up to 39 g were not associated with a statistically increased hazard rate; the hazard rate at ≥ 40 g was 2.1 (95% CI 1.3 to 3.3). Compared to no glucocorticoid use, cumulative doses per year up to 5.07 g were not associated with a statistically increased hazard rate; the hazard rate at ≥ 5.08 g per year was 2.4 (95% CI 1.5 to 3.8).

Taken together, next to inflammatory disease activity, traditional cardiovascular risk factors including comorbidities such as diabetes mellitus, and co-therapies—for example COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs)—, medium and high glucocorticoid doses and long duration of this therapy are cardiovascular risk factors. EULAR recommendations for cardiovascular disease risk management state that, to prevent cardiovascular disease (and other adverse effects), glucocorticoid should be prescribed in lowest effective dose and for the shortest period possible (Agca et al, 2017).

5.2 Infections

Medium to high dose glucocorticoid therapy, particularly when administered for prolonged periods of time, may lead to an increased risk of serious infections requiring hospitalisations, surgery, or both (Widdifield et al, 2013). Observational studies suggest an increased risk of infection with glucocorticoid therapy, in contrast to randomised clinical trials (Dixon et al, 2011b). Inconsistent reporting of safety outcomes in randomised clinical trials, and heterogeneity, confounding and publication bias in observational studies, impede robustness of conclusions. It is difficult to differentiate the independent effects of glucocorticoid use from those of other commonly used anti-rheumatic agents such as methotrexate and biologicals—for example, anti-tumour necrosis factor agents—and to differentiate adverse effects of glucocorticoid use from negative effects of

disease activity (Au et al, 2011). Retrospective studies using administrative data from Quebec, Canada found an increased risk of non-serious and serious infections associated with glucocorticoid therapy in RA patients aged ≥ 65 years; the risk was dose-dependent and higher than that seen with methotrexate, although confounding could not be fully excluded (Dixon et al, 2011a; Dixon et al, 2012). In another retrospective RA cohort of patients aged ≥ 66 years, there was a clear dose-dependent risk of infections; again bias could not be fully excluded, especially since surrogate markers for disease activity had been used as covariates in the analysis (Widdifield et al, 2013). Pneumocystis infections have been associated with glucocorticoid doses as low as 16 mg prednisone equivalent daily for 8 weeks (Yale and Limper, 1996), and RA patients treated with immunosuppressive agents including glucocorticoids also have a higher risk of acquiring herpes zoster (figure 6). To conclude, in patients treated with glucocorticoids, especially the elderly and those with comorbidities, physicians should anticipate a dose-dependent increased risk of infections with both typical and atypical microorganisms, appreciating that glucocorticoids may blunt classic clinical features of infection due to their anti-inflammatory actions and thus delay the diagnosis.

In order to prevent certain infections, vaccination may be considered. EULAR recommendations for vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD) suggest examination of the patient's vaccination status and – if possible – administer recommended vaccinations before starting anti-inflammatory therapy and ideally during stable disease. However, live attenuated vaccines should be avoided in immunosuppressed patients and the risk of triggering flares needs to be considered (van Assen et al, 2010). In general, every patient should also be advised to take infection-preventive hygienic measures.

Figure 4 Thoracic herpes zoster eruption in a patient on glucocorticoid therapy. (Reproduced with permission from Dr P Schulze, Department of Dermatology, Charité, Berlin, Germany.)



5.3 Gastrointestinal adverse effects

Glucocorticoids are considerably less toxic to the upper gastrointestinal tract than NSAIDs; glucocorticoids may have dual action on the gastric mucosa, gastroprotective and ulcerogenic (Filaretova et al, 2009). The relative risk of gastrointestinal problems, such as gastritis, ulceration and gastrointestinal bleeding, associated with glucocorticoid use without concomitant NSAIDs has been reported not to be increased (Piper et al, 1991), and to be increased twofold (Garcia Rodriguez and Hernandez-Diaz, 2001), compared to individuals not using glucocorticoids or NSAIDs. The relative risk is about 4 among users of NSAIDs not using glucocorticoids, compared to individuals not using NSAIDs or glucocorticoids (Garcia Rodriguez and Hernandez-Diaz, 2001; American College of Rheumatology, 2008), and is increased further among those using NSAIDs and glucocorticoids combined (Piper et al, 1991; American College of Rheumatology, 2008). These patients should be protected by using a proton pump inhibitor. The gastrointestinal risks of combined use of glucocorticoids (which inhibit selectively COX-2) and COX-2 selective NSAIDs are unknown.

There are case reports of diverticular perforation—possibly as a complication of glucocorticoid associated diverticulitis—but this association has to be confirmed. Glucocorticoids may cause pancreatitis: odds ratio 1.53, 95% confidence interval 1.27-1.84 (Sadr-Azodi et al, 2013), but this negative event may also be a complication of the disease treated, such as vasculitis or SLE. The risk of asymptomatic or symptomatic colonization of the upper gastrointestinal tract with *Candida albicans* is increased in patients treated with inhalation glucocorticoids and in those on systemic glucocorticoids, especially if combination immunosuppressive therapy is applied (Gupta et al, 1994).

5.4 Psychological and behavioural adverse effects

Psychological adverse effects during systemic glucocorticoid therapy are common (Warrington and Bostwick, 2006). Many patients suffering from RA report a slight increase in their overall sense of well-being when starting on low dose glucocorticoid therapy. This is often a temporary effect that appears to be independent of improvement in disease activity. Symptoms of mental and motor restlessness, insomnia, and, especially if on long-term therapy, depression are also observed in patients on glucocorticoids (Warrington and Bostwick, 2006). Memory impairment, particularly in older patients, may occur even at low doses and could relate to hippocampal dependent functions (Keenan et al, 1996). True glucocorticoid psychosis is uncommon at doses <20 mg prednisone/day; it is more frequently seen in patients with SLE than patients with RA. Insomnia and restlessness occur frequently during pulse therapy (Zhao et al, 2013).

5.5 Adverse effects on glucose metabolism

De novo developed frank diabetes as an adverse event of low-dose glucocorticoid therapy is uncommon. The risk of hyperglycaemia seems dependent on dose and duration of glucocorticoid therapy. Short-term

treatment with prednisolone 60 mg or 30 mg per day decreased disease activity without deterioration of glucose tolerance in patients with active RA (den Uyl et al, 2012). In a population-based case–control study among patients using oral glucocorticoids for different indications, the odds ratio of requiring therapy for hyperglycaemia was 1.8 at doses of 1–10 mg prednisone equivalent daily; it was 3 at doses of 10–20 mg, 6 at doses of 20–30 mg, and 10 at doses of 30 mg or more prednisone equivalent daily (Gurwitz et al, 1994).

Patients with diabetes mellitus will commonly have a higher risk of elevated blood glucose levels while taking glucocorticoids. However, ketoacidosis, a frequent and severe complication of type 1 diabetes, is very rare in glucocorticoid-associated diabetes, which is similar to type 2 diabetes (Di Dalmazi et al, 2012).

RA patients on low to medium dose glucocorticoid therapy had similarly decreased insulin sensitivity and β cell function as glucocorticoid-naïve RA patients (Hoes et al, 2011). However, the cumulative dose of glucocorticoids was shown to have a negative impact on glucose tolerance and insulin sensitivity (Hoes et al, 2011). Channelling bias cannot be excluded—for example, glucocorticoid users may have had more active disease than glucocorticoid naïve controls; active disease also negatively affects these parameters of glucose metabolism (Svenson et al, 1988).

5.6 Weight gain, Cushingoid appearance

Weight gain is an adverse effect of long-term endogenous or exogenous glucocorticoid excess, and is of high concern for patients and rheumatologists (van der Goes et al, 2010a). It is a consequence of increased appetite and alterations in fat and glucose metabolism, resulting in an increase of total body and trunk fat. Weight gain associated with low-dose glucocorticoid therapy for inflammatory diseases might, at least partly, also be due to effectiveness of treatment, as active disease has been reported to induce weight loss, possibly by cytokine effects and loss of appetite. In the CAMERA-II trial, mean weight gain among RA patients over 2 years was greater in the placebo-prednisone strategy group compared to the prednisone strategy group: 2.9 kg (SD 4.2) versus 1.3 kg (SD 5.3), respectively (Bakker et al, 2012*). In an additional analysis, the extra weight gain in the prednisone strategy group seemed largely attributable to a better reduction of weight-loss inducing disease activity, rather than this being an adverse effect of prednisone (Jurgens et al, 2013). Weight gain in RA patients on anti-tumour necrosis factor agents seems to be attributable to the same mechanism of suppressing disease activity (Chen et al, 2013).

Characteristic features of long-term high dose glucocorticoid use are moon face (figure 7), centripetal fat accumulation at the trunk (Stewart and Tomlinson, 2002), waist and abdomen with thin extremities—caused by fat redistribution and muscle atrophy—and atrophic skin with multiple ecchymoses (figure 8) and striae (figure 9). The incidence of this iatrogenic Cushing syndrome is dose-dependent and in general becomes evident after at least 1 month of glucocorticoid therapy. In one study, facial puffiness developed in 13% of patients receiving 5–15 mg prednisone equivalent daily for up to 60 days. Slight Cushingoid features may be

observed in over 5% of the patients exposed to ≥ 5 mg prednisone equivalent for ≥ 1 year, but a moon face—which is very troubling to patients—is uncommon at doses below 7.5 mg prednisone equivalent daily.

Figure 5 Cushingoid appearance/moon face caused by high-dose glucocorticoids. Patient consent obtained. (Reproduced with permission from Dziurla and Buttgereit, Z Rheumatol 2008;67:583–91; quiz 592.)



Figure 6 Skin thinning and ecchymoses in chronic glucocorticoid use. (Reproduced with permission from Dziurla and Buttgereit, Z Rheumatol 2008;67:583–91; quiz 592.)



Figure 7 Striae rubrae (red, recent striae). (Reproduced with permission from Dziurla and Buttgereit, *Z Rheumatol* 2008;67:583–91; quiz 592.)



5.7 Dermatologic adverse effects

Atrophic skin with ecchymoses is a common adverse effect of chronic medium dose glucocorticoid therapy in the lower range and low-dose therapy in the higher range, especially in the elderly. Atrophic skin results from glucocorticoid effects on keratinocytes, fibroblasts and fat tissue. To a lesser extent, hirsutism, acne, striae and thinning of scalp and genital hair may occur (Huscher et al, 2009). In RA-patients on low-to-medium glucocorticoid doses, easy bruising/ecchymosis, skin atrophy and impaired wound healing were associated with current and cumulative glucocorticoid use, whereas there was low occurrence of abnormal stretch marks, acne, perioral dermatitis, alopecia and hirsutism, which were –in this dose range– not associated with glucocorticoid use (Amann et al, 2017). Use of 10 mg prednisone equivalent/day by patients with ankylosing spondylitis was associated with 12.6 events per 1000 patient years for non-infectious cutaneous adverse effects, including acne and easy bruising (Zhang et al, 2015).

5.8 Suppressed hypothalamic–pituitary–adrenal axis

Prediction in the individual patient of suppression of the hypothalamic–pituitary–adrenal axis (HPA axis) and of tertiary adrenal insufficiency is not reliable, but this suppression appears to depend on the dose and duration of glucocorticoid treatment. Also, the extent of HPA axis suppression is determined by the kind of glucocorticoid used. Long-acting preparations like dexamethasone tend to be more suppressive due to their long tissue life (Chrousos et al, 2011). In clinical practice, it seems appropriate to anticipate potential adrenal insufficiency in patients who have received daily 7.5 mg prednisone equivalent or more for at least 3 weeks (Cooper and Stewart, 2003). Acute cessation of therapy then could lead to problems.

Patients with adrenal insufficiency present with obscure symptoms like fatigue, muscle weakness, weight loss, hypoglycaemia, nausea, vomiting, diarrhoea, abdominal pain and mood changes. In adrenal crisis the symptoms are severe, additionally including lethargy, hypotension, consciousness disturbance, seizures and fever (Bayman and Drake, 2017). In the case of acute injury or stress (eg, with surgery), adequate adaptation (ie, increase) of the glucocorticoid dose is important if the current dose is low. Often a temporary increase of the dose to 15 mg/day is sufficient for minor surgery. Ideally, patients should be informed about this possible complication and carry an emergency certificate in case of chronic glucocorticoid therapy.

5.9 Musculoskeletal adverse effects

5.9.1 Osteoporosis

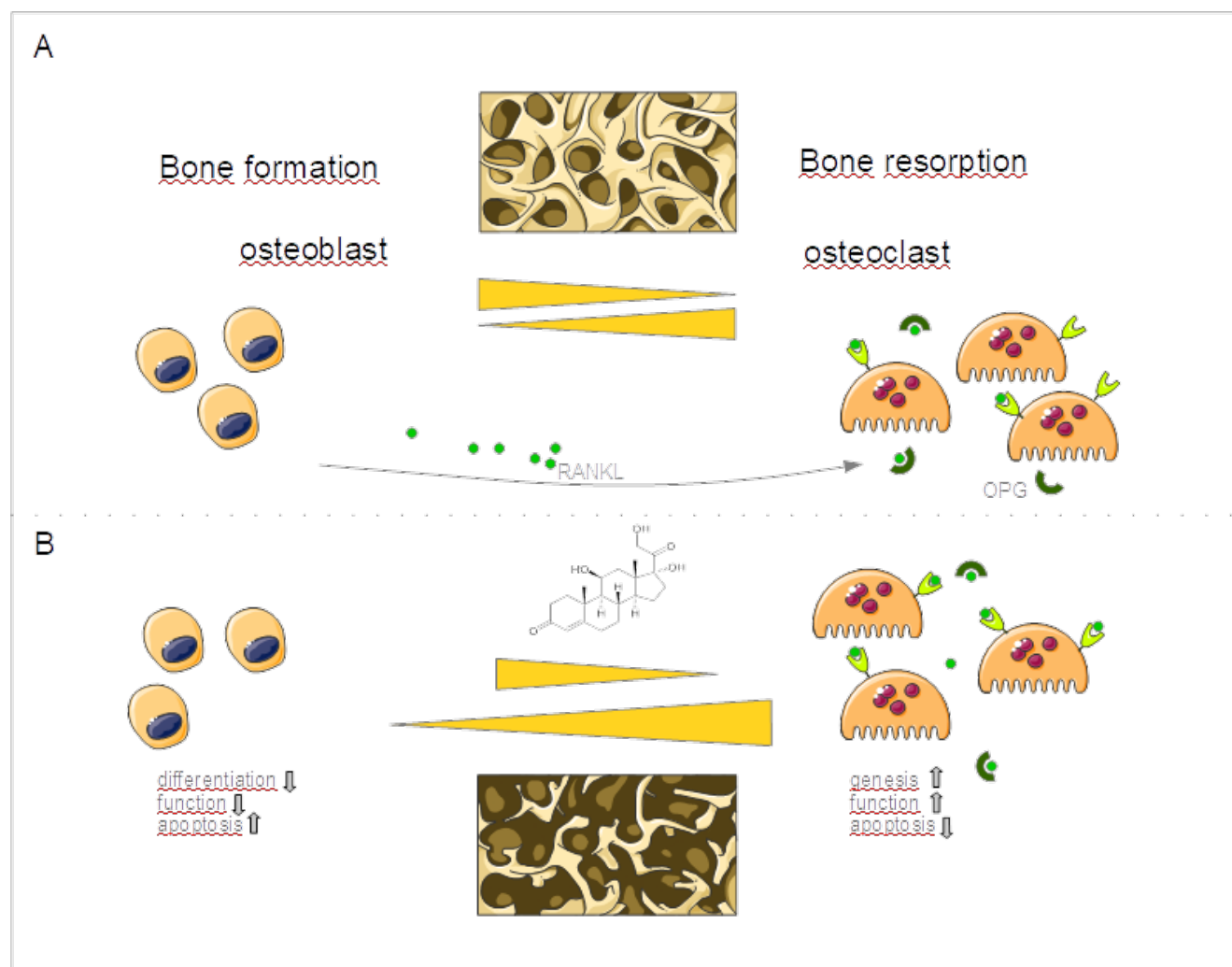
Glucocorticoid-induced osteoporosis is one of the most frequent and potentially devastating complications of prolonged glucocorticoid therapy, if not prevented and treated with effective strategies, including calcium, vitamin D, bisphosphonates (De Nijs et al, 2006*), parathyroid hormone, and denosumab. Without prevention, glucocorticoid treatment can result in rapid and profound reductions in bone mineral density and increased fracture risk, especially during the first 6–12 months of treatment (van Staa et al, 2002*; van Staa et al, 2003*). Glucocorticoid-induced osteoporosis initially affects predominantly trabecular bone at sites such as vertebrae and, with more chronic use, also cortical bone at sites such as the femoral neck.

Comparison of studies examining effects of glucocorticoids on bone is difficult, however, due to differences in timing of initiation of glucocorticoid therapy, variable dosing regimens, different diseases, varying levels of disease activity, different medications (including osteoporosis preventive therapy), use of different bone mass measurement techniques and machines, and disparities between the sites of measurement. Evidence for osteoporotic effects of low dose therapy for 1–2 years in patients with newly diagnosed RA is lacking; it might even be the case that by reducing disease activity which induces osteoporosis (Haugeberg et al, 2005), the development of osteoporosis is inhibited by glucocorticoids in these patients (figure 3). In the CAMERA-II trial, during the 2-year application of 10 mg prednisone daily with osteoporosis preventive therapy, no bone was

lost (van der Goes et al, 2013). In individual patients on prolonged glucocorticoid therapy, the cumulative dose appears to have the strongest predictive value for decreased bone mineral density (van Staa et al, 2002*). Algorithms have been developed to estimate of the future risk of fractures for individual patients, such as the internet tool Fracture Risk Assessment (FRAX; <https://www.shef.ac.uk/FRAX/>), which binary scores glucocorticoid use (yes/no; yes if the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone equivalent of 5 mg daily or more). Guidance for adjustments of FRAX according to glucocorticoid dosages have been published (Kanis et al, 2011). There are several national and international guidelines on the prevention and treatment of osteoporosis, including in general clinical risk factors (such as age, gender, menopausal status, smoking, patient and family history of osteoporosis and glucocorticoid use) and bone mineral density; in some guidelines, FRAX has been incorporated (Compston et al, 2013).

The precise mechanisms by which glucocorticoids affect bone are still not completely clear, but many mechanisms have been elucidated (Bultink et al, 2013). Glucocorticoids decrease calcium absorption, increase renal calcium loss, diminish sex and growth hormone production, induce muscle wasting (associated with less loading of bone, and thus bone loss, and with falls, leading to fractures), and directly negatively modulate signalling by, for example, receptor activator of nuclear factor kappa B ligand (RANKL) of (pre)osteoclasts (Bultink et al, 2013). This mechanism leads to enhanced osteoclast function and lifespan, resulting in increased bone resorption (figure 10). Consequently, markers of bone resorption are often increased in patients treated with glucocorticoids. Glucocorticoids also directly inhibit osteoblast function and promote apoptosis of osteoblasts, resulting in reduced bone formation; this is likely to be the most important negative effect of glucocorticoids on bone.

Figure 10 Glucocorticoids do negatively influence the bone structure. (A) Bone remodelling is characterized by a balanced system of bone formation and bone resorption depending on RANKL signalling. (B) Glucocorticoids do direct and indirect affect bone remodelling. RANKL signalling is disturbed leading to an increased function of osteoclast and thereby an enhanced bone resorption. RANKL receptor activator of nuclear factor kappa B ligand, OPG osteoprotegerin



Oral doses of prednisone as low as 2.5 mg daily have been shown to suppress levels of serum osteocalcin, a marker of bone formation. Finally, glucocorticoids promote apoptosis of osteocytes. So, the glucocorticoid-induced increased risk of osteoporotic fractures is based on multiple mechanisms, affecting bone mineral density, bone turnover, micro-architecture, collagen content and cross-linking, and other factors such as myopathy leading to a propensity to fall. This is reflected by the finding that at the same bone mineral density, the risk of osteoporotic fractures (figure 11) is higher in patients on glucocorticoids compared to patients not using glucocorticoids (van Staa et al, 2003*).

Figure 11 Osteoporotic mid-thoracic vertebral compression fractures. Radiograph on the left and magnetic resonance image on the right.



5.9.2 Osteonecrosis

Osteonecrosis—that is, avascular necrosis of bone—is an important adverse event of high dose glucocorticoid use; in contrast to osteoporosis, for osteonecrosis the cumulative dose of glucocorticoids seems less predictive than the (average/peak) height of the dose, perhaps owing to osteocyte and osteoblast apoptosis at higher dosages. In a Japanese study of osteonecrosis of the femoral head (figure 12), 35% of all cases was related to glucocorticoid treatment. Osteonecrosis occurs relatively frequently in SLE, attributable to the often higher doses of glucocorticoids applied in this disease, but probably also because SLE itself is a risk factor (Shigemura et al, 2011; Caramaschi et al, 2012). Several other disorders have been labelled as risk factors for osteonecrosis, including haemoglobinopathies, especially sickle cell disease, alcohol abuse, Caisson disease, Gaucher disease, and hypercoagulability states, such as antiphospholipid syndrome. It is not known whether glucocorticoid therapy in patients with these disorders increases the risk of osteonecrosis. Bisphosphonate therapy, especially intravenous therapy, may be complicated by osteonecrosis of the jaw. Glucocorticoid associated osteonecrosis typically, but certainly not exclusively, occurs in the femoral head; it may also be located in the humeral head and bone near the knee. Osteonecrosis rarely occurs in RA patients receiving low dose therapy or in SLE patients with glucocorticoid dosages below 20 mg prednisone equivalent per day. The

most sensitive and specific imaging modality is magnetic resonance imaging; bone scintigraphy is sensitive but not specific for osteonecrosis, and radiography is not sensitive for early osteonecrosis.

5.9.3 Myopathy

Similar to osteonecrosis, myopathy (loss of muscle mass) rarely occurs in patients receiving low dose glucocorticoids. Based upon results of small studies, fluorinated glucocorticoid preparations such as triamcinolone appear to be more closely associated with myopathy than prednisone. Myopathy has been reported to occur after 6 months treatment with a mean dose of 8 mg triamcinolone daily (equivalent dose: 10 mg prednisone) (Strandberg, 1962). In general, however, myopathy occurs at higher doses and with longer duration of treatment. Often, in patients on these doses, the glucocorticoid —increasing protein breakdown and decreasing protein synthesis— is not the only risk factor for myopathy and muscle degeneration; common associated factors are physical disability and catabolic effects of the inflammatory disease treated (Bautmans et al, 2013; Schakman et al, 2013). The diagnosis is mainly clinical, although muscle biopsy may reveal clues; serum creatinine kinase values are not elevated.

Figure 12 Hip osteonecrosis. Severe deformation of the femoral head with cysts and normal joint width, indicative of (late) damage caused by osteonecrosis of the femoral head.



5.10 Ophthalmologic adverse effects

5.10.1 Cataract

Posterior subcapsular cataract is a well-described complication of prolonged glucocorticoid use, and is dose and duration of therapy dependent. This type of cataract is also related to diabetes, and it is not typically age related. Some studies found no minimal safe dose with respect to this complication (Huscher et al, 2009). Others note that cataracts rarely occur in patients taking prednisone below 10 mg daily within the first year of treatment; however, after an average of 7 years, about a third of these patients will have developed cataract. Also cortical cataracts have been associated with glucocorticoid use (Urban and Cotlier, 1986; Klein et al, 2001).

5.10.2 Glaucoma

Glucocorticoid-treated patients may develop mildly increased intra-ocular pressure, which can lead to minor visual disturbances. This ophthalmologic adverse effect is also dose and duration of therapy dependent. The development of frank glaucoma, threatening eyesight, is rare at low dose therapy, and tends to afflict patients who are otherwise predisposed to the condition. A higher risk for glaucoma with glucocorticoids tends to occur in families with primary open-angle glaucoma, suggesting a genetic basis, and in patients with high myopia and diabetes (Tripathi et al, 1999). In these patients, an ophthalmologist should be consulted before and after initiation of therapy even with low dose glucocorticoids. In rheumatology practices, monitoring for glucocorticoid eye toxicity is not yet very common.

5.11 Glucocorticoid use during pregnancy and lactation: adverse effects on the unborn child and baby

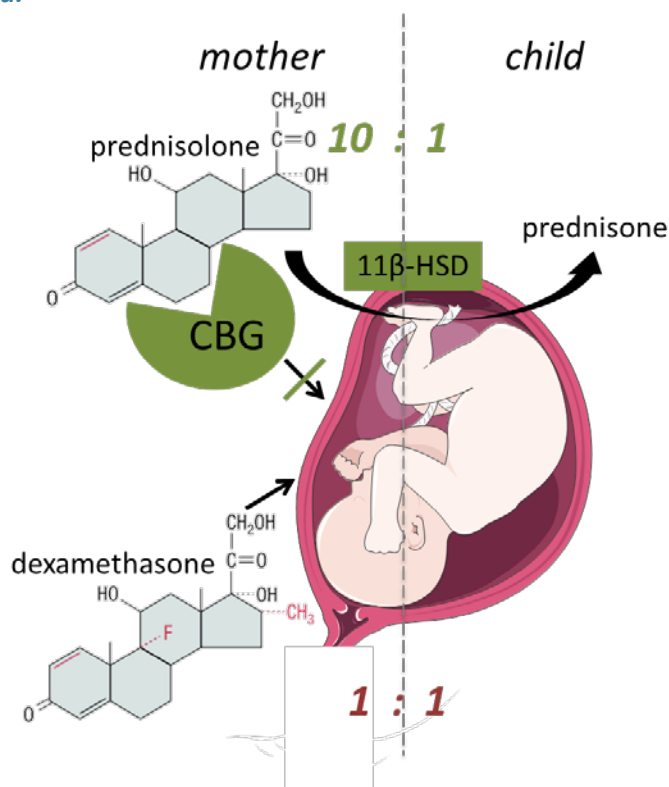
The foetus is protected from maternal glucocorticoids via two mechanisms. First, glucocorticoids bound to proteins cannot pass the placenta. Second, the enzyme 11 β -HSD in the placenta converts cortisol and prednisolone into the inactive 11-dehydro-prohormones, cortisone and prednisone, respectively. The prednisolone maternal-to-foetal blood concentration ratio is about 10:1, owing to these mechanisms. In contrast, dexamethasone has little or no affinity for transport proteins and is poorly metabolised by 11 β -HSD in the placenta; the maternal-to-foetal dexamethasone blood concentration ratio is about 1:1 (figure 13). So, if a pregnant woman has to be treated with glucocorticoids, prednisolone is a good choice to protect the unborn child. If the unborn child has to be treated, for example, to induce lung maturation in foetuses at risk of preterm delivery, or to treat congenital heart block associated with maternal Sjögren syndrome, dexamethasone would be indicated. The risk of adverse effects of antenatal exposure to glucocorticoids, such as reduced intrauterine growth and birthweight, neurocognitive adverse effects, and oral cleft, seems dose, duration of therapy and stage of pregnancy dependent (Park-Wyllie et al, 2000). Several studies report conflicting results regarding occurrence of these adverse effects (Wapner et al, 2007; Peltoniemi et al, 2009;

Khalife et al, 2013), but doses of glucocorticoid and indications for this therapy differ between studies. Furthermore, it is difficult to discriminate between the negative effects and complications of the foetal condition treated and the adverse effects of the glucocorticoid therapy (figure 3). It is advised to avoid high doses (1–2 mg/kg prednisone equivalent) in the first trimester of pregnancy (Park-Wyllie et al, 2000; Temprano et al, 2005), whereas low to moderate doses of prednisone seem to be safe (Temprano et al, 2005).

Breastfeeding is generally considered safe for an infant whose mother is taking prednisolone or prednisone, because these glucocorticoids are excreted only in small quantities in breast milk (Ost et al, 1985; American Academy of Paediatrics, 2001). The exposure of the infant seems to be minimised further if breastfeeding is given before the mother takes her daily dose, or if breastfeeding is avoided during the first 4 h after the intake of prednisolone (Ost et al, 1985), because curves of milk and serum concentrations of prednisolone are similar in time (Temprano et al, 2005). Medium and high dosed glucocorticoids may, even when applied as local injection, suppress lactation (Babwah et al, 2013).

Since a lot of autoinflammatory diseases occur in women of childbearing age, glucocorticoid use in pregnancy is an important topic to be approached to avoid misconceptions concerning the risks and benefits of this therapy. Patients complain about a lack of knowledge causing distrust and poor adherence to therapy (van der Goes et al, 2010a).

Figure 13 Glucocorticoid use in pregnancy. Prednisolone and cortisol, bound to corticosteroid binding globulin (CBG), hardly pass the placenta and are quickly inactivated by 11 β -HSD. On the contrary, dexamethasone has little affinity to the binding protein and enzyme and should be applied if treatment of the child is desired.



Summary : Although glucocorticoids are effective in the treatment of rheumatic diseases, these drugs can also trigger a variety of adverse effects. The risk and spectrum of these adverse effects depend on the dose and duration of therapy and patient-specific characteristics. Adverse reactions comprise for example effects on the cardiovascular system and the glucose metabolism, infections and osteoporosis. The complexity of different disease features complicate the assignment of the source of adverse events – is it a cause of the disease or of the drug with which the disease is treated?

6 Prophylactic measures and monitoring

Data on monitoring during glucocorticoid treatment are scarce. Standard good clinical care monitoring that is appropriate for patients with an inflammatory rheumatic disease does not need to be expanded if low-dose glucocorticoids are prescribed, except for monitoring for osteoporosis according to guidelines, and baseline checks for oedema, fasting blood glucose, and risk factors for glaucoma (van der Goes et al, 2010b). Some prophylactic measures have been proven effective in preventing complications of glucocorticoid therapy and may be contemplated at the start of this therapy (Hoes et al, 2007). When the patient has concomitant therapy with a non-selective NSAID or needs such therapy, dependent on the individual patient's cardiovascular risk, a non-selective NSAID with a proton pump inhibitor can be considered, or (switch to) a COX-2 selective NSAID. Also, the risk of osteoporosis can be minimised with calcium, vitamin D and bisphosphonate, if needed, according to national and international guidelines. Before start of chronic glucocorticoid therapy > 20 mg prednisone equivalents per day, clinicians should assess the patient's vaccination history and address deficiencies (Caplan et al, 2017). However, internationally accepted, glucocorticoid-specific guidelines on vaccination are lacking. During therapy, the dose, effect of treatment, and indication to continue glucocorticoid therapy should be regularly checked during treatment. If aiming at symptomatic improvement of symptoms such as pain, stiffness and physical impairment, the glucocorticoid dose should be kept as low as possible. When using low-dose glucocorticoids as a disease-modifying agent in early RA, a stable dose over a longer period of time (ie, 1–2 years) is needed.

In clinical trials, extensive standard monitoring not only contributes to safer treatment of patients, but also helps establish a valid adverse effects profile of glucocorticoids. This will give insights into the real incidence, prevalence and clinical relevance of adverse effects. This is the reason we propose more extensive monitoring for adverse effects in clinical trials (van der Goes et al, 2010b). To assess glucocorticoid-related adverse effects (and glucocorticoid-sparing effects of additional drugs), a glucocorticoid toxicity index has been developed (Miloslavsky et al, 2017).

Summary: Before starting glucocorticoid treatment, patients should be screened for risk factors predisposing to glucocorticoid-related adverse events. Important prophylactic measures to be considered include gastric protection and anti-osteoporotic therapy. General actions to be taken comprise a healthy lifestyle and hygienic measures to prevent metabolic effects and infections respectively.

7 The future

The increasing knowledge on therapeutic but also side effects enables a more sensible use of conventional glucocorticoids. New biological therapies have not and probably will not in the near future replace glucocorticoids as anchor drugs in therapeutic strategies for rheumatic diseases. Increased understanding of the pathophysiology of rheumatic diseases and the different mechanisms of glucocorticoid action provides interesting and sometimes advanced starting points for the development of optimised glucocorticoids; a case in point is the development of a modified-release prednisone tablet (discussed above). Research into development of GR ligands was based on the genomic mechanisms of 'transrepression' and 'transactivation', with the hypothesis that the first mechanism predominantly induces the anti-inflammatory properties of glucocorticoids and the latter mechanism predominantly induces metabolic adverse effects. However, this simplified theory has often been criticized and this seems to be supported by the fact that either study results are available yet (although several clinical trials analysing the efficacy and safety of different SEGAs are completed) or that to date no SEGAs have entered the market.

Other research focused on nitro-steroids, which are capable of releasing low levels of nitric oxide, and long-circulating liposomal glucocorticoids, aimed at enhanced anti-inflammatory properties and reduced unwanted effects. However, the development of nitro-steroids seems to have been stopped (Strehl et al 2017).

Another approach are long-circulating PEG (polyethylene glycol)-liposomes, in which the active drug is enclosed. These substances accumulate at sites of inflammation resulting in very high local glucocorticoid concentration. Animal studies are promising: a single injection of 10 mg/kg liposomal prednisolone revealed a complete remission of the inflammatory response, whereas free prednisolone shows only mild effects, even after repeated daily injections (Metselaar et al, 2003). Results from clinical studies are still missing. There is one clinical trial (NCT02534896 (www.clinicaltrials.gov)) evaluating the efficacy and safety of intravenous PEGylated liposomal prednisolone sodium phosphate compared with intramuscular injections of methylprednisolone acetate in subjects with a flare of disease activity of rheumatoid arthritis. The estimated study completion date is December 2017, thus we will see if the convincing preclinical study data are reflected in these clinical trial.

Genetic developments might, in the future, lead to personalised medicine (Burska et al, 2014), tailoring treatment to the individual patient's genomic information, increasing efficacy and avoiding adverse effects, but this still seems a long way off.

Summary : Although some developments seem to be very promising, the only product which has already entered the market very successfully is the modified-release prednisone. Clinical trial evaluating the efficacy of SEGRAs and liposomal glucocorticoids are still ongoing.

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EULAR on-line course on Rheumatic Diseases

Glucocorticoids

Lisa Ehlers, Cindy Strehl, Rene Westhovens

Previous versions were co-authored by Frank Buttgereit, Cornelia Spies, John Kirwan, Johannes Jacobs, Marlies van der Goes, Barbara Neerinckx, Rene Westhovens



IN-DEPTH DISCUSSION I

Glucocorticoids in pregnancy

Inflammatory autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, often occur in women of childbearing age. Treatment of these disorders during pregnancy is an important aspect of management. The relative benefits and risks of specific medications to the mother and the foetus depend on the specific clinical context and may be dependent on the stage of pregnancy. Moreover, untreated active disease itself also carries risks, to the mother as well as to the unborn child.

In pregnancy, the administration of glucocorticoids can be beneficial and in some circumstances even life-saving for both mother and foetus. Recommendations based on evidence and expertise suggest that low dose glucocorticoids are safe for the foetus [1;2] but different perspectives on this issue might exist between the patient and the treating physician [3].

Pharmacokinetics

The pharmacokinetics of glucocorticoids in pregnancy remain unclear. During pregnancy, significant pharmacological alterations occur secondary to profound changes in the renal, gastrointestinal and cardiovascular system. Certain obstetrical conditions, such as preeclampsia, diabetes and multiple gestations, are associated with different volumes of distribution, interactions and clearance rates of medications, adding further complexity to the therapeutic use of glucocorticoids.

Metabolism

Oral glucocorticoids are absorbed in the upper jejunum, with peak plasma concentrations between 30 and 100 minutes after ingestion. These drugs bind to plasma proteins, corticosteroid-binding globulin and albumin, and only the free drug fraction is pharmacologically active. Low serum albumin state, as seen in pregnancy, may thus give rise to potentially higher therapeutic but also toxic effects of glucocorticoids with a high affinity for albumin [1].

After administration of a glucocorticoid to the pregnant woman, there is a rapid transfer to the placenta. Glucocorticoids are metabolised by the placental 11β hydroxysteroid dehydrogenase (11β -HSD) into their inactive 11-dehydro-prohormones, but the conversion of prednisolone is particularly effective, deactivating about 87% of an injected dose of prednisolone [4]. In addition, the fetoplacental unit is relatively lacking enzymes that convert the prohormone prednisone into prednisolone [2]. The maternal-to-foetal blood concentration of prednisone is 10-to-1, in comparison to that of hydrocortisone: 6-to-1 and of dexamethasone: 3-to-1. The higher transplacental passage of dexamethasone is due to its little affinity to transport proteins and the poor metabolism of this molecule by the placental 11β -HSD. Thus, foetal exposure is reduced to a minimum if prednisone and prednisolone are used to treat maternal disorders. On the other hand, if foetal therapy is desired, dexamethasone and betamethasone are preferred.

The effect of high-dose or pulse therapy during pregnancy has not been determined, but these doses affect the immune system also via other (non-genomic) mechanisms compared to lower doses; the high doses are associated with a higher risk of adverse-effects, probably also during pregnancy [5].

Safety

For obvious reasons, large controlled studies on the use of drugs in pregnancy, especially during the first trimester, are lacking. Most data available are from animal studies, but their results are not necessarily generalisable to the human context [1]. However, since the introduction of antenatal glucocorticoid prophylaxis in obstetric practice in 1972 to reduce incidence of respiratory distress syndrome in premature infants [6], there is a large body of evidence that this use is safe.

Orofacial clefts

Animal studies showed numerous toxic effects of glucocorticoid administration in pregnant animals: diminished growth of the foetal brain, thymus, spleen, lung, as well as of the placenta, and congenital abnormalities, particularly cleft palate in the rodent foetus [1]. Studies on the effect of glucocorticoid exposure on cleft palate formation in pregnant women show conflicting results. Cases of cleft palate have been described in children after in utero glucocorticoid exposure, but the incidence is rare. A case control study among 1092 infants with orofacial clefts (palate/lip) showed a significantly increased risk associated with maternal glucocorticoid use during the periconceptional period (one month before to three months after conception) [7]. A systematic meta-analysis also reported an overall odds ratio for bearing a child with cleft palate of 3.4 (95% confidence interval 1.97-5.69) in women who used glucocorticoids during pregnancy [8]. In contrast to these observations, no increase in cleft palate was identified in a nationwide cohort study involving 832636 live births in Denmark, in which data of 51973 infants exposed to glucocorticoids during the first trimester of the pregnancy were compared with those of unexposed infants [9].

Suppression of hypothalamic-pituitary-adrenal axis

Hypothalamic-pituitary-adrenal axis suppression in the pregnant woman may be present after approximately 7-10 days administration of 15-20mg of prednisone daily. Labour and delivery should then be covered with stress doses of glucocorticoids. Suppression of the hypothalamic-pituitary-adrenal axis in the newborn exposed intra-uterine to glucocorticoids is infrequent and transient [10].

Other

Other occasionally reported adverse effects of glucocorticoid use in pregnancy are premature rupture of membranes and intra-uterine foetal growth inhibition [11], and a higher relative risk of neonatal hypoglycaemia:

relative risk (95% CI) 1.61 (1.38-1.87) [12]. Glucocorticoid use during pregnancy might increase the risk of several pregnancy-associated maternal complications, such as hypertension, fluid retention and gestational diabetes.

The frequent use of antenatal glucocorticoids to promote foetal pulmonary maturity has provided very useful follow up data showing no long-term detrimental effects regarding physical development or psychological behaviour of children [2, 13]. Possibly, more frequent hospital admissions because of infections during the first years of life are seen in the antenatal 12mg betamethasone-treated group [13]. Thus, the most important implication of intra-uterine exposure to glucocorticoids for the newborn child possibly is a higher susceptibility to infections.

In the EULAR guidelines it is formulated like this without specifying glucocorticoid dosing : “Current evidence indicates no increased rate of congenital malformations. Prednisone/prednisolone can be continued at the lowest effective dose during pregnancy “[14].

Practical guide

Practical recommendations include the following:

1. Use the lowest dose possible to control the disease [13].
2. A once daily dose is preferred to divided doses over the day.
3. Prednisone/prednisolone is product of choice.
4. Pregnant women who received high dose of glucocorticoids before delivery should be watched for eventual suppression of the hypothalamic-pituitary-adrenal function and managed accordingly during labour and delivery.
5. In severe, refractory maternal disease during pregnancy, methylprednisolone pulses may be considered [13].
6. If the mother was treated with glucocorticoids during pregnancy, be aware of a possible higher susceptibility for infections in the newborn.

Breastfeeding

Prednisone and prednisolone are considered safe in breastfeeding mothers since only a small percentage (<10%) of active drug is secreted to breast milk [10]. Medium and high dosed glucocorticoids may, even when applied as local injection, suppress lactation [15].

If a lactating patient requires high dosages of glucocorticoids (>20mg of prednisone a day [1] or in the EULAR guidelines even 50mg a day [13]), not nursing for 4 hours following medication ingestion is suggested [10]; in the early morning, nursing can be done before taking the glucocorticoid.

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IN-DEPTH DISCUSSION II

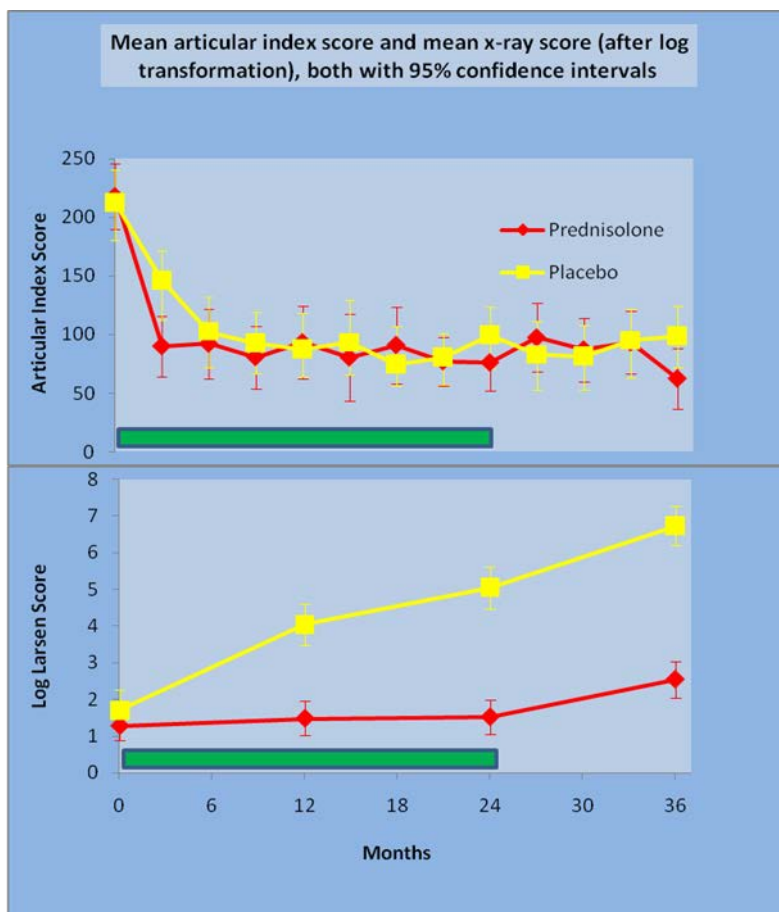
**Effects of glucocorticoids in early rheumatoid arthritis:
fast action and prevention of radiological progression**

During the past two decades, treatment goals in rheumatoid arthritis (RA) have evolved from a concept of symptom control to a concept of disease control.[1] This has resulted in a more intensive therapeutic approach with earlier introduction of disease-modifying anti-rheumatic drugs (DMARDs),[1, 2] which have been proven to reduce structural joint damage. This damage is often evaluated assessing joint space narrowing and bone erosions on radiographs of hands and feet.[3] Not all patients with RA will develop erosions, and therefore it is unclear if the mechanisms of joint inflammation are the same as the mechanisms of joint destruction.[4]

Glucocorticoids have been used in RA for many decades.[8, 9] There are multiple clinical effects of glucocorticoids. These therapeutic effects range from pain relief and disease modifying effects to strong immunosuppressive actions. Low dose glucocorticoid therapy (i.e. ≤ 7.5 mg prednisone equivalent) is effective in relieving symptoms such as pain, stiffness, and functioning. A review provided evidence of short term benefit in RA, with a large effect size of 1.75 on pain.[10]. However, long term benefit on symptom relief was less impressive: a review of 7 studies (253 patients in total) evaluating the symptomatic effect of glucocorticoids in RA concluded that, when administered for a period of approximately 6 months, glucocorticoids had an effect size for pain of 0.43.[11] Improvement has been documented regarding several clinical parameters, including pain scales, joint scores, morning stiffness and fatigue, and also regarding acute phase reactants, such as erythrocyte sedimentation rate and C-reactive protein. Although after 6 months of therapy the clinically beneficial effects of glucocorticoids in general seem to diminish, many clinicians report that if this therapy is then tapered off or stopped, patients may experience aggravation of symptoms.

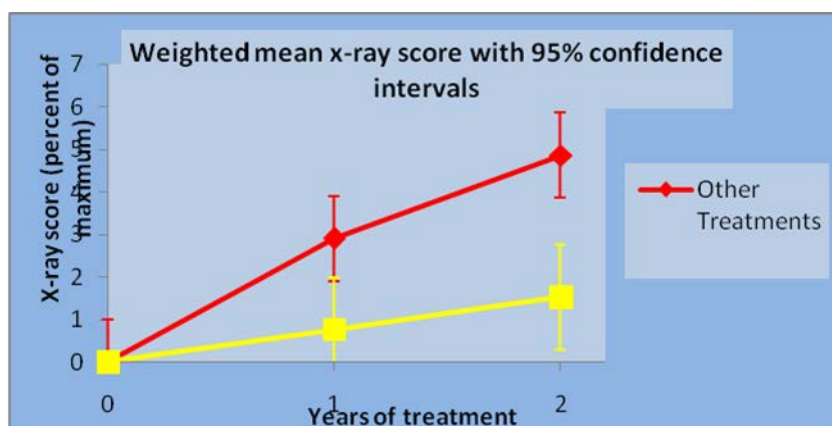
Although glucocorticoids are associated with generalized increased bone loss and increased risk of osteoporotic fractures, they have positive effects on periarticular bone in early RA (defined as less than 2 years after diagnosis), as joint-sparing agent. The first study able to specifically address this question was published in 1995 and compared two groups of patients with early RA starting on disease modifying therapy with the addition of prednisolone 7.5 mg daily or with placebo (Figure 1).[12, 13] In this study, low dose glucocorticoids caused an early improvement in articular pain and swelling; this was only superior to standard therapy for a few months. Second, radiographic progression, as measured by the Larsen score, was inhibited by low dose prednisolone. Third, clinical symptoms did not change after discontinuation of prednisolone, whereas x-ray progression resumed, see Figure 1.

Figure 1 Mean (95% CI) articular index (upper chart) and Larsen score after log transformation (lower chart) for 75 patients with radiographs at all-time points. Horizontal bars represent the treatment period (disease modifying therapy plus prednisolone 7.5 mg daily or placebo). After two years treatment patients continued a blinded discontinuation regimen taking the tablets on alternate days for two weeks, and then every third day for two weeks. The difference between groups for articular index is significant at 3 months only. The difference between groups for radiographic progression is significant at 1, 2 and 3 years.



Fifteen studies [12, 14-27] have been included in a Cochrane meta-analysis published in 2007.[28] The results of this analysis show clear cut evidence for the ability of glucocorticoids to substantially reduce the rate of radiographic progression in early RA and the authors concluded: “Even in the most conservative estimate, the evidence that glucocorticoids given in addition to standard therapy can significantly reduce the rate of erosion progression in RA is convincing.” Indeed, even including studies with very low doses of glucocorticoids and patients not also taking DMARDs, the average reduction in the rate of progression was almost 70% (Figure 2). This makes glucocorticoids by far the most powerful DMARD in early RA, particularly when used in combination with other DMARDs.

Figure 2 Radiographic (X-ray) progression in patients treated with or without glucocorticoid in six randomized controlled trials lasting 2 years. Glucocorticoids slowed progression over 2 years from 4.87 to 1.54 units, a reduction of 68%.



According to the 2013 EULAR recommendations on the management of RA, low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more conventional DMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible .[5] It has been shown by several studies that in treat-to-target approaches in early RA high doses of glucocorticoids are not necessary, but that the use of low-dose or low-to medium dose glucocorticoids is beneficial. One of these studies is the CAMERA-II trial (second Computer Assisted Management in Early Rheumatoid Arthritis trial).[29] In this study, the effects of the addition of 10 mg prednisone daily to tight control methotrexate-based treatment were studied in patients with early RA. Co-treatment with prednisone instead of placebo led to better control of disease activity, and to reduced erosive joint damage. The mean of maximum doses of methotrexate was lower and the need for biological treatment was less in the prednisone strategy group. Analysing the number of patients experiencing at least once a specific AE during the study, there were no significant differences, except for less patients in the prednisone group experiencing nausea ($p=0.006$), ALAT > upper limit of normal ($p=0.006$), and ASAT > upper limit of normal ($p=0.016$) compared to patients in the placebo group. This could be attributed to the lower mean of maximum doses of methotrexate needed in the prednisone strategy group.

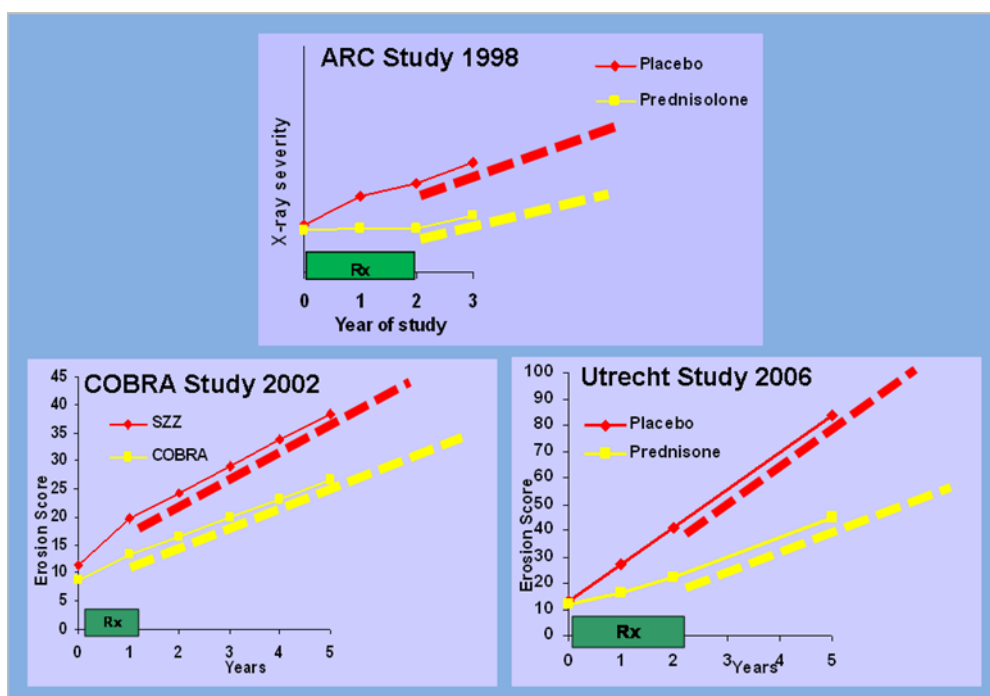
The Cobra-light study shows comparable favourable effects in early RA on disease activity, functional ability and radiological outcome in the COBRA-light strategy (methotrexate 25 mg/week + initial prednisolone dose 30 mg/day), compared to the COBRA strategy (methotrexate 7.5 mg/week, sulfasalazine 2mg/day and initial prednisolone dose 60 mg/day).[30] The tREACH trial is another study showing benefits from medium dose glucocorticoids (start 15mg prednisone daily, tapered to zero in 10 weeks) in early RA.[31] Recent step down strategies in early RA incorporating bridging glucocorticoid therapy, might not only make use of the therapeutic window of opportunity for preventing damage and loss of function but could also help to meet the specific patients preferences in early disease.[32] While current practice and recommendations suggest the early concomitant use of glucocorticoids for severe and poor prognosis patients, new evidence makes clear

that current prognostic markers are insufficient predictors and that step down strategies might be helpful in the initial treatment of every patient.[33;34]

Finally, some very encouraging observations of long term follow up have been reported which raise the possibility that GC might have enduring effects on disease progression long after therapy with GCs has been discontinued.[35-37] During 4 to 5 years of follow up of the COBRA trial, the radiographic progression rate was 8.6 Sharp points per year in those not treated with glucocorticoids during the original study, but was only 5.6 in the patients who had previously been treated with glucocorticoids during the trial.[36] After 11 years of follow up, this difference was still present.[37]

Another study followed patients from the Utrecht trial after they had been treated with 10 mg prednisolone daily or placebo for 2 years.[35] This study showed that during an additional 3 years of follow-up, radiographic scores showed significantly less progression in the original prednisone group than in the original placebo strategy group. This continuing response, years after stopping glucocorticoids, indicates a sustained suppression of radiographic progression in patients with RA, independent of subsequent anti-rheumatic therapy. However, it has not yet been established whether or not glucocorticoids cause additional inhibition of progression of erosions when started in RA of longer duration or when used for more than 2 years in early RA.

Figure 3 Persistent anti-erosive effect of glucocorticoids in rheumatoid arthritis. There is a persistent reduction in the rate of erosion progression, even after treatment has been stopped. This benefit persists for several years.



Summarizing, glucocorticoids can be classified as DMARDs in early RA, since they have been proven effective in retarding the progression of erosive joint damage in multiple clinical trials. Inclusion of glucocorticoids is

beneficial, specifically in modern tightly controlled treatment regimens for early RA providing rapid benefit, and the effect on damage prevention seems to persist after quitting glucocorticoid treatment.

Treatment Tip

Based on the evidence reviewed here, low-dose and medium dose glucocorticoids should be considered as part of the initial treatment strategy in early RA (in combination with one or more conventional DMARDs) for up to 2 years. Effective retardation of the progression of erosive joint damage in early RA has been proven for dosages of 5 to 10 mg prednisone equivalent daily and for the COBRA and the COBRA light schemes, starting with 60 mg and 30 mg prednisone equivalent daily, respectively and rapidly tapering to stop at 28 weeks. Consultation time will be required to educate patients, their relatives and their primary care physicians about the nature of the treatment and the necessity of careful monitoring during treatment. Recommendations on the management of RA and glucocorticoid therapy can be of help in this situation.[5-7]

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Cryoglobulinaemia and Hepatitis C Virus

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LEARNING OBJECTIVES

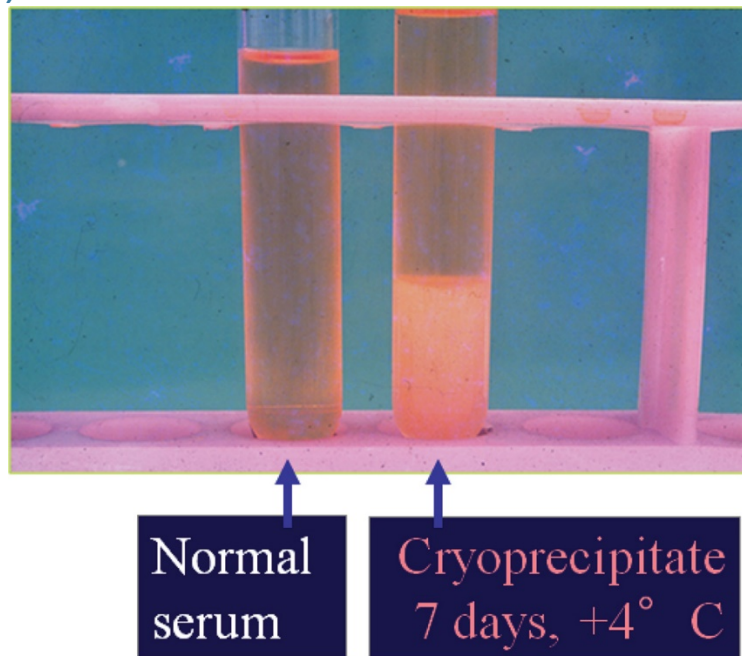
- Correctly classify/diagnose cryoglobulinaemia and mixed cryoglobulinaemia (MC).
- Use the correct technical procedures to detect and characterise cryoglobulins.
- Describe and explain the main mechanisms involved in the aetiopathogenesis of MC syndrome (cryoglobulinaemic vasculitis).
- Outline the epidemiology, prognosis and main clinical manifestations of MC syndrome.
- Make a differential diagnosis between MC syndrome and other autoimmune rheumatic disorders (Sjögren's syndrome, rheumatoid arthritis, other systemic vasculitides).
- Define the main organ, systemic autoimmune disorders, and neoplastic complications possibly triggered by hepatitis C virus (HCV) infection, the HCV syndrome.
- Describe and explain the pathogenetic mechanisms of HCV-related autoimmune and lymphoproliferative disorders.
- List the main levels of intervention (etiological, pathogenetic, and symptomatic) and targets of HCV-mixed cryoglobulinaemia therapy: clinical response (organ target manifestations), virological response (HCV RNA) and immunological response (cryoglobulinaemia, C4 serum level).
- Understand that antiviral therapy is the cornerstone of HCV-mixed cryoglobulinaemia treatment.
- State that B cell depleting therapy (rituximab) is an interesting additional therapeutic option.
- Explain the timing of action and the limitations of rituximab.
- Explain concerns about immunosuppressant agent use in HCV-related mixed cryoglobulinaemia.
- Describe the use of steroids, immunosuppressant agents and plasmapheresis.

1 Cryoglobulinaemia

1.1 Definition

The presence in the serum of one (monoclonal cryoimmunoglobulinaemia) or more immunoglobulins (mixed cryoglobulinaemia, MC), which precipitate at temperatures below 37°C and redissolve on rewarming, is termed cryoglobulinaemia or cryoimmunoglobulinaemia and is an in vitro phenomenon (figure 1) (Ferri, 2002*; Ferri, 2008*). Various hypotheses have been suggested to explain the cold precipitation of immunoglobulin(s): it can be secondary to the intrinsic characteristics of both mono- and polyclonal immunoglobulin (Ig) components or can be caused by interaction among single components of the cryoprecipitate. However, the intimate mechanism(s) of cryoprecipitation remains obscure.

Figure 1 Comparison of cryoglobulinaemic and normal serum samples. Cryoprecipitate, evaluated after 7 days' storage at 4°C, is present in a serum sample from a patient with mixed cryoglobulinaemia compared with normal serum (left).



1.2 Classification

Cryoglobulinaemia is usually classified into three subgroups according to immunoglobulin composition (table 1). Type I cryoglobulinaemia consists of only one isotype or subclass of immunoglobulin. Both type II and type III mixed cryoglobulins are immune complexes (IC) composed of polyclonal IgGs, autoantigens and mono- or polyclonal IgMs, respectively; the IgMs are the corresponding autoantibodies with rheumatoid factor (RF) activity. With more sensitive methodologies (ie, immunoblotting or two-dimensional polyacrylamide gel electrophoresis), type II mixed cryoglobulins often show a microheterogeneous composition; in particular, oligoclonal IgM or a mixture of polyclonal and monoclonal IgM can be detected (Ferri, 2002*; Ferri, 2008*). This particular serological subset, termed type II–III MC, could represent an intermediate, evolutive state from

type III to type II MC. Moreover, type II–III MC could fit together with the most recent molecular studies showing the presence of oligoclonal B lymphocyte proliferation in liver and bone marrow biopsy specimens from patients with MC. In two-thirds of patients with type II MC, a cross-idiotype WA monoclonal RF (first isolated from the serum of a patient with Waldenström’s macroglobulinaemia) has been demonstrated (Ferri, 2002*; Ferri, 2008*).

Table 1 Classification and clinico-pathological characteristics of different cryoglobulinaemias

Classification	Composition	Pathological findings	Clinical associations
Type I cryoglobulinaemia	Monoclonal Ig, mainly IgG, or IgM, or IgA self-aggregation through Fc fragment of Ig	Tissue histological alterations of underlying disorder	Lymphoproliferative disorders: MM, WM, CLL, B-NHL
Type II mixed cryoglobulinaemia	Monoclonal IgM (or IgG, or IgA) with RF activity (often cross-idiotype WA-mRF) and polyclonal Ig (mainly IgG)	Leucocytoclastic vasculitis B lymphocyte expansion with tissue infiltrates	Infections (mainly HCV), autoimmune/lymphoproliferative disorders, rarely ‘essential’
Type II–III mixed cryoglobulinaemia	Oligoclonal IgM RF or mixture of poly/monoclonal IgM (often cross-idiotype WA-mRF)	Leucocytoclastic vasculitis B lymphocyte expansion with tissue infiltrates	Infections (mainly HCV), autoimmune/lymphoproliferative disorders, rarely ‘essential’
Type III mixed cryoglobulinaemia	Polyclonal mixed Ig (all isotypes) with RF activity of one polyclonal component (usually IgM)	Leucocytoclastic vasculitis B lymphocyte expansion with tissue infiltrates	Infections (mainly HCV), more often autoimmune disorders, rarely ‘essential’

B-NHL, B cell NHL; CLL, chronic lymphocytic leukaemia; HCV, hepatitis C virus; Ig, immunoglobulin; MM, multiple myeloma; NHL, non-Hodgkin’s lymphoma; RF, rheumatoid factor; WM, Waldenström’s macroglobulinaemia.

Type I cryoglobulinaemia is usually associated with well-known haematological disorders but is often itself asymptomatic (Ferri, 2002*; Ferri, 2008*). Similarly, circulating mixed cryoglobulins can be detected in a great number of infectious or systemic disorders; generally they represent an isolated laboratory finding with no clinical consequences. In contrast, ‘essential’ MC represents a distinct disorder, which is classified as one of the systemic vasculitides. Cryoglobulinaemic vasculitis (figure 2) is secondary to vascular deposition of circulating IC, mainly cryoglobulins and complement, with the possible contribution of both haemorheological and local factors. According to its clinical and histological features, MC is included in the subgroup of small-vessel systemic vasculitides, which also include cutaneous leucocytoclastic vasculitis and Henoch–Schönlein purpura (table 2).

Table 2 Proposed classification of systemic vasculitides

Vessels	Primary	Secondary
Large–medium arteries	Takayasu’s arteritis, giant cell arteritis	Infectious arteritis (syphilis), rheumatoid arthritis
Medium arteries	Kawasaki’s arteritis, polyarteritis nodosa	RA, SLE, SSc, PM/DM, Behçet’s syndrome, HBV+, SS
Medium–small arteries	Granulomatosis with polyangiitis (Wegener’s), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), microscopic polyangiitis	Cogan syndrome, recurrent polychondritis, drugs, HBV, HCV, HIV infection
Small arteries, capillaries, venules	‘Essential’ MC (<10%),* cutaneous leucocytoclastic vasculitis, Henoch–Schönlein purpura	MC (HCV+ 90%; HBV+ <5%),* HIV infection, others, drugs, lymphoproliferative disorders

*The percentages refer to a Italian mixed cryoglobulinaemia series.

HBV, hepatitis B virus; HCV, hepatitis C virus; MC, mixed cryoglobulinaemia; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren’s syndrome; SSc, systemic sclerosis.

Figure 2 Cutaneous manifestations of mixed cryoglobulinaemia (MC). (A) Recent-onset orthostatic purpura; at this stage the histopathological evaluation shows (B) the classic necrotising leucocytoclastic vasculitis characterised by diffuse fibrinoid necrosis and disintegrated neutrophil permeation of the vessel walls. (C) Symmetrical hyperpigmentation of the skin on the legs after repeated episodes of purpura, (D) severe vasculitic manifestation and (E) a large skin ulcer, often resistant to treatment. Both orthostatic purpura (A) and permanent ochraceous lesions (C) are typical skin manifestations of MC.



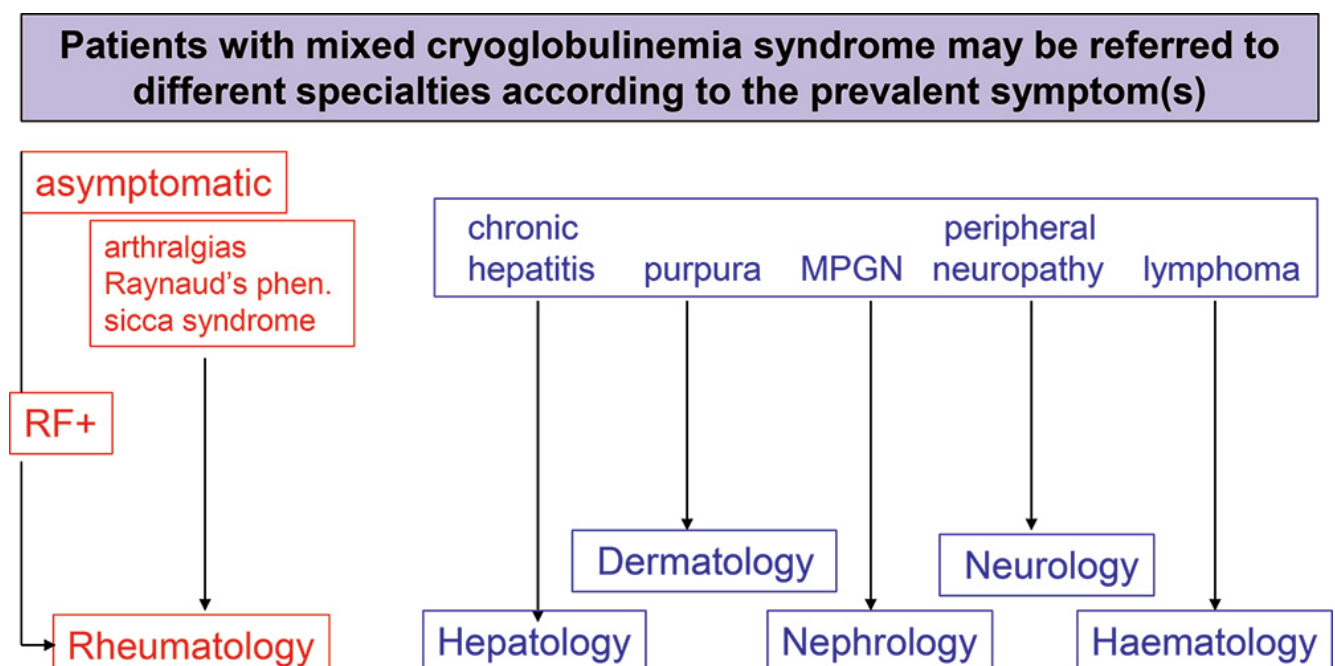
Leucocytoclastic vasculitis is the histopathological hallmark of MC (figure 2). It may involve small- and medium-sized vessels and may be responsible for multiple organ involvement (Ferri, 2002*; Ferri, 2008*). The term ‘cryoglobulinaemic vasculitis’ is often used as a synonym and better describes the typical histopathological alterations commonly detectable in the biopsy of cutaneous lesions.

2 Mixed cryoglobulinaemia (cryoglobulinaemic vasculitis)

2.1 Epidemiology

MC is considered to be a rare disorder, but no adequate epidemiological studies of its overall prevalence have been carried out. Numerous cohort studies of series of patients from different countries suggest that the prevalence of MC is geographically heterogeneous; the disease is more common in southern Europe than in northern Europe or North America. MC is characterised by clinical polymorphism – a single manifestation (skin vasculitis, hepatitis, nephritis, peripheral neuropathy, etc) is often the only apparent or clinically predominant feature – so that patients with MC are often referred to different specialties (figure 3). Consequently, a correct diagnosis might be delayed or overlooked entirely. Thus, we can understand why the true prevalence of MC might be underestimated (Ferri, 2002*; Ferri, 2008*; Ferri, 2016).

Figure 3 Distribution of patients with mixed cryoglobulinaemia (MC) among different medical specialties. Given its clinical polymorphism, MC syndrome may develop with different, often unpredictable symptoms. Consequently, patients with MC may be referred to different specialties according to the prevalent or apparently unique clinical manifestations, such as membranoproliferative glomerulonephritis (MPGN) or purpuric skin lesions. Patients with very mild manifestations, often arthralgias and/or serum rheumatoid factor (RF) positivity, are generally referred to a rheumatology clinic. phen, phenomenon.



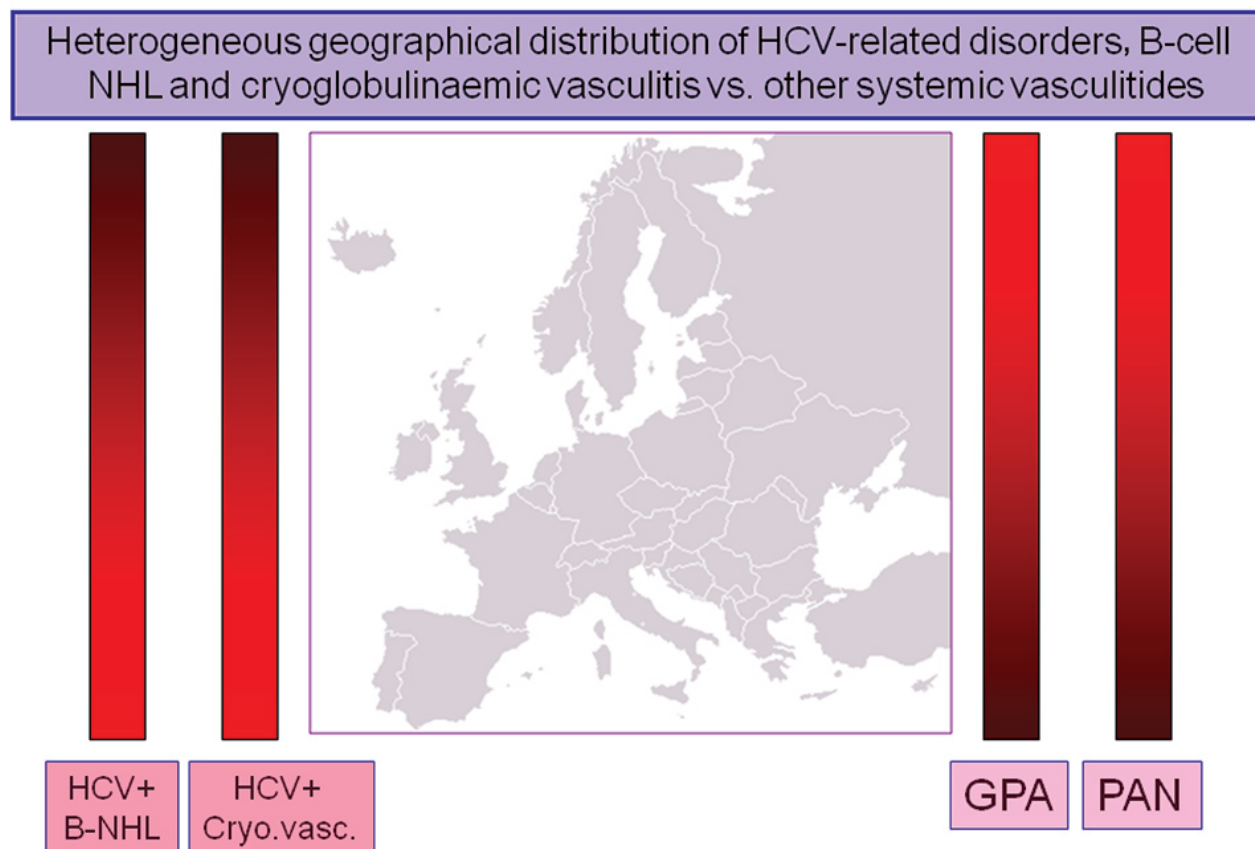
For the above reasons, mainly the frequent dispersion of patients among different specialties, symptom composition in MC syndrome may vary greatly among patient series from various tertiary care facilities (figure

3). Overall, MC is more common in women than in men (female to male ratio of 3:1), disease onset is particularly common in the fourth to fifth decades and in older people, and the disease is rarely seen in young people.

The epidemiology of MC associated with hepatitis C virus (HCV) infection has been examined in cohort studies focusing on HCV-infected subjects, which reported low levels of circulating mixed cryoglobulins in over 50% of cases, while overt cryoglobulinaemic syndrome developed in about 5%. HCV infection is particularly diffuse worldwide; therefore, an increasing incidence of some late complications of HCV infection, such as MC, could be observed, especially in underdeveloped countries where HCV is prevalent in the general population.

In contrast, 'essential' MC is generally seen in a significantly lower proportion of patients with MC, being quite rare in some geographical areas, such as southern Europe (figure 4).

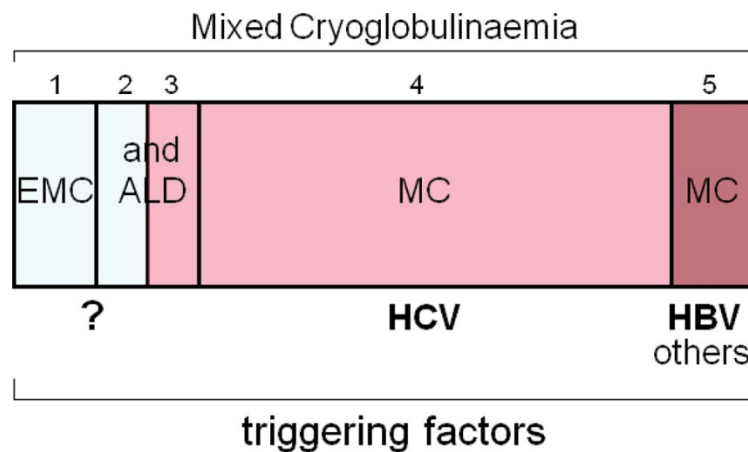
Figure 4 Geographical distribution of some hepatitis C virus (HCV)-related and non-HCV-related disorders. The prevalence of HCV-related disorders, such as mixed cryoglobulinaemia (cryoglobulinaemic vasculitis (Cryo. vasc.) and B cell non-Hodgkin's lymphoma (B-NHL)) shows large geographical heterogeneity. For example, these disorders are more prevalent in southern than in northern Europe, in contrast to the distribution seen for other diseases, such as some systemic vasculitides (granulomatosis with polyangiitis (GPA) and polyarteritis nodosa (PAN)).



2.2 Aetiopathogenesis

Several clinico-epidemiological studies reported that chronic hepatitis was one of the most common symptoms of MC; its prevalence progressively increases to over two-thirds of patients during the clinical course of the disease. This observation suggested a possible role for hepatotropic viruses in the pathogenesis of the disease and so a causative role for hepatitis B virus (HBV) has been sought since the 1970s. The same virus has been just correlated with another systemic vasculitis, namely, polyarteritis nodosa. However, HBV viraemia was rarely recorded, while anti-HBV antibodies varied among different groups of patients with MC (Ferri et al, 2002*; Ferri, 2008*). HBV may be a causative factor of MC in <5% of people (figure 5).

Figure 5 Schematic representation of different clinical and virological subsets of mixed cryoglobulinaemia (MC) syndrome. (1) 'Essential' MC (EMC); (2,3) EMC and hepatitis C virus (HCV)-associated MC syndrome in the setting of definite autoimmune-lymphoproliferative disorders (ALD), such as autoimmune hepatitis, Sjögren's syndrome or B cell lymphomas; (4) the most common subset of HCV-associated MC syndrome; and (5) MC associated with other infectious agents such as hepatitis B virus (HBV).



In 1989, the discovery of HCV as the major aetiological agent of non-A-non-B chronic hepatitis, was crucial for the aetiopathogenetic studies of MC syndrome. A possible role of HCV infection in MC was proposed independently by two pioneering reports which showed a significantly higher prevalence of serum anti-HCV antibodies in these patients than in the general population (Ferri, 2015* review). This hypothesis was deeply confirmed in 1991, when the presence of HCV RNA was detected by polymerase chain reaction (PCR) in 86% of Italian patients with MC (Ferri, 1991*). Following this, an increasing number of studies including clinico-epidemiological observations, as well as both histopathological and virological investigations (HCV RNA detection by PCR and/or in situ hybridisation) established the important role of HCV in the pathogenesis of MC. The prevalence of serum anti-HCV antibodies and/or HCV RNA in patients with MC ranged from 70% to almost 100% among different patient populations. Given the striking association between MC and HCV infection, the term 'essential' is now used to refer to a minority of patients with MC (in Italy <10%; figure 5) (Ferri, 2002*; Ferri, 2008*).

The clinical development of MC is closely linked to the natural history of chronic HCV infection. MC phenotypes are also the result of genetic and/or environmental cofactors, which remain largely unknown (figure 6). HCV has been recognised to be both a hepato- and lymphotropic virus, as suggested by the presence of active or latent viral replication in the peripheral lymphocytes of patients with type C hepatitis or MC. HCV is an RNA virus without reverse transcriptase activity; therefore, the viral genome cannot integrate in the host genome. It is probable that HCV chronically stimulates the immune system through different viral proteins, such as core protein. Chronic stimulation of the lymphatic system exerted through viral epitopes, autoantigen production and/or a molecular mimicry mechanism has been suggested. In this respect, particularly interesting is the presence, in HCV-positive patients, of anti-GOR antibodies, which are cross-reactive autoantibodies directed both to the HCV core and a nuclear antigen called GOR. Another pathogenetic hypothesis suggested that HCV, in association with very low-density lipoprotein (LDL), might induce a T-independent primordial B cell population, producing monoclonal immunoglobulin with WA idiotype. In turn, HCV–very LDL complexes may trigger RF production as a consequence of somatic mutations of WA clones; the possible evolution to B cell lymphomas might be the consequence of the accumulation of stochastic genetic aberrations. The chronic stimulation of B lymphocytes by HCV epitopes may cause expansion of some B cell subpopulations with favourable and/or dominant genetic characteristics (Ferri et al, 2002*; Ferri, 2008*). This hypothesis recalls the pathogenetic role of *Helicobacter pylori* in MALT lymphoma of the stomach, for which different evolutive phases are required.

The interaction between the HCV E2 envelope protein and CD81 molecule, a ubiquitous tetraspannin present on the surface of B cells, may represent another important pathogenetic factor in MC. The consequence of this interaction may be a strong and sustained polyclonal stimulation of the B cell compartment (figure 6). A following pathogenetic step of HCV-related autoimmune-lymphoproliferative disorders may be the t(14;18) translocation found in B cells of HCV-infected subjects. Even if not definitely confirmed, the t(14;18) translocation may lead to increased expression of Bcl-2 protein with consequent inhibition of apoptosis and abnormally prolonged B cell survival. Interestingly, a significantly high prevalence of t(14;18) translocation is found in patients with HCV-related MC (85% in type II MC), and also in patients with isolated hepatitis type C (about 37–38%). It can be hypothesised that during chronic HCV infection, several factors (including the interaction between the HCV E2 protein and CD81 molecule, the high viral variability and the persistent infection of both hepatic and lymphatic cells) may favour a sustained and strong B cell activation (figure 6). This latter may in turn favour the t(14;18) translocation and Bcl-2 overexpression; the consequent B lymphocyte expansion is responsible for autoantibody production, including the cryoglobulins. In addition, the prolonged B cell survival may represent a predisposing condition for further genetic aberrations, which may lead to frank B cell malignancy as a late complication of MC syndrome (Ferri et al, 2002*; Ferri, 2015*).

Of interest, HCV-driven lymphoproliferation may also explain the pathogenetic role of HCV infection in 'idiopathic' B cell lymphomas. This association was first described in unselected Italian patients with idiopathic B cell lymphomas and later confirmed by different epidemiological and laboratory studies, mainly in the same geographical areas as those in which HCV-associated MC is commonly found (figure 4).

Given its biological characteristics, HCV may be involved in many autoimmune and lymphoproliferative disorders. Figure 6 summarises the main causative factors – infectious, toxic, genetic and/or environmental – that are potentially involved in the pathogenesis of MC. These factors, alone or in combination, may trigger two multistep pathogenetic processes, not mutually exclusive, responsible for MC and other HCV-related disorders. The first process produces a 'benign' polyoligoclonal B lymphocyte proliferation responsible for organ- and non-organ-specific autoimmune disorders, including immune-complex-mediated cryoglobulinaemic vasculitis; the second is characterised by different oncogenetic alterations, which ultimately may lead to malignant complications. Comparable pathogenetic mechanisms could be also hypothesised for HCV-negative MC; this intriguing clinical subset might be correlated with other infectious agents or associated with some well-known autoimmune/rheumatic or lymphoproliferative disorders (figures 5 and 6) (Ferri et al, 2002*; Ferri, 2015*).

MC with or without overt clinical syndrome has been reported in patients with a great number of infectious agents, usually as anecdotal observations. A significant prevalence of MC has been found in patients with human immunodeficiency virus (HIV) infection, with and without HCV co-infection. HIV alone may exert a continuous antigenic stimulation of B lymphocytes; these latter may be responsible for type III MC production earlier in the course of HIV infection. In some patients, the B cell disorder may evolve into monoclonal MC with a typical clinical syndrome. As observed for HCV infection, the prevalence of other virus-related MC is variable among patient series from different geographical areas (figure 4). Moreover, a number of clinico-epidemiological studies showed a heterogeneous distribution of different HCV-related extrahepatic manifestations, including some autoimmune disorders such as primary Sjögren's syndrome (pSS) (Ferri et al, 2002*; Ferri et al, 2007*; Ferri, 2015*).

Cryoglobulinaemic syndrome may share a number of aetiopathogenetic events and clinical features with both autoimmune diseases such as autoimmune hepatitis (AIH), Sjögren's syndrome and polyarthritis, and B cell lymphomas. Therefore, a differential diagnosis should be carefully made in all patients with MC syndrome (figure 7) (see also section 2.5); correct disease classification may decisively affect the overall clinico-therapeutic approach and prognosis.

Figure 6 Aetiopathogenesis of mixed cryoglobulinaemia (MC) and other HCV-related disorders: the HCV syndrome. The figure summarises the putative mechanisms involved in the aetiopathogenetic cascade of MC and other HCV-related disorders. This is probably a multifactorial and multistep process: the remote events include some infectious agents, mainly HCV (see also Fig. 5), predisposing host factors and, possibly, unknown environmental/toxic triggers. Viral antigens (eg, HCV core, envelope E2, NS3, NS4, NS5A proteins) may exert a chronic stimulus on the host immune system through specific lymphocyte receptors, such as CD81, which may interact with the viral E2. Predisposing host factors may include particular HLA alleles, and metabolic and hormonal conditions. The main consequence is a 'benign' B cell proliferation with a variety of autoantibodies produced, among which are rheumatoid factor (RF), and cryo- and non-cryoprecipitable immune complexes (IC). These serological alterations may be correlated with different organ- and non-organ-specific autoimmune disorders, including MC syndrome (or cryoglobulinaemic vasculitis). Moreover, the activation of Bcl2 proto-oncogene, responsible for prolonged B cell survival, may be a predisposing condition to other genetic aberrations, which may lead to frank B cell lymphomas and other malignancies. The appearance of malignant neoplasias can be seen in a small but significant percentage of patients, usually as a late complication. Both immunological and neoplastic disorders show a clinico-serological and pathological overlap. Often, autoimmune organ-specific manifestations may evolve to systemic conditions, such as MC, and less frequently to overt malignancies (right). Conversely, it is not uncommon that patients with malignancies develop one or more autoimmune manifestations. In this scenario, MC syndrome is at the junction between autoimmune and neoplastic disorders. HCV, hepatitis C virus; IC, immune complexes; PCT, porphyria cutanea tarda; RF, rheumatoid factor; sicca s., sicca syndrome.

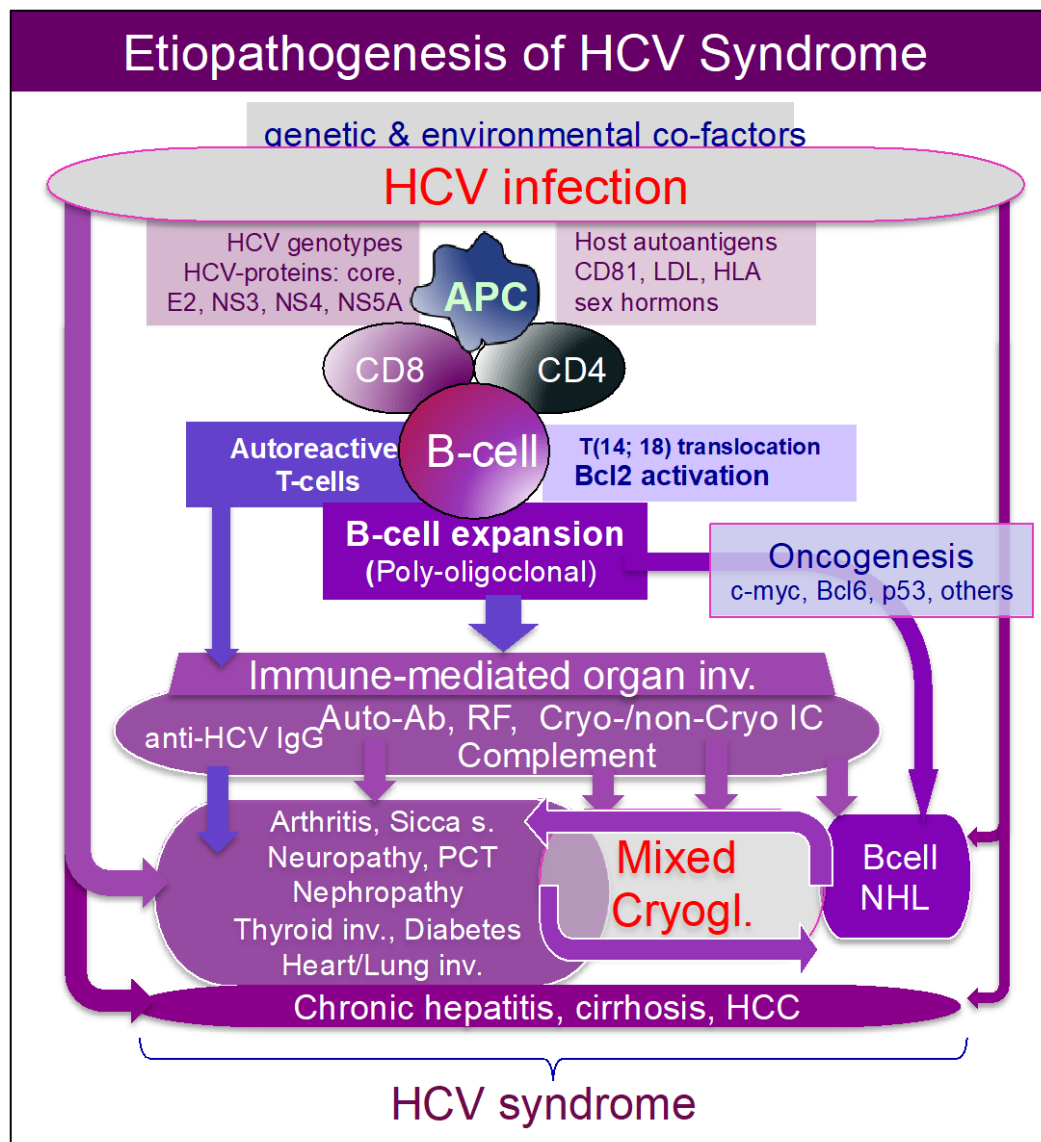
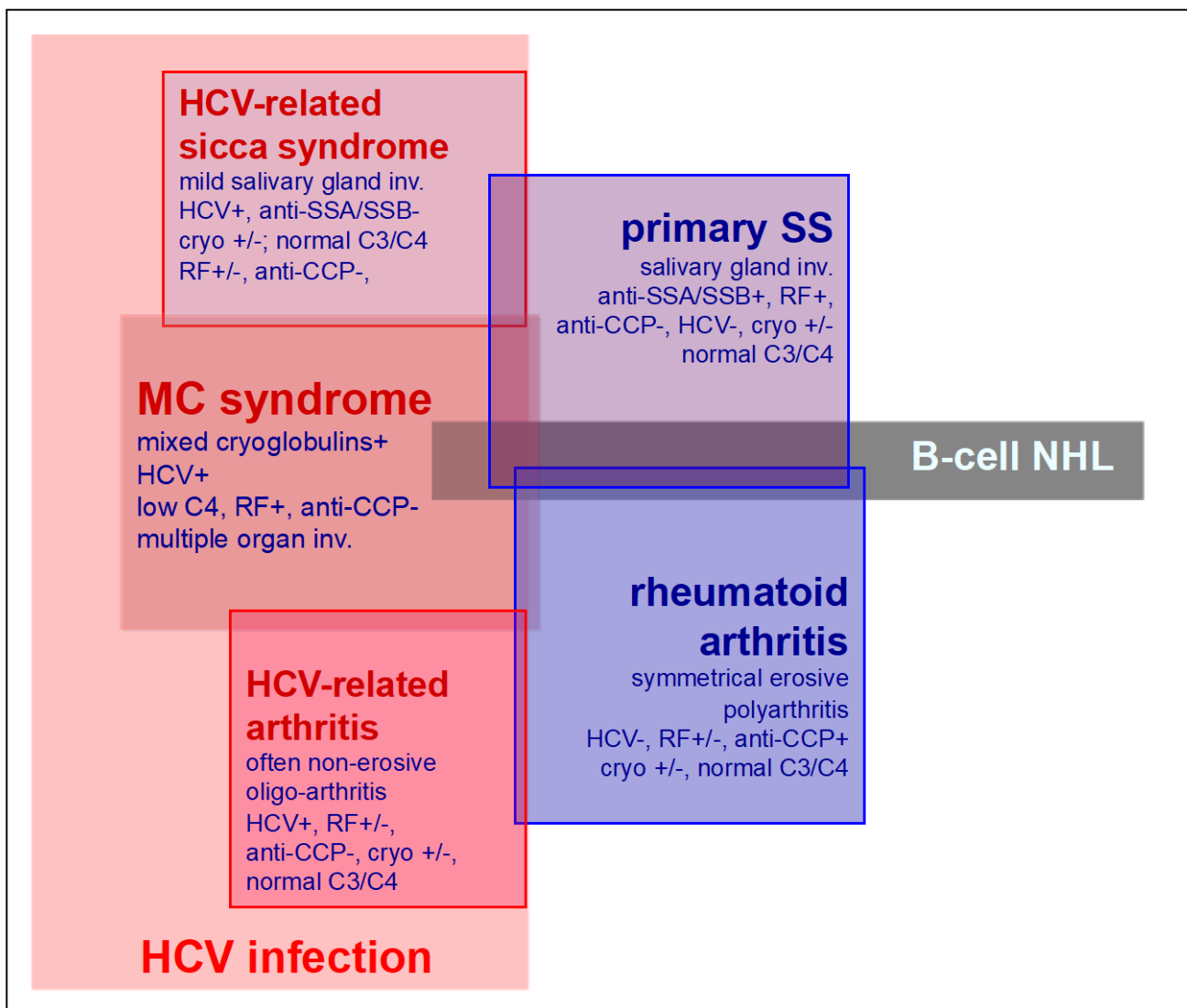


Figure 7 Clinical overlap and differential diagnosis among some possible hepatitis C virus (HCV)-related rheumatic diseases. Mixed cryoglobulinaemia (MC) syndrome, primary Sjögren's syndrome (SS) and rheumatoid arthritis (RA) show a clinico-pathological overlap, including a possible association with HCV infection. The following information may be useful for a correct differential classification/diagnosis: primary SS shows a typical histopathological pattern of salivary gland involvement (inv.) and specific autoantibodies (anti-RoSSA/LaSSB), which are rarely found in patients with MC; conversely, cutaneous leucocytoclastic vasculitis, visceral organ involvement (glomerulonephritis, hepatitis), low C4 and HCV infection, are typically found in MC. Moreover, erosive symmetrical polyarthritis and serum anticyclic citrullinated peptide antibodies (anti-CCP) characterise classic RA. Finally, B cell non-Hodgkin's lymphoma (B-NHL) may complicate these diseases, more frequently MC and primary SS. B-NHL may be suspected following careful clinico-serological monitoring and diagnosed by bone marrow/lymph node biopsies and total body CT scan. RF, rheumatoid factor.



2.3 Clinical manifestations

MC syndrome, or cryoglobulinaemic vasculitis, is characterised by a clinical triad of purpura, weakness and arthralgias, and by a variable combination of symptoms, including chronic hepatitis, membranoproliferative glomerulonephritis (MPGN), peripheral neuropathy, skin ulcers, diffuse vasculitis and, less frequently, lymphatic and hepatic malignancies. The clinical pattern of cryoglobulinaemic vasculitis is comparable in

patients with type II or type III MC. Table 3 gives the prevalence of MC manifestations in an Italian patient population referred to our university-based division of rheumatology. Patient recruitment at different specialist centres may influence the symptom composition of MC series; for example, patients with MC recruited at nephrology units naturally show a higher percentage of glomerulonephritis compared with those seen at rheumatology units (figures 3 and 13). This factor together with the different geographical origins of patient series reported in the literature may be responsible for the variable prevalence of individual MC symptoms (Ferri, 2015*).

Table 3 Demographic, clinico-serological and virological features of 250 patients with mixed cryoglobulinaemia evaluated at the end of patient follow-up

Features	Value
Epidemiological features	
Age at disease onset (years), mean (SD) (range)	54 (13) (29–72)
Female:male ratio	3
Disease duration (years), mean (SD) (range)	12 (10) (1–40)
Clinical features	
Purpura	98
Weakness	98
Arthralgias	91
Arthritis (non-erosive)	8
Raynaud's phenomenon	32
Sicca syndrome	51
Peripheral neuropathy	81
Renal involvement*	31
Liver involvement	73
B cell non-Hodgkin's lymphoma	11
Hepatocellular carcinoma	3
Serological and virological features	
Cryocrit (%), mean (SD)	4.4 (12)
Type II/type III mixed cryoglobulins	2/1
C3 (mg/dL), mean (SD) (normal 60–130)	93 (30)
C4 (mg/dL), mean (SD) (normal 20–55)	10 (12)
Antinuclear antibodies	30
Antimitochondrial antibodies	9
Antismooth muscle antibodies	18
Antiextractable nuclear antigen antibodies	8
Anti-HCV antibodies ± HCV RNA	92
Anti-HBV antibodies	32
HBsAg	1
HCV-/HBV-	7

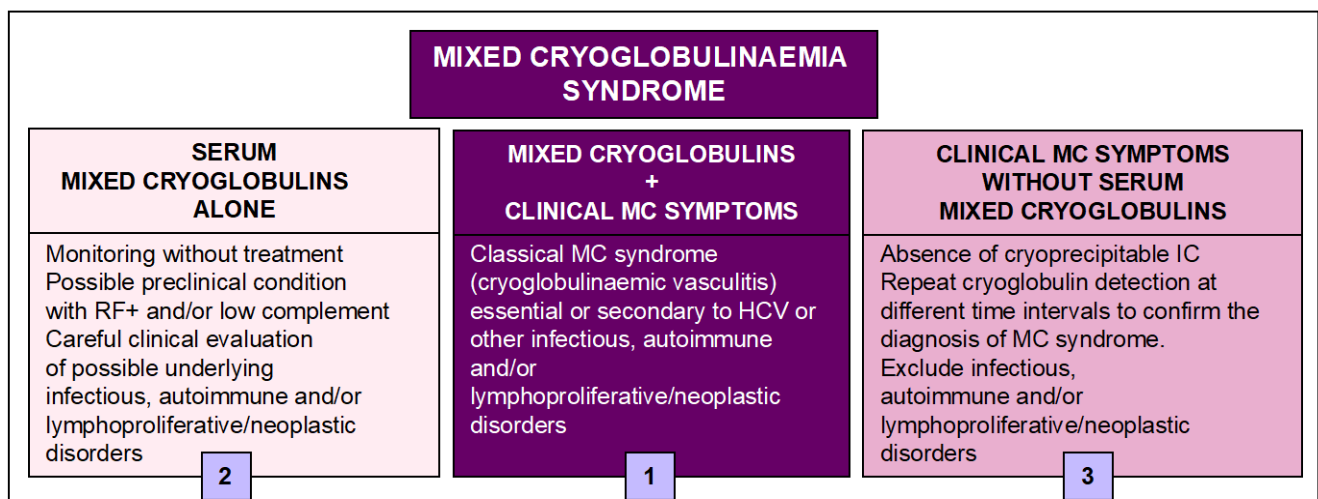
Results are shown as percentages unless otherwise stated.

*Invariably membranoproliferative glomerulonephritis.

HBV, hepatitis B virus; HCV, hepatitis C virus.

At patient anamnesis, the presenting symptoms of MC vary greatly among cryoglobulinaemic patients; similarly, at the first examination, MC shows different clinico-serological patterns, varying from apparently isolated serum mixed cryoglobulins, in some cases associated with mild manifestations such as arthralgias and/or sporadic purpura, to severe cryoglobulinaemic syndrome with multiple organ involvement (figure 8). The disease shows a combination of serological findings (mixed cryoglobulins with RF activity and frequently low C4) and clinico-pathological features (purpura and leucocytoclastic vasculitis with multiple organ involvement). In some chronically HCV-infected subjects, asymptomatic serum mixed cryoglobulins can be found. This condition may precede the clinical onset of disease by years or decades. On the other hand, some patients show typical cryoglobulinaemic syndrome without serum cryoglobulins, the hallmark of the disease (figure 8). MC is characterised by a large amount of cryoprecipitable IC, with the cryoglobulins representing a variable percentage of them among different patients as well as in the same patient during follow-up. Therefore, the absence of serum cryoglobulins may be a transient phenomenon owing to this variable percentage of cryoprecipitable IC; repeated cryoglobulin determinations are necessary for a correct diagnosis in these subjects (Ferri et al, 2002*; Ferri, 2008*).

Figure 8 Different clinico-serological patterns of mixed cryoglobulinaemia (MC). (1) *Definite MC syndrome (or cryoglobulinaemic vasculitis) is a combination of serological findings (mixed cryoglobulins with rheumatoid factor (RF) activity and often low C4) and typical clinico-pathological features (purpura, leucocytoclastic vasculitis and frequent multiple organ involvement) (also see table 3). However, incomplete MC syndrome can be seen at any time during the natural history of the disease. In particular, (2) isolated serological alterations may be detected in the early stages of the disease or during clinical remission. In contrast, (3) the absence of serum cryoglobulins in patients with overt MC syndrome may be a transient phenomenon due to the wide variability in the percentage of cryoprecipitable immune complexes (IC) during the natural history of the disease or, less frequently, to switching from 'benign' B cell lymphoproliferation to malignant lymphoma.*



The most common manifestations of MC are cutaneous lesions. Orthostatic purpura is generally intermittent, with the dimensions and diffusion of purpuric lesions varying greatly from sporadic isolated petechiae to severe vasculitic lesions, often complicated by torpid ulcers of the legs and malleolar areas (figure 2). In a

significant proportion of patients, repeated episodes of purpura may lead to stable, often confluent, areas of ochraceous colouration on the legs (figure 2). Cutaneous manifestations, in particular orthostatic purpura and ulcers, are the direct consequence of vasculitic alterations with the possible contributions of various cofactors, in particular chronic venous insufficiency and physical stress, mainly prolonged standing and/or muggy weather. In addition, haemorheological disturbances due to high cryocrit levels may also be a contributing factor. In this respect, the purpuric outbreaks are often seen late in the afternoon when the highest cryocrit levels are generally found, often following prolonged standing (Ferri et al, 2002*; Ferri, 2008*).

Patients with MC frequently have arthralgias, while clear signs of arthritis (usually mild, non-erosive oligoarthritis) are less often seen.

Almost half of the patients with MC complain of mild sicca syndrome, that is, xerostomia and xerophthalmia; however, only a few cases meet the current criteria for the classification of pSS (see section 2.5).

Peripheral neuropathy may frequently complicate the clinical course of MC, in most cases as mild sensory neuritis. The common symptoms are paraesthesias with painful and/or burning sensations in the lower limbs, often with nocturnal exacerbation. The patient's quality of life may be severely compromised because of the chronicity of these symptoms together with their poor response to treatment. In a minority of cases, the peripheral neuropathy may be complicated by severe sensorimotor manifestations, which usually appear abruptly, often as asymmetric mononeuritis. In some patients, peripheral neuropathy may complicate interferon (IFN) α treatment, possibly in predisposed subjects, often during the first weeks of antiviral therapy. Central nervous system involvement, including dysarthria and hemiplegia, is rarely seen; in older patients, it is often difficult to distinguish these symptoms from the most common atherosclerotic vascular manifestations (Ferri et al, 2002*; Ferri, 2015*; Ferri, 2016*).

In over two-thirds of patients (table 3), overt chronic hepatitis, generally with a mild to moderate clinical course, can be seen throughout the natural history of the disease. This manifestation, uncommon in other systemic vasculitides, is the direct consequence of HCV infection that represents the underlying disorder in MC. In our experience, chronic hepatitis may evolve to cirrhosis in one-quarter of patients, while only seven patients (3%, 7/250; see table 3) developed hepatocellular carcinoma. In a few cases, especially in patients with renal failure due to chronic glomerulonephritis, hepatorenal syndrome develops as a major life-threatening complication. On the whole, the clinical course and prognostic value of chronic hepatitis seem to be less severe than for classic type C hepatitis without MC syndrome; similarly, hepatocellular carcinoma less often complicates MC syndrome compared with the total population of HCV-positive subjects. These differences are quite intriguing, but difficult to fully explain. It may be that patients with MC characterised by a relatively low prevalence of HCV genotype 1b, along with a lower median consumption of alcohol, develop a rather benign clinical course of liver involvement.

MPGN type 1 is another important complication, which may severely affect the prognosis and survival of patients with the disease. MC-related nephropathy is a typical IC-mediated glomerulonephritis, although other immunological mechanisms have also been hypothesised.

Widespread vasculitis involving medium to small arteries, capillaries and venules with multiple organ involvement may develop in a small proportion of patients. This extremely severe complication may involve the skin, kidney, lungs, central nervous system and gastrointestinal tract. In rare cases, intestinal vasculitis may suddenly complicate the disease, often in patients with renal and/or liver disease; pain simulating an acute abdomen is the presenting symptom of intestinal vasculitis. A timely diagnosis and aggressive treatment are necessary for this life-threatening complication.

Interstitial lung disease has been anecdotally observed in MC syndrome as well as in patients with isolated HCV infection. Almost invariably, lung involvement in MC is characterised by subclinical alveolitis, as demonstrated by bronchoalveolar lavage in an unselected patient series; this condition may predispose to pulmonary infectious complications and, in rare cases, may lead to clinically evident interstitial lung fibrosis.

The hyperviscosity syndrome due to high levels of serum cryoglobulins is another rare clinical manifestation of MC, although haemorheological alterations may contribute to some clinical symptoms such as orthostatic purpura, skin ulcers and renal involvement.

Generally, there are no associations between the severity of clinical symptoms, such as glomerulonephritis, skin ulcers and/or diffuse vasculitis, and the serum levels of cryoglobulins and/or haemolytic complement (Ferri et al, 2002*; Ferri, 2008*). Low complement activity is almost invariably detected in MC. It is characterised by a typical pattern independently of disease activity; namely, low or undetectable C4 with normal or slightly reduced C3 serum levels (table 3). Moreover, in vitro consumption of complement can also be seen owing to the anticomplement activity of some cryoimmunoglobulins. In clinical practice, it is interesting to note sudden variations in C4, rising from very low to abnormally high levels, in some patients with MC developing a B cell lymphoma. The lack of correlation between circulating cryoglobulin levels and the severity/activity of MC manifestations might be explained by different hypotheses: the pathogenic role of other non-cryoprecipitable IC, their intrinsic ability to activate the complement and/or the in situ formation of IC, with a relative concentration of HCV virions.

Some endocrinological disorders are significantly more common in patients with MC than in the general population, including thyroid disorders, diabetes and gonadal dysfunction. The most common thyroid disorders are autoimmune thyroiditis, subclinical hypothyroidism and thyroid cancer; while hyperthyroidism is less common, it may appear as a reversible complication of IFN treatment. Moreover, a significantly increased incidence of diabetes mellitus type 2 has been found in HCV-positive patients with and without MC syndrome compared with the general population. Finally, HCV-positive men with or without cryoglobulinaemic vasculitis

may develop erectile dysfunction, attributable to hormonal or neurovascular alterations, or both (Ferri et al, 2002*; Ferri, 2008*).

B cell lymphoma is the most common malignancy found, often as a late manifestation of MC syndrome. This complication may be related to peripheral B lymphocyte expansion and to lymphoid infiltrates found in the liver and bone marrow, which represent the pathological substrate of the disease. In particular, these infiltrates have been regarded by some authors as 'early lymphomas', since they are sustained by lymphoid components indistinguishable from those of B cell chronic lymphocytic leukaemia/small lymphocytic lymphoma (B-CLL) and immunocytoma. However, unlike frank malignant lymphomas, they tend to remain unmodified for years or even decades and are followed by overt lymphoid tumours in approximately 10% of cases. These characteristics justify the proposed term 'monotypic lymphoproliferative disorder of undetermined significance (MLDUS)'. Interestingly enough, the incidence of type II MC-related MLDUS is highest in those geographical areas where about 30% of patients with 'idiopathic' B cell lymphomas also display HCV positivity and where an increased prevalence of HCV genotype 2a/c has been found in both MC and lymphomas (figure 4). Type II MC-associated MLDUS presents two main pathological patterns, namely, the B-CLL-like and the immunocytoma-like. In clinical practice, malignant B cell lymphomas are often seen in patients with MC with a mild clinical course, sometimes unexpectedly during a routine evaluation. It is possible to observe a sudden decrease or disappearance of serum cryoglobulins and RF, sometimes associated with abnormally high levels of C4 as the presenting symptom of complicating B cell malignancy (Ferri et al, 2002*; Ferri, 2008*).

Other neoplastic manifestations, for example, hepatocellular carcinoma or papillary thyroid cancer, are less often seen. Thus, MC can be regarded as a pre-neoplastic disorder; consequently, careful clinical monitoring is recommended, even in the presence of mild MC syndrome.

2.4 Diagnosis

To date there are no available diagnostic criteria for MC; in 1989 the Italian Group for the Study of Cryoglobulinaemias proposed preliminary criteria for MC classification, later revised with the inclusion of clinico-pathological and virological findings. This classification is mainly based on the serological and clinical hallmarks of the disease, namely, circulating mixed cryoglobulins, low C4 and orthostatic skin purpura. Moreover, leucocytoclastic vasculitis, involving medium and, more often, small blood vessels (arterioles, capillaries and venules) is the typical pathological finding of affected tissues. It is easily detectable by a skin biopsy of recent vasculitic lesions (within the first 24–48 h).

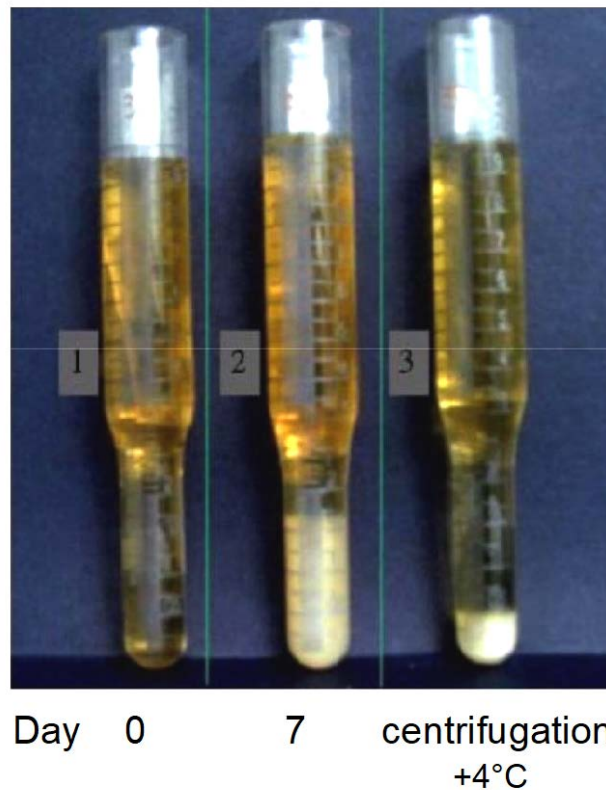
More recently, classification criteria for cryoglobulinaemic vasculitis have been validated by a cooperative study using a standardised methodology from a larger number of countries; these criteria may be usefully

employed in epidemiological and clinico-pathogenetic studies, as well as in therapeutic trials (Quartuccio, 2014*).

In all cases, the detection of cryoglobulins in the serum is necessary for a definite classification of MC syndrome (figure 1) and their characterisation as type II (IgG+IgM monoclonal) or type III (IgG+IgM polyclonal) mixed cryoglobulins (table 3). Unfortunately, there are no universally accepted methodologies for cryoglobulin measurement, but simple standardised indications are often sufficient for testing for cryoglobulinaemia. Cryoglobulins are characterised by high thermal instability. For a correct evaluation of serum cryoglobulins, it is necessary to avoid false-negative results due to immunoglobulin cold precipitation which also occurs at room temperature. Blood sampling for cryoglobulin detection should be carried out immediately after blood is drawn or blood should be rapidly transported to the laboratory using a thermostable device (37°C). In general, to avoid the possible loss of cryoglobulins, the first steps (blood sampling, clotting and serum separation by centrifugation) should always be carried out at 37°C. In contrast, isolated serum for cryoglobulin determination and characterisation should be managed at 4°C. The serum with cryoglobulins should be tested for reversibility of the cryoprecipitate by re-warming an aliquot at 37°C for 24 h. Cryocrit measurement is usually carried out in a serum sample stored at 4°C for 7 days. The cryocrit corresponds to the percentage of packed cryoglobulins with reference to the total serum after centrifugation at 4°C (figure 9); it should be determined on blood samples without anticoagulation to avoid false-positive results due to cryofibrinogen or heparin-precipitable proteins. Without the above relatively simple precautions, the quantities of cryoglobulins measured will be incorrect and the test may completely fail to detect cryoglobulins (Ferri et al, 2002*; Ferri, 2008*).

After isolating and washing the cryoprecipitate, the cryoglobulin components can be identified by immunoelectrophoresis or immunofixation. These analyses must be performed at 37°C to avoid precipitation and hence loss of the cryoglobulin during the procedures. More sophisticated methodologies, such as immunoblotting or two-dimensional polyacrylamide gel electrophoresis, may be used for laboratory investigations. Although the detection of serum cryoglobulins is fundamental for the diagnosis of MC, the levels of serum cryoglobulins usually do not correlate with the severity and prognosis of the disease. Very low levels of cryocrit, often difficult to quantify, can be associated with severe and/or active cryoglobulinaemic syndrome; in contrast, high cryocrit values may characterise a mild or asymptomatic disease course. In rare cases, very high cryocrit levels, possibly associated with a cryogel phenomenon, may be associated with classic hyperviscosity syndrome. A sudden decrease or disappearance of serum mixed cryoglobulins, with or without abnormally high levels of C4, should be regarded as an alarming signal of complicating B cell malignancy (Ferri et al, 2002*; Ferri et al, 2015*; Ferri, 2016*).

Figure 9 Isolation and measurement of serum cryoglobulins. Graduated glass tubes with serum samples from a cryoglobulinaemic patient at different time intervals: 0, soon after serum separation from the blood sample (at least 20 mL of whole blood); 7, after 7 days at 4°C; and centrifugation of the serum for cryocrit measurement, always at 4°C.



Box 1 summarises the clinico-serological investigations at a patient's first evaluation in order to classify the MC syndrome correctly and to identify possible overlapping disorders (figure 7) (see section 2.5) or comorbidities, or both. The prevalence of these latter, in particular atherosclerosis, may be correlated with the disease duration, and with cumulative side effects of prolonged treatments. Diagnosis and monitoring of the major MC manifestations is essential for their timely treatment, especially for life-threatening liver, renal and/or neoplastic complications.

Box 1 Clinico-diagnostic assessment of mixed cryoglobulinaemia syndrome (see also Ref. Ferri et al, 2016*)**Clinical and serological investigations at a patient's first evaluation:**

- Past clinical history, physical examination
- Chest X-ray examination, ECG, abdominal ultrasonography (US), blood chemistry and urine analysis
- Cryoglobulin detection and characterisation (see table 1)
- Rheumatoid factor, C3 and C4, antinuclear antibodies (abs), antiextractable nuclear antigen abs, antineutrophil cytoplasmic abs, antismooth muscle abs, antimitochondrial abs, antiliver/kidney microsome type 1 abs, other abs
- Virological markers: hepatitis C virus (genotyping), hepatitis B virus, others
- Evaluate possible comorbidities (cardiovascular, endocrine/metabolic, etc)
- Mixed cryoglobulinaemia (MC) classification (definite, essential, secondary)

Diagnosis and monitoring of major MC complications

- Chronic hepatitis, cirrhosis, hepatocellular carcinoma:
 - Monitoring (every 6–12 months) of alanine aminotransferase, alkaline phosphatase
 - Liver US (biopsy, CT scan)
- Glomerulonephritis:
 - Monitoring of urine analysis and serum creatinine (kidney US, biopsy)
- Peripheral neuropathy:
 - Clinical monitoring
 - Electro-neuro-physiological studies
- Skin ulcers:
 - Exclusion of vascular comorbidities (arteriovenous Doppler evaluation)
- Sicca syndrome:
 - Differential diagnosis with primary Sjögren's syndrome
- Arthritis:
 - Differential diagnosis with rheumatoid arthritis
- Thyroid involvement:
 - Hormones
 - Autoantibodies
 - Neck US
 - Fine-needle aspiration
- B cell lymphoma:
 - Clinical monitoring
 - Bone marrow/lymph node biopsies
 - Total body CT scan

2.5 Differential diagnosis

Initially, the term 'essential' referred to MC as an autonomous disease once other well-known systemic, infectious or neoplastic disorders had been ruled out by a wide clinico-serological investigation. However, in some patients a definite diagnosis may be difficult because of the clinical polymorphism of the MC. Moreover, the association of MC with HCV infection may further complicate the differential diagnosis as there is frequent clinico-pathological overlapping among different HCV-related disorders. Cryoglobulinaemic syndrome can represent a crossroads between some autoimmune diseases (AIH, Sjögren's syndrome, polyarthritis, glomerulonephritis, thyroiditis, type 2 diabetes, etc) and malignancies (B cell lymphomas, hepatocellular carcinoma) (Ferri et al, 2002*; Ferri et al, 2015*; Ferri, 2016*). We can observe in the same patient a slow

progression from mild HCV-associated hepatitis to various extrahepatic manifestations (arthralgias, sicca syndrome, Raynaud's phenomenon, RF positivity, etc) and, ultimately, to overt MC syndrome with typical clinico-serological manifestations. In a minority of patients with MC, a malignancy may develop, generally after a long follow-up period. Therefore, a careful patient evaluation is necessary for a correct diagnosis of MC syndrome, particularly to differentiate it from other RF-positive, systemic rheumatic disorders such as rheumatoid arthritis (RA) and pSS (figure 7).

Arthralgias are one of the most common symptoms, while clear signs of synovitis are quite rare. Patients may develop mild, non-erosive oligoarthritis, often sensitive to low doses of glucocorticoids with or without hydroxychloroquine. In contrast, rheumatoid-like polyarthritis is more common in patients with HCV-related hepatitis without MC syndrome. In patients with HCV-associated MC and symmetrical, erosive polyarthritis, the diagnosis of overlapping MC/RA syndrome can be suspected. In these cases, the detection of serum anticyclic citrullinated peptide antibodies, markers of classic RA, may be a useful tool for the differential diagnosis.

Sicca syndrome may be suspected in about half of the patients with MC; however, current criteria for the classification of pSS are satisfied in only a few cases. MC and pSS may share various symptoms: xerostomia and/or xerophthalmia, arthralgias, purpura, RF and serum cryoglobulins and possible complication with B cell lymphoma. However, a careful patient clinical assessment is usually sufficient for a correct diagnosis in the large majority of cases following consideration of some important findings: histopathological alterations of the salivary glands and the specific autoantibody pattern (anti-Ro/SSA-La/SSB) of pSS are rarely found in patients with MC; conversely, HCV infection, cutaneous leucocytoclastic vasculitis and visceral organ involvement (MPGN type 1, chronic hepatitis) are seldom recorded in pSS (figure 7). In view of the above considerations, it has been recently proposed that the presence of HCV infection itself should be considered an exclusion criterion for the classification of pSS. In rare cases in which the differential diagnosis is very difficult, particularly in HCV-negative patients, it might be correct to classify the disorder as an overlap syndrome. Patients with MC/pSS overlap syndrome are often characterised by a more severe clinico-prognostic evolution; they show a significantly low prevalence of anti-Ro/SSA-La/SSB together with a high prevalence of MC, hypocomplementaemia, systemic autoimmune manifestations and complicating lymphomas. In clinical practice, this particular condition might be better regarded as a vasculitic syndrome with relevant implications for patient prognosis and treatment (Ferri, 2008*; Ferri, 2015*).

Finally, AIH, the old 'lupoid' hepatitis, may be associated with HCV infection, generally in the same countries in which HCV-associated MC is more commonly found. AIH may share with MC syndrome a number of extrahepatic symptoms, including serum mixed cryoglobulins. The differential diagnosis between these two conditions may be problematic: some typical features of MC (leucocytoclastic vasculitis,

hypocomplementaemia, glomerulonephritis), as well as the presence of serum autoantibodies commonly found in AIH (antismooth muscle antibodies), should be taken into account.

2.6 Prognosis

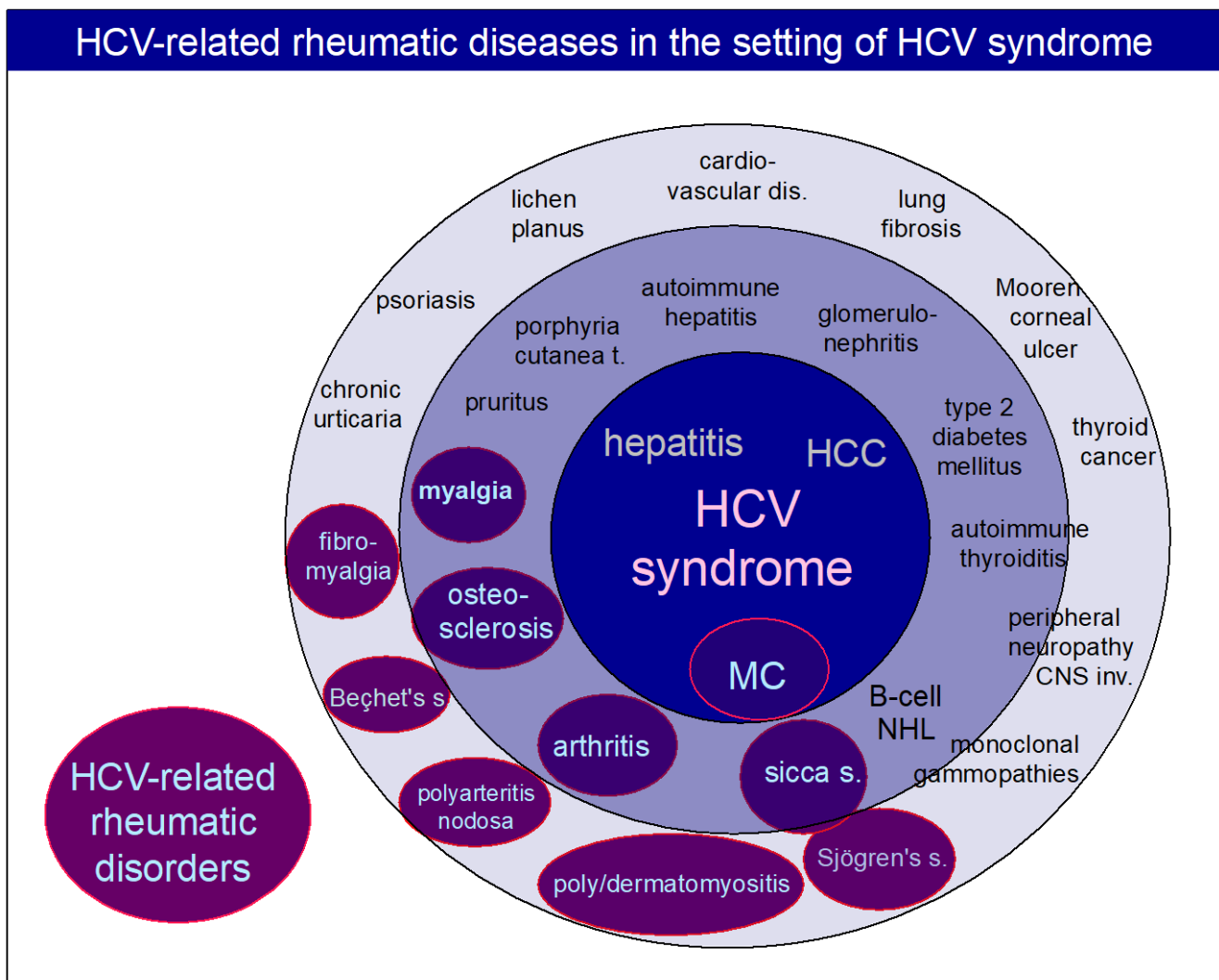
The natural history of MC is not predictable and strongly depends on concomitant diseases and complications and response to treatment. Morbidity due specifically to cryoglobulinaemia may also be significant (infections, cardiovascular diseases, progressive renal failure, advanced neuropathy). The overall prognosis is worse in patients with renal disease, liver failure, lymphoproliferative disease and malignancies. Mean survival is estimated to be about 50–60% at 10 years after diagnosis (Ferri et al, 2004*). Careful monitoring of life-threatening complications (mainly nephropathy, widespread vasculitis and B cell lymphoma or other malignancies) should be carried out in all patients with MC.

3 HCV-related extrahepatic disorders

HCV chronic infection is diffuse worldwide and may in a low but significant percentage of patients trigger a large number of extrahepatic manifestations. These include a variety of autoimmune and neoplastic disorders, among which MC is the prototypic HCV-associated extrahepatic disease (see section 2). It is a complex immunological disorder characterised by multiple organ involvement. Since MC syndrome, strongly associated with HCV infection, mimics other immune-mediated and neoplastic disorders, a possible role of HCV in these conditions has been also investigated. The spectrum of possible HCV-associated diseases includes a wide number of organ-specific and systemic diseases. Polyoligoclonal B lymphocyte expansion seems to be the common underlying alteration in a significant percentage of HCV-infected patients, some of whom may develop a variable combination of both hepatic and extrahepatic manifestations; the term ‘HCV syndrome’ refers to this complex clinical condition.

HCV-related diseases can be grouped into three different categories according to the strength of association with the viral infection based on clinico-epidemiological, histopathological and molecular biology studies (figure 10).

Figure 10 Possible clinical manifestations of hepatitis C virus (HCV) syndrome showing the strength of association between HCV and different diseases in the context of HCV syndrome. The spectrum of different HCV-associated immunological and neoplastic disorders may be classified on the basis of clinico-epidemiological, histopathological and molecular biology studies, into three different levels: (1) high: the association with HCV infection characterises the large majority of patients; HCV infection is one of the major triggering agents of the disease; (2) medium: the disease shows a significantly higher prevalence of HCV infection compared to controls; the putative pathogenetic role of HCV is also supported by pathogenetic studies and may identify at least a specific disease subset; and (3) low: the possible association is suggested by limited clinico-epidemiological observations; a pathogenetic link in at least a specific disease subset from some geographical areas is probable, but needs to be definitely demonstrated. Red circles indicate the main rheumatic diseases potentially HCV related. CNS, central nervous system; dis., disease; HCC, hepatocellular carcinoma; inv., involvement; MC, mixed cryoglobulinaemia; s., syndrome; t., tarda.



3.1 Pathogenesis of HCV-related autoimmune and lymphoproliferative disorders

The main pathogenetic insights into HCV syndrome have been provided by studies of the biological peculiarities of this virus and its possible interaction with the host immune system. In addition, studies of HCV-associated MC provided important insights into the pathogenesis of other HCV-related disorders. HCV lymphotropism is an important step in the pathogenesis of virus-related immunological disorders. A number of

epidemiological studies suggested a pathogenetic role for HCV in MC, a disorder characterised by 'benign' B lymphocyte expansion. Interestingly, the same immune-pathological alteration may also develop in a significant number of HCV-infected subjects, often in association with one or more serum autoantibodies or mixed cryoglobulins, or both.

Since HCV is a positive, single-stranded RNA virus without a DNA intermediate in its replicative cycle, viral genomic sequences cannot be integrated into the host genome. One possible hypothesis is that HCV infection exerts a chronic stimulus on the immune system, which facilitates clonal B lymphocyte expansion (Ferri et al, 2002*; Ferri et al, 2007*; Ferri, 2008*).

The t(14;18) translocation has been demonstrated in a significant percentage of peripheral blood lymphocytes from HCV-infected subjects, with consequent activation of the Bcl2 proto-oncogene (figure 6). In addition, identification of the HCV envelope protein E2, which can bind the CD81 molecule expressed on both hepatocytes and B lymphocytes, seems to be crucial for HCV-driven autoimmunity. CD81 is a cell-surface protein that, on B cells, is part of a complex with CD21, CD19 and Leu 13. This complex reduces the threshold for B cell activation by bridging antigen-specific recognition and CD21-mediated complement recognition. The interaction between HCV-E2 and CD81 might increase the frequency of VDJ rearrangement in antigen-reactive B cells. VDJ rearrangement could be responsible for the above-mentioned Bcl2 activation. The activated Bcl2 proto-oncogene can inhibit apoptosis; the consequence is an abnormally extended B cell survival. In turn, B lymphocyte expansion is responsible for the wide autoantibody production found in HCV-infected subjects, including cryo- and non-cryoprecipitable IC (figure 6). Specific autoantibodies may characterise some autoimmune disorders, while mixed cryoglobulins are the serological hallmarks of MC syndrome.

Other mechanisms such as molecular mimicry involving particular HCV antigens and host autoantigens could be responsible for B lymphocyte activation and autoantibody production (figure 6). In all cases, prolonged B cell survival can expose these cells to other genetic aberrations, which may lead in predisposed subjects to overt malignant lymphoma (figure 6). The oncogenic potential of HCV has been confirmed in patients with hepatocellular carcinoma and in a significant percentage of B cell lymphomas. Of interest, the same virus could be also involved in other malignancies such as thyroid cancer (Ferri et al, 2002*; Ferri et al, 2015*; Ferri, 2016*).

There is great geographical heterogeneity in the prevalence of HCV-related immunological or neoplastic disorders (figure 4). This epidemiological observation contrasts with the homogeneous diffusion of HCV infection worldwide. In this respect, we can hypothesise that HCV itself might be insufficient to drive the different autoimmune-lymphoproliferative disorders seen in infected subjects. The involvement of particular HCV genotypes, environmental and/or host genetic cofactors (figure 6) may contribute to the pathogenesis of

HCV syndrome. However, the actual pathogenetic relevance of the above cofactors still remains to be fully demonstrated.

It is well known that most HCV-infected subjects remain asymptomatic, some for a long time. In a small but significant percentage of patients, the virus is responsible for both hepatic and extrahepatic disorders, usually as late manifestations (figure 6). These clinico-epidemiological observations suggest that HCV syndrome is the consequence of a multifactorial and multistep pathogenetic process. It is quite common to see in the same patient a progression from mild, often isolated manifestations, to systemic manifestations and, finally, to overt malignancies (figure 6).

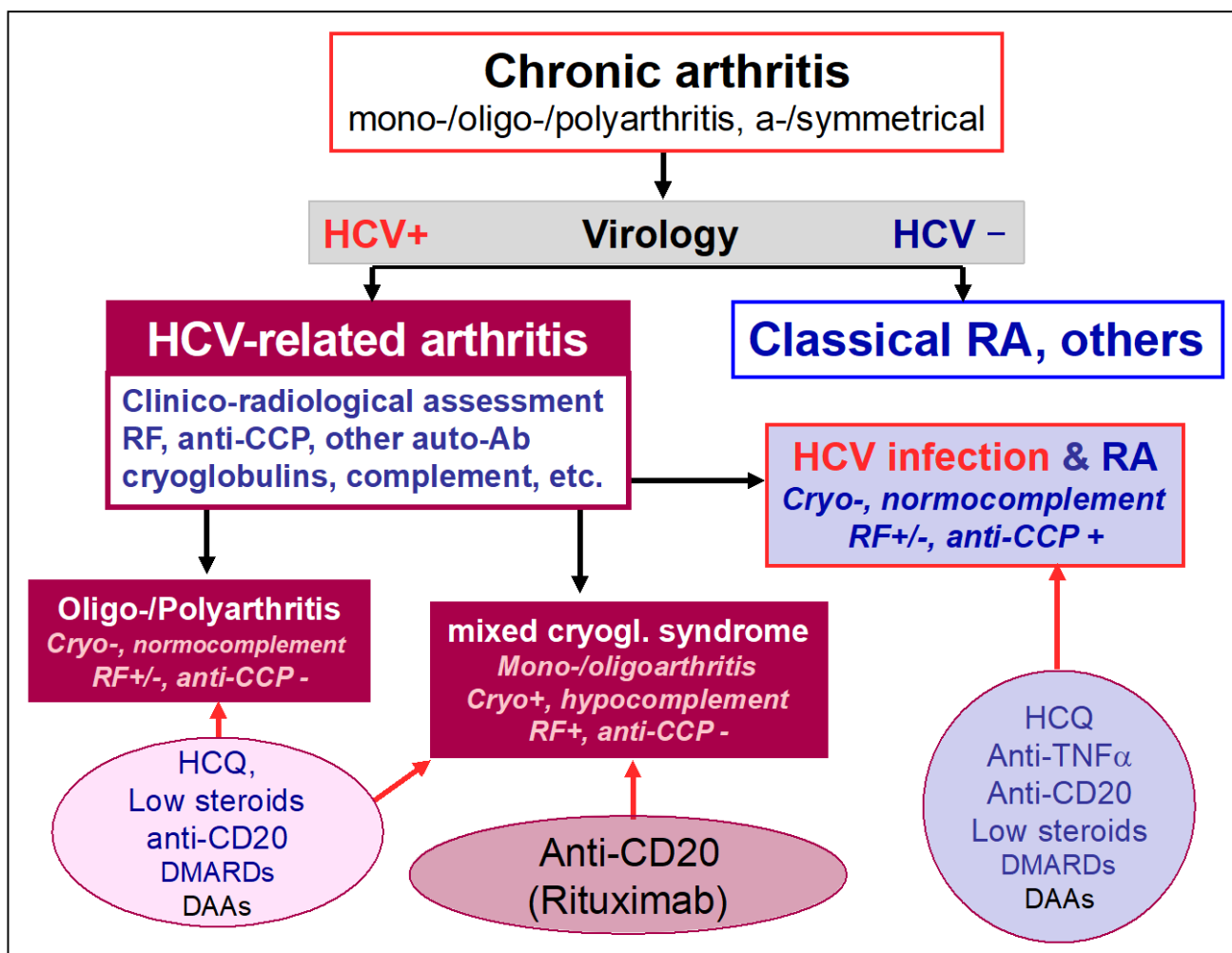
3.2 HCV and rheumatic diseases

Various inflammatory rheumatic disorders are the most common extrahepatic manifestations of HCV syndrome. Among these, MC is at the junction between classic rheumatic diseases, such as RA and Sjögren's syndrome, and other autoimmune/lymphoproliferative disorders (figures 5 and 10) (Ferri et al, 2002*; Ferri et al, 2015*; Ferri, 2016*).

Because of its clinical polymorphism, cryoglobulinaemic vasculitis may overlap with other rheumatic disorders such as Sjögren's syndrome and RA (figure 7); on the other hand, these rheumatic disorders may be occasionally associated with HCV infection (figure 7). The possible aetiopathogenetic role of HCV in pSS remains controversial. Patients with HCV-associated Sjögren's syndrome show a significantly low rate of anti-Ro/SSA-La/SSB (23%) together with a high prevalence of MC (50%), hypocomplementaemia (51%) and systemic vasculitic manifestations (58%) (figure 7). This particular condition cannot be classified as pSS; at least 50% of patients might be better classified as having cryoglobulinaemic vasculitis, which has important clinico-prognostic and therapeutic implications. The example of overlapping MC/Sjögren's syndrome suggests that in genetically predisposed subjects, HCV infection may trigger complex immune system alterations, which may produce variable phenotypes mimicking different well-known diseases, namely Sjögren's syndrome, RA, dermatopolymyositis, etc (figures 6, 7 and 10).

Chronic oligo-polyarthritis can be found in HCV-infected subjects, is often non-erosive and is barely progressive. In patients with HCV-related cryoglobulinaemic vasculitis, the joint involvement is generally characterised by mild oligoarthritis, while symmetrical rheumatoid-like polyarthritis may complicate IFN treatment in patients with type C hepatitis. Finally, given the relatively high prevalence of the two diseases, it is not uncommon to observe a simple association between classic RA and HCV infection (figure 11). Figure 7 summarises the main clinico-serological parameters for differential diagnosis between MC, pSS and RA in the setting of HCV syndrome.

Figure 11 Proposed flow chart for the classification of patients with chronic arthritis and hepatitis C virus (HCV) infection. Patients referred for either symmetrical polyarthritis or mono-oligoarthritis should undergo careful clinical and laboratory investigation, including virological evaluation. On the basis of different immunological tests, namely, rheumatoid factor (RF), anticyclic citrullinated peptides antibodies (anti-CCP), antinuclear antibodies (ANA), cryoglobulins and complement, it is possible to correctly classify anti-HCV-positive patients into two main groups: (a) those with simple association rheumatoid arthritis (RA)+HCV infection, and (b) those with HCV-related arthritis. This latter condition may include patients with arthritis in the setting of chronic HCV infection and a variable degree of liver involvement and patients with HCV-related cryoglobulinaemic syndrome. A possible therapeutic approach to different clinical subsets includes: for HCV-related arthritis, sequential treatment with antiviral agents, that is, direct-acting antiviral agents (DAAs,), and immunomodulating treatments (steroids, hydroxychloroquine (HCQ) and other disease-modifying antirheumatic drugs, rituximab) can be usefully employed (see text). In patients with concomitant HCV infection and arthritis, the use of tumour necrosis factor α blocking agents (anti-TNF α) seems to be useful and safe,. auto-Ab, autoantibodies; Cryo, cryoglobulins; DMARDs, disease modifying anti-rheumatic drugs.



Osteosclerosis is a rare condition described in adults with HCV infection; it can be defined as an acquired, painful skeletal disorder characterised by a marked increase in bone mass (figure 10). Osteosclerosis is clinically characterised by non-specific, often diffuse bony pain and tenderness over involved bones due to periosteal stretching, in the absence of joint swelling or motion limitation. The radiograph examination shows

bony sclerosis and thickening of the long-bone cortices, mainly the diaphyseal cortices. Laboratory investigations frequently reveal abnormally increased markers of bone formation (alkaline phosphatase and bone-specific alkaline phosphatase, osteocalcin); these alterations were mirrored by a marked increase in bone mass (bone mineral density, BMD) and enhanced radionuclide uptake at scintigraphy (^{99m}Tc -MDP). Bone biopsy shows an increased number and thickness of trabeculae with a parallel reduction in bone marrow. Only a very small percentage of infected patients develop osteosclerosis compared to the widespread diffusion of HCV. The pathogenesis of this rare condition is still unknown; it has been suggested that HCV alone or in combination with other unknown agent(s) may infect and alter bone cells or their precursors in predisposed subjects. These alterations might be mediated by the production of bone growth factors, such as insulin-like growth factors or osteoprotegerin. The pathogenetic role of the latter factor seems to be relevant; an imbalance in the osteoprotegerin/RANKL system leading to a predominance of osteoprotegerin has been documented.

To date, only 16 cases of HCV-associated osteosclerosis have been reported in the literature. In some cases, a partial or complete spontaneous remission of symptoms and/or bone sclerosis was observed during the follow-up period. Treatment with antiresorptive agents in some patients was ineffective, while symptomatic therapies may provide some benefit. The beneficial effect of HCV eradication observed in one patient is quite intriguing, but should be confirmed in larger numbers of patients.

The number of HCV-associated rheumatic diseases, as well as of other extrahepatic disorders, has grown during the last two decades (figure 10). In addition to the conditions described above, other rheumatic diseases have been associated with HCV infection, namely, myalgia, fibromyalgia, poly/dermatomyositis, polyarteritis nodosa, Behçet's syndrome, systemic lupus erythematosus and antiphospholipid syndrome.

In a large series of HCV-infected individuals, myalgia was mentioned by a significant number (15%) of patients. The pathogenesis of this symptom remains difficult to explain; the detection of viral genomic sequences within muscle fibres suggested a direct involvement of HCV in the pathogenesis of diffuse muscle pain. Fibromyalgia was also reported by some authors in a significant percentage of patients with chronic HCV infection, but other studies carried out in patients with typical clinical manifestations of fibromyalgia did not confirm this association. On the other hand, the differential diagnosis between fibromyalgia and muscle pain, frequently associated with weakness and arthralgias, may be very difficult in the setting of HCV-positive patients. Similarly to that proposed for sicca syndrome and pSS, some authors suggest considering HCV-associated myalgia and classic fibromyalgia as distinct entities.

The association of poly/dermatomyositis with HCV infection is described in numerous anecdotal observations, more often in patients with long-lasting viral infection or during IFN α treatment. Similarly, cases of vasculitis involving medium arteries suggesting the diagnosis of polyarteritis nodosa have been associated with HCV

infection; moreover, HCV seropositivity has been reported in a significant percentage of patients with polyarteritis nodosa. This latter association is not surprising in light of the well-known relationship between polyarteritis nodosa and another hepatotropic virus, namely HBV. Polyarteritis nodosa may share numerous clinical symptoms with cryoglobulinaemic vasculitis; thus, patients with suspected HCV-associated polyarteritis nodosa should be correctly classified by means of wide clinico-serological and pathological investigation. As regards other possible HCV-associated disorders, namely Behçet's syndrome, systemic lupus erythematosus and antiphospholipid syndrome, the data reported in the literature are generally anecdotal. Since a pathogenetic link with HCV cannot be totally excluded, the therapeutic approach in these patients is difficult (Ferri et al, 2002*; Ferri et al, 2015*; Ferri, 2016*).

As regards HCV-associated MC, patients with concomitant HCV infection and autoimmune systemic disorders, such as poly/dermatomyositis, polyarteritis nodosa and systemic lupus erythematosus, may be usefully treated with immunosuppressors (cyclophosphamide, rituximab, etc) with some important precautions and limitations due to viral infection. In all instances, a preliminary clinical evaluation of liver involvement and viral replication is necessary before any therapeutic decisions are made. The latter may be based on standard immunosuppressive treatments, possibly integrated into sequential/combined antiviral treatment.

3.3 Other HCV-related autoimmune disorders

A variety of organ- and non-organ-specific, immune-mediated diseases can be correlated with HCV infection. Cutaneous manifestations are often seen in HCV-infected subjects. Among these, porphyria cutanea tarda (PCT) is one of the most investigated. It is the commonest type of porphyria and is characterised by reduced activity of uroporphyrinogen decarboxylase, an enzyme involved in the haem biosynthetic pathway, and by frequent chronic liver disease. Since uroporphyrinogen decarboxylase deficiency is an essential condition, but not sufficient, for definite classification/diagnosis of PCT, various triggering factors, including viral infection, should be taken into account. A role of HCV infection has been investigated in several studies worldwide, which have reported a variable percentage of associations. The pathogenesis of HCV-related PCT is particularly intriguing: both metabolic factors – in particular, altered genes involved in iron metabolism – and a cross-reactivity of host versus HCV antigens have been proposed. Generally, HCV-positive patients without PCT do not show significant alteration in porphyrin metabolism; therefore, it may be supposed that a genetically driven reactivity is decisive, while HCV may exert an indirect role, possibly as a triggering factor (Ferri et al, 2002*; Ferri, 2008*; Ferri, 2015*; Ferri, 2016).

HCV-related lichen planus is another important association, in particular, oral lichen planus, which has a variable geographical prevalence. Moreover, several mucocutaneous manifestations are variably reported in HCV-infected subjects, generally based on limited or anecdotal observations. HCV-positive patients may develop acute episodes or chronic manifestations of well-known skin diseases; these symptoms are an

expression of immune-mediated cutaneous injury, triggered by HCV antigens and often amplified by IFN treatment. In many cases these cutaneous manifestations, often with a contribution from peripheral nerve alterations, severely affect patients' quality of life. Peripheral neuropathy is a common complication of HCV infection, mainly in cryoglobulinaemic vasculitis, while central nervous system involvement is less common. Peripheral neuropathy is more often seen in patients with overt MC syndrome. Vascular manifestations, including central nervous system involvement, may represent late comorbidities of HCV syndrome, particularly in patients with more severe extrahepatic manifestations and receiving long-term steroid treatment. Some cardiovascular manifestations have been reported during HCV infection, mainly in patient series from eastern Asian countries; if confirmed by further studies, they may support the role of genetic and/or environmental cofactors in the pathogenesis of HCV-related diseases.

An intriguing, still controversial, aspect is the possible aetiopathogenetic role of HCV in AIH. Patients with AIH may present serum mixed cryoglobulins, HCV infection and extrahepatic manifestations such as thyroiditis, sicca syndrome and arthritis; conversely, patients with HCV infection show one or more non-organ-specific autoantibodies and different organ involvements. In this respect, the antigenic target specificity of HCV-related autoantibodies shows only quantitative differences compared with those associated with 'primary' AIH. Again, the heterogeneous geographical distribution of HCV-associated AIH suggests a possible involvement of various pathogenetic cofactors; among these HCV might trigger a peculiar AIH clinico-serological subset which is prevalent in specific geographical areas (figure 4).

Glomerular and tubulointerstitial renal involvement in both native and transplanted kidneys may be associated with HCV infection (Ferri, 2017 review). HCV-related glomerulonephritis may include various histopathological types: MPGN with and without MC and, less frequently, membranous nephropathy, fibrillary and immunotactoid glomerulonephritis, rapidly progressive glomerulonephritis and exudative-proliferative glomerulonephritis. Cryoglobulinaemic glomerulonephritis – namely, type I MPGN – is more commonly found, while 'primary' MPGN represents less than one-third of HCV-associated MPGN. This latter disease has been described mainly in the USA and Japan. However, the real prevalence of MPGN without detectable cryoglobulinaemia is difficult to assess; it may represent a subclinical form of MC, possibly owing to difficulties and/or inadequate methods of detecting serum cryoglobulins. The possible methodological biases have been examined in section 2.4.

In some patients, MPGN is the presenting symptom of MC syndrome that may develop later in the course of the disease. Renal involvement is one of the most harmful complications of HCV-associated MC syndrome, and may severely affect the patient's clinical outcome. It is the consequence of cryoprecipitable and non-cryoprecipitable IC deposition in the glomeruli. However, the exact role of HCV in the aetiology of glomerulonephritis is not universally accepted. The presence of HCV particles in IC seems to support an indirect involvement of this virus in the pathogenesis of glomerulonephritis.

Thyroid involvement is perhaps the most common and thoroughly investigated endocrine alteration in HCV-positive patients (Ferri, 2017 review). The prevalence of abnormally high levels of antithyroid antibodies found in these patients varies markedly, ranging from 2% to 48%, with a heterogeneous geographical distribution (figure 4). These discrepancies may be correlated with variable genetic predisposition and environmental cofactors, such as iodine intake or diffusion of other infectious agents. Moreover, subclinical hypothyroidism has been found in 2–9% of patients with chronic hepatitis C, while miscellaneous thyroid alterations and raised serum thyroid autoantibodies are generally higher in chronic hepatitis C than in hepatitis B or D. More recently, the prevalence of thyroid involvement was investigated in a large series of patients with chronic hepatitis C and compared with that in control groups from the general population from regions with different iodine intake, as well as that in patients with chronic hepatitis B. Autoimmune thyroid involvement and hypothyroidism were significantly more common in patients with chronic hepatitis C than in the comparison groups, whereas the prevalence of hyperthyroidism was similar. Comparable findings were also found in another study focusing on the thyroid abnormalities of HCV-positive patients with MC (Ferri et al, 2002*; Ferri et al, 2015*; Ferri, 2016*).

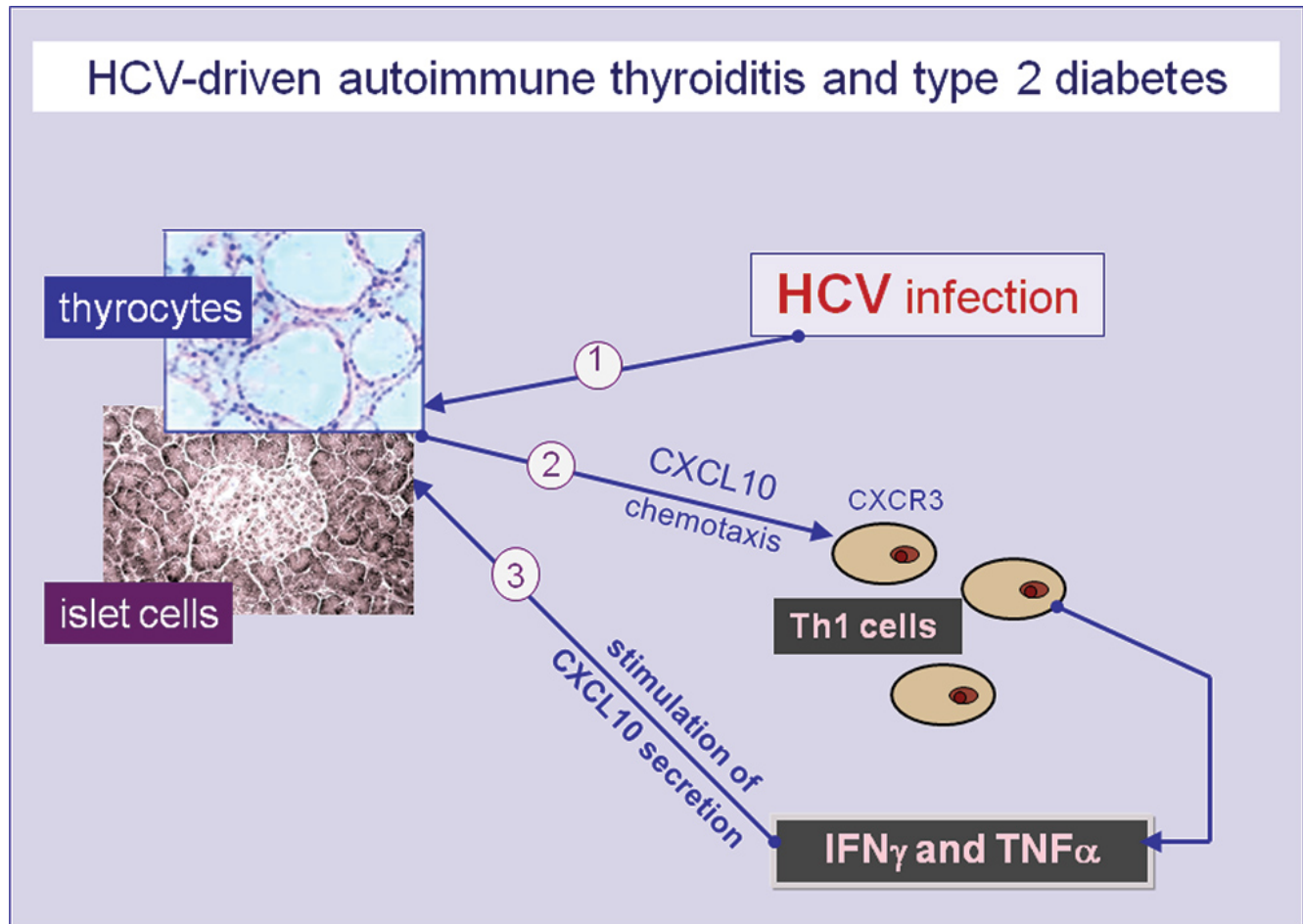
Recent studies have focused on the possible pathogenetic mechanisms responsible for HCV-related thyroid disorders. HCV thyroid infection may act by upregulating CXCL10 gene expression and secretion in thyrocytes (as previously shown in human hepatocytes) recruiting Th1 lymphocytes, which secrete IFN γ and tumour necrosis factor α (TNF- α). In turn, these cytokines may induce CXCL10 secretion by thyrocytes, thus perpetuating the immune cascade. The consequence may be the appearance of thyroid autoimmune disorders in genetically predisposed subjects (figure 12). This hypothesis has been recently confirmed by a study that evaluated CXCL10 serum levels in HCV-positive patients with MC, in the presence or absence of autoimmune thyroid involvement. Chronic immune-mediated inflammatory thyroid lesions may be responsible for the papillary thyroid cancer found in a significant percentage of HCV-infected subjects compared with controls.

Analogous pathogenetic mechanisms can be involved as a consequence of HCV infection of pancreatic β cells responsible for the upregulation of CXCL10 gene expression and secretion. The recruited Th1 lymphocytes, which secrete IFN γ and TNF- α , amplify CXCL10 secretion by β cells, thus perpetuating the immune cascade. The final result is the appearance of β cell dysfunction, with the probable contribution of genetic predisposition.

The abnormalities in thyroid function should be included among the complications of HCV syndrome. These patients should be periodically screened for thyroid involvement to identify those needing treatment and to diagnose the rare but harmful neoplastic complication at an early stage.

Type 2 diabetes may be another important manifestation of HCV syndrome, regardless of the presence and severity of liver damage.

Figure 12 Possible aetiopathogenetic mechanisms of hepatitis C virus (HCV)-related thyroid disorders and diabetes type 2. HCV thyroid infection may act by upregulating CXCL10 gene expression and secretion in thyrocytes (as previously shown in human hepatocytes) recruiting Th1 lymphocytes, which secrete interferon γ (IFN γ) and tumour necrosis factor α (TNF α). In turn, these cytokines may induce CXCL10 secretion by thyrocytes, thus perpetuating the immune cascade. The consequence may be the appearance of thyroid autoimmune disorders in genetically predisposed subjects.



Initially, clinic-based studies found an excess of type 2 diabetes in non-cirrhotic HCV-positive patients compared with patients with chronic hepatitis of other origin; however, this was not confirmed by another large study. An Italian case-control study evaluated 564 non-cirrhotic HCV-positive patients compared with 302 control subjects without a history of alcohol abuse, drug addiction or positivity for markers of viral hepatitis and 82 non-cirrhotic HBV-positive patients. A significantly high prevalence of type 2 diabetes was recorded in non-cirrhotic HCV-positive patients compared with control subjects (12.6% vs 4.9% and 7%, respectively; $p = 0.008$). Interestingly, the prevalence of type 2 diabetes in non-cirrhotic HBV-positive patients (7%) was within the range of the reported age-adjusted prevalence rates for the Italian population (4%).

A comparison between the clinical phenotype of hepatic and diabetic patients showed that non-cirrhotic HCV-positive type 2 diabetes was characterised by slightly older age, higher body mass index (BMI), elevated serum triglycerides, raised blood pressure levels and lower high-density lipoprotein cholesterol concentrations. Moreover, type 2 diabetic non-cirrhotic HCV-positive patients had a significantly lower BMI than type 2

diabetic control subjects and a slightly but significantly ($p < 0.05$) higher BMI than non-diabetic non-cirrhotic HCV-positive patients. Type 2 diabetes itself is characterised by older age, overweight, dyslipidaemia and higher blood pressure levels, the so-called 'metabolic syndrome' phenotype. In contrast, non-diabetic non-cirrhotic HCV-positive patients were lean and had low LDL cholesterol levels. Low LDL cholesterol levels have been correlated with HCV-induced hypo- β -lipoproteinaemia due to a binding competition between the virus and hepatic LDL receptor (Ferri, 2008*).

An immune-mediated mechanism for HCV-associated diabetes has been postulated and a similar pathogenesis might be involved in the diabetes of HCV-positive patients with MC. This hypothesis is strengthened by the finding that autoimmune phenomena in patients with type 2 diabetes are more common than previously thought. Similarly to the above-mentioned pathogenetic mechanisms involved in HCV-related thyroid disorders, we can hypothesise that HCV infection of β cells may act by upregulating CXCL10 gene expression and secretion. The recruited Th1 lymphocytes, which secrete IFN γ and TNF- α , amplify CXCL10 secretion by β cells, thus perpetuating the immune cascade. The final result is the appearance of β cell dysfunction, possibly in genetically predisposed subjects (figure 12).

Finally, sex hormone alterations have been observed in HCV-positive MC. Erectile dysfunction has been anecdotally reported in patients with HCV-related chronic hepatitis undergoing treatment with IFN α .

To investigate the possible role of HCV infection in gonadal dysfunction, 207 male patients with HCV infection (102 with cryoglobulinaemic vasculitis) were compared with 207 age-matched men, randomly selected from a series of 2010 subjects from the Italian general population previously investigated for erectile dysfunction. Exclusion criteria were patients aged >55 years, IFN α treatment during the past 12 months, and the presence of diabetes, renal failure, hypothyroidism, and cardiovascular and psychiatric disorders. Erectile dysfunction was significantly more common in HCV-infected subjects than in control subjects ($p < 0.001$). Sex hormone determinations showed that total and free testosterone plasma levels were abnormally reduced in HCV-positive patients with erectile dysfunction. Neither erectile dysfunction nor low levels of total and free testosterone were related to the severity of liver damage. These sex hormone alterations along with the possible contribution of peripheral neuropathy may be responsible for erectile dysfunction, which should be confirmed by further investigations. The above findings further support the role of the host hormonal environment in the pathogenesis of HCV-driven autoimmune disorders. We can hypothesise that reduced endogenous immunosuppressive activity due to low levels of adrenal-gonadal androgens may amplify the autoreactive lymphocyte proliferation triggered by HCV infection.

3.4 HCV and malignancies

HCV infection is the major aetiological factor in hepatocellular carcinoma. The oncogenic role of the virus in hepatocellular carcinoma has been definitely established. Since 1993, a possible role of this virus in the

pathogenesis of malignant B cell neoplasias has also been suggested. This hypothesis was initially suspected because of the striking association between HCV and MC, a condition that may be complicated by B cell lymphomas, and was further reinforced by the demonstration of HCV lymphotropism. In 1994, a surprisingly high prevalence of HCV infection in unselected Italian patients with B cell non-Hodgkin's lymphoma (B-NHL) was first reported. After this initial observation, an increasing number of epidemiological and laboratory investigations in patient series from different countries, as well as in animal models, confirmed the aetiopathogenetic role of HCV in a significant percentage of patients with B-NHL (figure 6). As for HCV-related MC, this association has a variable geographical distribution. The HCV-induced B cell malignancies have two main variants: the lymphomas complicating HCV-positive MC and isolated HCV-positive B-NHL. B-NHL complicating MC syndrome is discussed in section 3.3 (Ferri, 2015*; Ferri, 2016).

A significantly high prevalence of thyroid cancer complicating HCV-related hepatitis and HCV-related MC compared with controls was first noted in 1999. These data were subsequently confirmed in a case–control study, which reported a high prevalence of HCV in patients undergoing surgery for papillary thyroid cancer. Overall, HCV infection was associated with a high risk for liver cancer, multiple myeloma, B-NHL and thyroid cancer (figure 6). Furthermore, a high prevalence of thyroid cancer in subjects with a history of transfusion and/or liver disease indirectly supports the role of HCV in this malignancy. A review of the literature shows discordant results, possibly owing to important epidemiological and methodological bias. The results of a recent study on a large number of HCV-infected patients seem to confirm the high prevalence of thyroid papillary cancer, excluding the influence of some possible biases such as gender, age and iodine intake.

In our studies, features of thyroid autoimmunity were more commonly found in patients developing thyroid papillary cancer irrespective of whether they had type C hepatitis or HCV-related MC syndrome. This observation suggests that thyroid autoimmunity may be a predisposing condition for this malignancy. Although a possible association between thyroid cancer and HCV infection is suggested by the above clinico-epidemiological studies, this needs to be verified by further investigations.

3.5 HCV syndrome

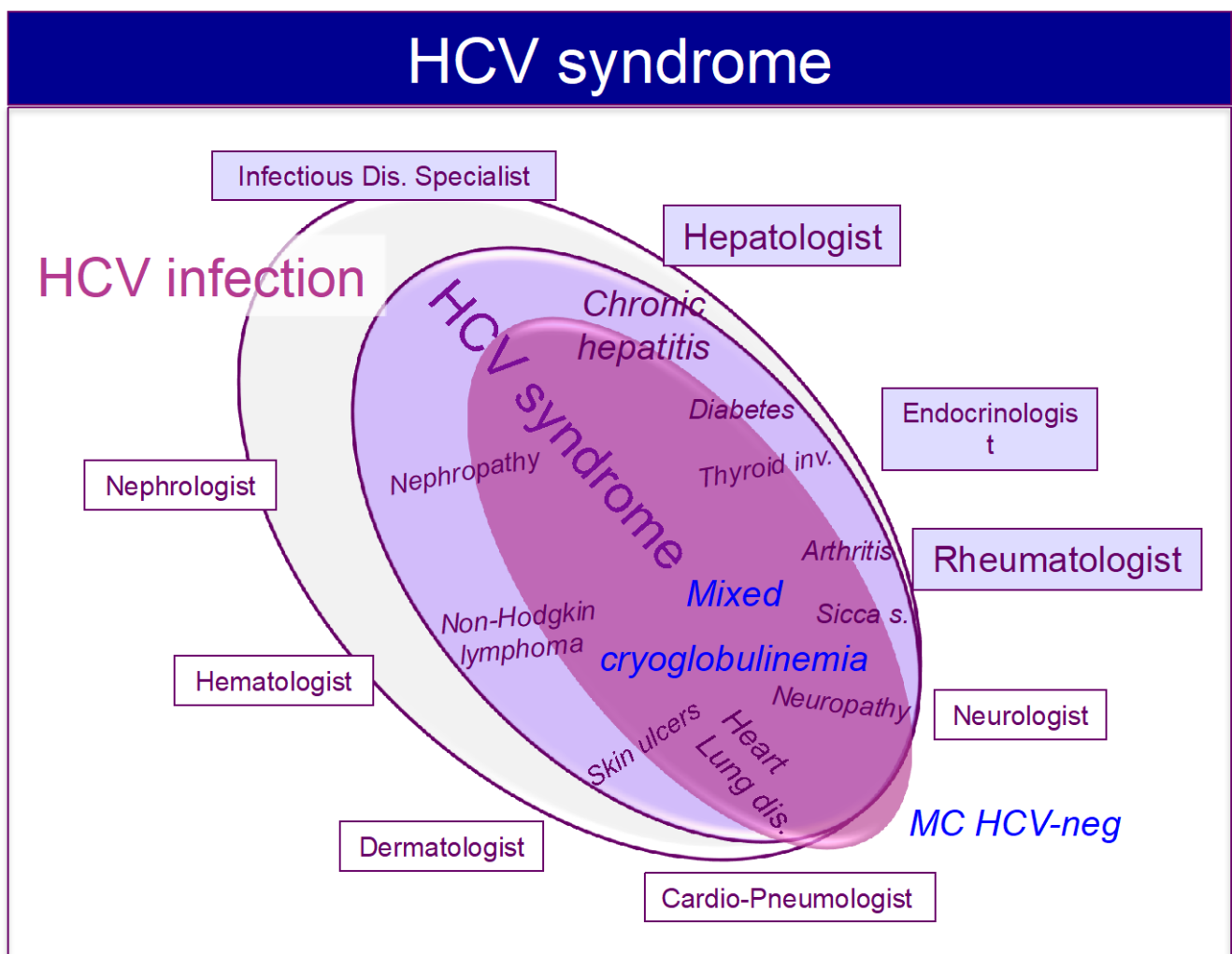
The strength of association as well as the pathogenetic role of HCV varies greatly among different diseases and for each disease among series of patients from different countries (figures 4,, 10 and 13; Ferri, 2015*; Ferri, 2016). Often, each disease itself represents a clinical syndrome which may comprise different clinico-serological subsets. These latter are the resulting phenotypes of a variable combination of different – genetic, environmental, infectious – pathogenetic cofactors. In this scenario, HCV infection, with the contribution of other pathogenetic agents, may produce distinct autoimmune or neoplastic disease subsets. The complex of HCV-related disorders is a continuum, as suggested by the clinical history of some patients, which may display the entire spectrum. It is not uncommon to see HCV-infected subjects with mild, often limited manifestations,

which may progress, generally during a long follow-up period, to more severe systemic manifestations, including malignancies (figure 6).

In general, HCV syndrome (Ferri et al, 2015*) is a multifaceted, clinico-pathological condition (figure 6 and 13); the challenge for future investigations is to better elucidate the exact boundaries of this syndrome and the actual pathogenetic role of the virus in different conditions.

Fig. 13. The HCV syndrome.

The figure schematically reproduce the spectrum of Hepatitis C virus (HCV) infection and diseases. HCV is an hepato- and lymphotropic virus responsible for a wide spectrum of both hepatic and extrahepatic diseases. The term 'HCV syndrome' refers to the multiform complex of all HCV-related diseases (Ferri, 2015*). Besides HCV-infected patients without clinical manifestations or isolated liver involvement, HCV-related extrahepatic manifestations (HCV-EHMs) may include a variety of non-organ and organ-specific autoimmune/lymphoproliferative and neoplastic disorders (Ferri, 2015*); therefore HCV-positive patients are commonly referred to different specialists according the prevalent clinical manifestation(s). Mixed cryoglobulinemia syndrome (MCs), also termed cryoglobulinemic vasculitis, represents the prototype of extra-hepatic systemic immune-mediated disorder characterized by multiple organ involvement (Ferri, 2015*). Only a minority of MC patients is HCV-negative (see also Fig. 5; Ferri, 2016*; Galli, 2017*)



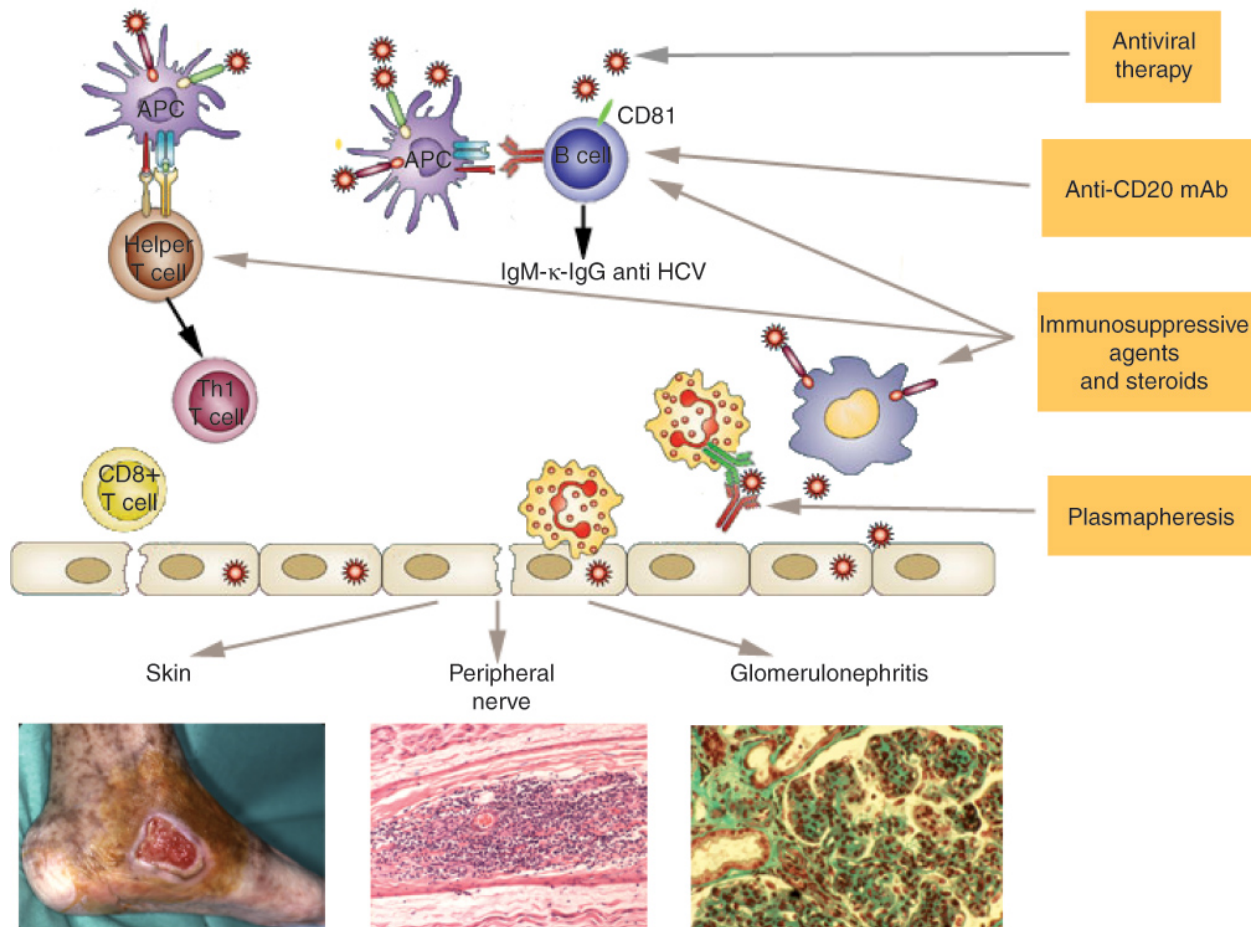
4 Current and future therapeutic strategies for treating mixed cryoglobulinaemia

Cryoglobulinemia are immune complexes that may induce systemic cryoglobulinemic vasculitis (MC), a small vessel vasculitis involving the skin, the joints, the peripheral nerve system, and the kidneys (Ferri C, 2002, 2008, 2015). With the discovery of hepatitis C virus (HCV) as the etiologic agent for most cases of cryoglobulinemia vasculitis (CV) new opportunities and problems for crafting therapy of HCV-MC have emerged. A new and major concern was the potential adverse effects that immunosuppressive therapy with glucocorticoids and cytotoxic drugs could have on an underlying chronic viral infection. Alternatively the discovery of HCV provided the opportunity to control HCV-MC with antiviral therapy (AVT) as the underlying infection drives immune complex formation and resultant vasculitis (Ferri C, 2002, 2008; Saadoun D, 2006, 2013).

Despite the successes with combination antiviral treatment, HCV-MC remains a severe disease. Most series reporting on the effects of treatment reported a mortality rate of 8-15%. The 1-year, 3-year, 5-year, and 10-year survival rates are 96%, 86%, 75%, and 63%, respectively. At the time of the diagnosis of HCV-related systemic vasculitis, severe liver fibrosis and the severity of vasculitis were the main prognostic factors (Terrier *B et al*, 2011). Although there is still controversy, the occurrence rate of B-cell NHL remains higher in MC patients compared with the general population.

The treatment of HCV and consequently the treatment of HCV-CV has evolved over the years. Figure 14 illustrates the therapeutic interventions according to the aetiopathogenesis of cryoglobulinaemic vasculitis.

Figure 14 Therapeutic interventions according to the aetiopathogenesis of cryoglobulinaemic vasculitis. mAb, monoclonal antibody.



Etiologic treatment:

- The historical treatment of HCV cryoglobulinemia vasculitis was **Interferon alpha (IFN)** in monotherapy, then in combination with **Ribavirine (RBV)**.
- Then, the treatment was based on the combination of **(Pegylated(Peg)-IFN plus RBV)**, but efficacy was limited and the side effects were frequent.
- Recently, major therapeutic advances appeared in the treatment of HCV infection, with the possibility to eradicate HCV following new **direct acting antiviral therapies (DAA)** (Gagnani L et al 2015). The first generation of HCV NS3 protease inhibitors - also known as “-previrs” - block the catalytic site of NS3, preventing the poly-protein cleavage and thus HCV replication. Currently approved “-previrs” include **Telaprevir and boceprevir** (first wave). The first generation of DAAs needed the combination of Peg-IFN and RBV and prolonged treatments.
- The second wave of previrs includes **simeprevir, paritaprevir and grazoprevir**. Two different classes of second wave DAAs have been introduced : the NS5A and the NS5B inhibitors:
 - The NS5A inhibitors block the stage of membranous genesis; they are also known as “-asvirs” (**daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir**).
 - The NS5B polymerase inhibitors or “-buvirs”, include nucleos(t)ide analogues (**sofosbuvir**) acting as chain terminators within the polymerase catalytic site, and non-nucleotide inhibitors (**dasabuvir**), causing conformational changes and making the polymerase ineffective.

4.1 Treatment of HCV cryoglobulinemia vasculitis

A. Antiviral agents

a) Interferon alpha (IFN) monotherapy, IFN plus Ribavirin

Treatment of HCV-MC with Interferon alpha (IFN) was associated with a relatively poor response and a high relapse rate, especially in severe cases. IFN monotherapy was effective in 50 to 100% of patients with purpuric skin lesions, but did not demonstrate efficacy on nerve or renal involvement. Combination therapy with IFN plus ribavirin showed a greater antiviral efficacy with sustained virological response in 35-80% of patients with chronic hepatitis C (Saadoun D, 2006, 2013). Such combination therapy showed much better short and long-term results in patients with HCV-MC than reported with IFN monotherapy. In three uncontrolled studies, combination therapy with standard IFN- α and ribavirin demonstrates enhanced efficacy on main HCV-related vasculitic manifestations (cutaneous, 100% ; renal, 50% ; and neural, 25-75%). Two studies reported a loss of proteinuria and haematuria in sustained viral responders treated by IFN α plus ribavirin. In a study of 27 patients with chronic hepatitis C complicated by systemic vasculitis, patients received IFN with ribavirin during 20 ± 14 months. After a mean follow-up of 57 months, 25/27 patients (93%) were alive, whereas 2 patients died secondary to cirrhosis. Most patients (75%) with a negative viraemia at the end of follow up were complete clinical responders for their HCV-MC vasculitis. Careful monitoring for adverse effects is mandatory since some manifestations of HCV-MC, such as peripheral neuropathy or skin ulcers, may worsen under IFN-based therapy. The tolerance of ribavirin is also reasonable with the exception of haemolytic anaemia requiring dosage reduction in some patients and adjusted dose in case of renal insufficiency.

b) Peg-Interferon alpha plus Ribavirin

The treatment of HCV infection (i.e. in the absence of HCV-MC) has continued to progress. It was based during the last decade on the standard of pegylated interferon alpha (Peg-IFN α) plus ribavirin leading to a sustained virological response in nearly 60% of patients (Saadoun D, 2006, 2013).

Mazzaro et al have reported the results of 18 HCV-MC patients treated with Peg-IFN α 2b plus ribavirin for 12 months. At the end of follow-up, only eight (44%) patients were still sustained clinical and virological responders. One major weakness of this study was the lower Peg-IFN dosage used in comparison with that usually recommended in HCV therapeutic guidelines.

In a monocentric study, 72 consecutive HCV-MC patients received treatment with IFN α -2b (n=32) (3 million IU x 3/week) or Peg-IFN α -2b (n=40) (1.5 μ g/kg/week), both combined with oral ribavirin (600 to 1,200 mg/day) for at least 6 months. Peg-IFN α plus ribavirin combination achieved a higher rate of complete clinical (67.5% vs 56.2%), virological (62.5% vs 53.1%) and immunological response (57.5% vs 31.2%) as compared with IFN α .

plus ribavirin, regardless of HCV genotype and viral load. Sub-group analysis of the 40 HCV-MC patients treated with Peg-IFN α plus ribavirin showed a complete recovery of skin involvement in 21/24 (87.5%), arthralgia in 18/22 (81.8%), peripheral neuropathy in 20/27 (74%) and nephropathy in 5/10 (50%) cases, respectively. Compared with standard IFN α -2b/ribavirin, there was a shorter duration of HCV therapy (13.2 vs. 18.3 months), less frequent use of corticosteroids (35 vs. 47%) and a lower rate of death (5 vs. 18.7%) with Peg-IFN α 2b/ribavirin. An early virologic response (i.e. negativation or > 2 log drop viraemia at month +3) (odds ratio [OR], 3.53; 95% CI 1.18 to 10.59) was independently associated with a complete clinical response of MC. A glomerular filtration rate lower than 70 ml/min (OR 0.18; 95% CI 0.05 to 0.67) was negatively associated with a complete clinical response of MC. Epidemiological features, viral load, transaminases or liver damage did not influence the clinical outcome of MC. The reappearance of HCV RNA was observed in 8 (11.1%) patients and 6 of them experienced a relapse of MC. In 39/70 (56%) patients, side effects included fatigue (47.2%), fever (37.5%), anaemia (33.3%), myalgia (25%), neutropenia (20%), depression (15.2%), thrombocytopenia (5%), pruritus (4.1%) and alopecia (2.7%). When compared with IFN α 2b/ribavirin, patients who received Peg-IFN α 2b/ribavirin had a similar rate of adverse events (53.1% vs 55%, respectively).

c) Direct acting antiviral drugs (DAA)

c.1) First generation DAAs: Peg-Interferon alpha plus Ribavirin and protease inhibitors

The first generation of DAAs needed the combination of Peg-IFN and RBV and prolonged treatments. Use of triple therapy with Peg-IFN α , ribavirin, and a specifically targeted antiviral agent (i.e. Boceprevir or Telaprevir) led to improve sustained virological response rates in patients infected with HCV genotype 1. In a prospective cohort study, the efficacy of an NS3 protease inhibitor (boceprevir or telaprevir [thrice daily]), in combination with Peg-IFN α 2a (180 μ g) or 2b (1.5 μ g/kg) and ribavirin (800 to 1,400 mg/day) has been evaluated in 23 HCV-MC patients with genotype 1. Thirteen patients (56.5%) were complete clinical responders, and ten (43.5%) were partial responders at week 24. The virological response (i.e. HCV RNA negativation) was of 69.6% at week 24 ($p=0.005$). The cryoglobulin level decreased from 0.44 to 0.06 g/l ($p=0.0006$) and the C4 level increased from 0.09 to 0.15 g/l ($p=0.045$). Grade 3 and 4 adverse events (mainly anaemia, neutropenia and thrombocytopenia) were observed in 10 cases (43.5%). Twenty patients (87%) received erythropoietin, 9 (39.1%) had red cell transfusion and 2 (8.7%) had granulocyte stimulating agents. Antiviral therapy discontinuation was required in 8 (34.7%) patients for virological non response ($n=5$), virological relapse ($n=2$) and depression ($n=1$). Four patients received the combination of rituximab plus Peg-IFN α /ribavirin/protease inhibitor combination with clinical improvement in all cases of whom 2 were complete clinical responders.

Recently, Saadoun et al (2015) reported the efficacy and the safety of this combined therapy in 30 CV patients, of whom 67% were complete clinical and virological responders while severe side effects occurred in 47%. Another study (Gragnani L, 2014) confirmed the good efficacy of such combination in 22 cryoglobulinemic

subjects, with a cryoglobulin disappearance in 86% but a lower sustained virological response (SVR) rate in cryoglobulinemic patients than in patients without mixed cryoglobulinemia (23.8% vs 70%, $p=0.01$). Stine et al. (2014) in a small case series of CV patients treated with triple AVT (Peg-IFN plus RBV plus sofosbuvir or first generation DAAs) suggested a longer treatment for cirrhotic patients, apparently more refractory to clear glucocorticosteroids.

c.2) Second DAAs generation:

The second DAAs generation protocols, are IFN-free (sometimes RBV free). Limited, but essentially concordant data, are available regarding patients with CV. The first study reported the effects of a sofosbuvir/RBV combination for 24 weeks in 24 CV patients; SVR was scored in 74% patients, with high rate of clinical response (87%) and low rates of serious adverse events. The rate of SVR was that expected from used AVT protocols. Sise et al. (2016), using sofosbuvir-based combinations in 12 CV subjects, obtained an improvement in renal function with or without immunosuppressant and SVR12 in 83%. An interim analysis, mostly based on the combination of paritaprevir/ritonavir, ombitasvir, plus dasabuvir, showed a cryocrit decrease and a clinical response even during treatment. The clinical improvement rate gradually increased from the inhibition of viral replication, end of treatment and SVR12. A very recent prospective study (Gragnani L, 2016) assessed efficacy and safety of sofosbuvir-based individually tailored therapy, in a cohort of 44 consecutive CV patients (median after treatment follow-up: 42 weeks, range 27–53). All patients obtained viral eradication and an overall 100% rate of clinical (complete or partial) response at week 24 post-treatment. Interestingly, a progressive increase of complete response rate over time, confirmed previous, preliminary observations. This is also suggested by another recent study conducted on 64 patients with circulating CGs (35/64 with CV) mostly treated in IFN-free regimens (Bonacci 2016). Recently, Hegazy et al. (2016) described a cohort of Egyptian and Italian CV subjects and Kondili et al. (2016) reported results of a nationwide Italian study, showing the disappearance or improvement of more than 50% of CV symptoms in 31/37 (84%) patients after DAA. Available data suggest that IFN-free AVT is safe, generally well tolerated and effective in CV patients.

B. Non-etiological treatment :

a) Rituximab:

Rituximab (RTX) binding to CD20 causes a B-lymphocytes depletion thus justifying the extensive use in B-lymphoproliferative disorders and severe autoimmune diseases. The safety and efficacy of RTX monotherapy in CV were clearly shown.

RTX is especially recommended in case of HCV related CV with severe clinical manifestations, preferring it to more conventional treatments. RTX can improve various manifestations of CV, including skin symptoms (purpura and ulcers), fatigue, arthralgias/arthritis, glomerulonephritis (GN) and peripheral neuropathy in a

relevant number of cases. It has been reported that RTX is able to restore some CV-related immune abnormalities; it can decrease cryocrit and rheumatoid factor level, increase C4 level, and induce the disappearance of bone marrow B cell clonal expansion (Saadoun, 2008).

In a literature review, 13 references reported a total number of 57 cases. Patients had a cryoglobulinemia vasculitis secondary to chronic active HCV infection in 75.4%. Most patients (48/57) received 4 weekly consecutive i.v. infusions of 375 mg/m² of rituximab. The mean follow up after rituximab infusions lasted 9.7 months (range, 3 to 24). Rituximab infusions were effective on main vasculitis signs, with a complete clinical response in 24/33 (73%). Cryoglobulinemic vasculitis relapse was noted in 13/36 (36.1%) patients within few days to nineteen months (mean 6.7 months) after the last rituximab infusion. This relapse was predictable due to the absence of viral eradication and therefore to the persistence of the viral antigenic triggering factor causing vasculitis.

In 2008, Saadoun *et al*, reported on 16 consecutive HCV-MC patients being treated with rituximab (375 mg/m² intravenously each week for 4 weeks) combined with Peg-IFN α -2b (1.5 μ g/kg/week, subcutaneously) plus ribavirin (600–1200 mg/day orally) for 12 months. Fifteen patients (93.7%) showed clinical improvement, 10 of whom (62.5%) were clinical complete responders at 12 months. Rituximab combined with Peg-IFN α 2b-ribavirin represents a safe and effective treatment option in severe refractory HCV-MC.

In 2010, Saadoun *et al* reported, 38 HCV-MC patients who received a combination of rituximab (375 mg/m²) once a week for 1 month followed by Peg-IFN (2a: 180 μ g, or 2b: 1.5 μ g/kg) weekly plus ribavirin (600–1200 mg) daily for 48 weeks. They were compared to 55 HCV-MC patients treated with Peg-IFN α /ribavirin with the same modalities. Compared with Peg-IFN α /ribavirin, patients treated with rituximab plus Peg-IFN α /ribavirin had a shorter time to clinical remission (5.4 \pm 4 vs 8.4 \pm 4.7 months; $p=0.004$), better renal response rates (80.9% vs 40% complete response; $p=0.040$) and higher rates of cryoglobulin clearance (68.4% vs 43.6%; $p=0.001$) and clonal VH1–69+ B cell suppression ($p<0.01$). Treatment was well tolerated with no worsening of viraemia under rituximab and with 11% of discontinuations due to antiviral therapy. Taken together, rituximab combined with Peg-IFN/ribavirin was well tolerated and more effective than Peg-IFN/ribavirin in HCV-MC. Rituximab synergises the immunological effect of antiviral therapy.

Dammacco *et al* reported on 22 patients with HCV-related MC who received Peg-IFN α (2a: 180 μ g, or 2b: 1.5 μ g/kg) weekly plus ribavirin (1000 or 1200 mg) daily for 48 weeks, and rituximab (375 mg/m²) once a week for 1 month followed by two 5-monthly infusions (termed PIRR) (Dammacco F, 2010). Fifteen additional patients received Peg-IFN α /ribavirin with the same modalities as the PIRR schedule. Complete response was achieved in 54.5% (12/22) and in 33.3% (5/15) of the patients who received PIRR and Peg-IFN α /ribavirin, respectively ($p<0.05$). Clearance of HCV RNA and conversion of B cell populations from oligoclonal to polyclonal in liver, bone marrow and peripheral blood was maintained for up to 3 years in 10 of 12 (83.3%) and in two of five

(40%) patients receiving PIRR and Peg-IFN α /ribavirin, respectively ($p < 0.01$). Cryoproteins in 22.7% (5/22) of patients treated with PIRR and in 33.3% (5/15) treated with Peg-IFN α /ribavirin persisted despite sustained HCV RNA clearance. No response occurred in the remaining five patients in both groups. PIRR therapy was well tolerated and more effective than the Peg-IFN α /ribavirin combination in HCV-related MC. Its effect may last for more than 3 years.

Data about combined RTX plus DAA-based therapy are still scarce. However, it is conceivable to figure out promising successes of combination with IFN-free schedules.

The exact place of RTX in the field of CV has to be more precisely defined. With the approval of recent DAAs IFN-free combination, which proved very highly and rapidly effective on viremia, we will have to define in the next future the remaining place of RTX. For example, as a first-line option for severe and life threatening conditions needing urgent intervention and as a second-line option for those maintaining significant symptoms after SVR.

Most studies used the standard haematological treatment schedule (375 mg/m² in four consecutive weekly infusions). Lower doses and/or shorter treatment have been also reported, i.e., 1g every two weeks for two infusions or 250 mg/m² in two administrations.

In most studies, tolerance of Rituximab was good. One potential concern regarding the use of such therapy reported in initial studies is its suspected propensity to worsen HCV viraemia. Some patients may experience systemic drug reactions after rituximab infusion. Six cases of HCV-MC patients who developed a severe flare of vasculitis one or two days after rituximab infusion have been reported. Two patients developed serum sickness syndrome 7 and 9 days after the first 1,000 mg rituximab infusion. Compared with patients without drug reactions, those with drug reactions had higher mixed cryoglobulin levels and more of them received 1,000 mg high-dose rituximab protocol.

b) Other treatments

Immunosuppressive agents have been given for many decades to patients with severe MC disease manifestations such as membranoproliferative glomerulonephritis, severe neuropathy and other life-threatening complication. A combination of corticosteroids and immunosuppressants, such as cyclophosphamide and azathioprine, has been used for the control of severe vasculitis lesions.

Mycophenolate mofetil may represent an alternative therapeutic option in patients refractory or intolerant to these immunosuppressive drugs. In a large retrospective study of 105 patients with renal disease associated with CV, 80% were administered corticosteroids and/or cytotoxic agents, while 67% underwent plasmapheresis. Despite this aggressive approach, long lasting remission of the renal disease was achieved in only 14% of cases, and the 10-year survival rate was only 49%.

Corticosteroids, used alone or in addition to IFN, did not favourably affect the response of HCV-CV manifestations in two controlled studies. In a randomized trial, methylprednisolone alone given for one year was associated with clinical response in 16.7% of patients, compared with 53.3% and 52.9% in patients receiving IFN α or IFN α plus methylprednisolone, respectively. GCs are commonly used to control inflammation and pain. Low-medium doses of GCs (0.1–0.5 mg/kg/day) usually control mild to moderate symptoms, whereas high-dose pulse therapy (1–10 mg/kg) is commonly indicated to manage severe and acute conditions, specifically renal failure, neurologic manifestations or hyperviscosity syndrome.

Plasmapheresis offers the advantage of removing the pathogenic cryoglobulins from the circulation of patients with MC and is particularly effective for rapidly progressive glomerulonephritis and/or severe skin necrosis or ulcers (Ferri C, 2008). Immunosuppressive therapy is usually needed associated with plasma exchange in order to avoid the rebound increase in cryoglobulin serum level seen after discontinuation of apheresis. When used in combination with HCV treatment, plasmapheresis did not modify the virologic response if IFN α was given after each plasma exchange session.

4.2 Treatment of non HCV cryoglobulinemia vasculitis

In non-HCV cryoglobulinemia vasculitis, the treatment depends of the severity of the vasculitis, of the associated aetiology (B cell lymphoma, MGUS, myeloma, Sjögren's syndrome..) and of the type of cryoglobulin (type 1 vs type 2 and 3). Low dose corticosteroids may help to control minor intermittent inflammatory signs such arthralgia or purpura, but do not succeed in cases of major organ involvement (i.e. neurologic, renal, cardiac), or in the long-term control of vasculitis. Plasmapheresis is particularly effective for rapidly progressive glomerulonephritis, life threatening organ involvement and/or severe skin necrosis or ulcers. Saadoun et al. (2012) reported the safety and efficacy of fludarabine (40 mg/m² orally on days 2–4), cyclophosphamide (250 mg/m² orally on days 2–4), and rituximab (375 mg/m² on day 1), every 4 weeks, for 3 to 6 cycles in 7 consecutive patients with severe and refractory MC associated with B-NHL. Clinical features of MC included purpura (n = 7), polyneuropathy (n =6), and kidney (n =4) and cardiac involvement (n =2). Previous treatment included rituximab (n= 5), corticosteroids (n = 5), antiviral therapy (n= 5), cyclophosphamide (n =3), and plasmapheresis (n =2). All patients achieved clinical response, with 3 (42.9%) patients achieving a complete remission and 4 (57.1%) patients a partial remission.

a) Type 1 cryoglobulinemia vasculitis

Type I cryoglobulinemia vasculitis is usually associated with plasma cell hematologic disease while MC is more likely related to low grade B cell NHL or Sjögren's syndrome. The treatment of type I cryoglobulinemia vasculitis is primarily that of the underlying haematological malignancy and the use of thalidomide or lenalidomide, and bortezomib-based regimens seem to be interesting options. In patients with MGUS-related type I cryoglobulinemia vasculitis the initiation of therapy is only justified by the severity of the vasculitis. A

recent series have reported clinic-biological characteristics and treatment of 64 patients diagnosed with type I cryoglobulinaemia. Cryoglobulinaemia was IgG in 60% and IgM in 40% of all cases and was asymptomatic in 16 patients (25%). Cold-triggered ischaemic skin manifestations were observed in 33 patients (51%). Neurological manifestations were observed in 15 patients and renal manifestations in 13. Most of the patients with necrotic purpura (14/16, $P = 0.009$) and renal manifestations (11/13, $p = 0.057$) had IgG cryoglobulinaemia. IgG cryoglobulinaemia was associated with monoclonal gammopathy of undetermined significance (MGUS), myeloma, chronic lymphocytic leukaemia and lymphoplasmocytic lymphoma in 18, 13, 5 and 2 patients, respectively. IgM cryoglobulinaemia was associated with MGUS and Waldenström macroglobulinaemia in 8 and 18 cases, respectively. One third of patients did not receive any specific treatment. Various treatments, including rituximab, were administered to 25/31 patients with IgG cryoglobulinaemia and 6/25 patients with IgM cryoglobulinaemia due to cryoglobulinaemia-related symptoms. Rituximab was ineffective in all cases associated with a predominantly plasmacytic proliferation.

b) Mixed cryoglobulinemia vasculitis

In non HCV-mixed cryoglobulinemia (MC) vasculitis, rituximab plus corticosteroids combination therapy showed the greater efficacy compared with corticosteroids alone and alkylating agents plus corticosteroids for clinical, renal, and immunologic responses and corticosteroid-sparing effect. There is no significant difference in the efficacy of rituximab therapy whether patients presented with HCV-induced or essential cryoglobulinemia vasculitis. Rituximab plus corticosteroids regimen is associated with frequent severe infections, particularly when high doses of corticosteroids are used. These infections occur in a particular subset of patients, characterized by older age, renal failure ($GFR < 60 \text{ mL/min}$), and the use of high-dose corticosteroids. The efficacy of rituximab in type I cryoglobulinemia vasculitis remains controversial. The absence of CD20 expression on plasma cells was supposed to explain its lack of efficacy.

4.3 Treatment of MC vasculitis relapses.

Clinical relapses of HCV-related vasculitis are usually associated with relapsing HCV viraemia. Vasculitis relapses usually present the same vasculitis manifestations as were noted at presentation. Recurrence of vasculitis-related symptoms after withdrawal of antiviral therapy with virological relapse (HCV RNA repositivation) can be successfully treated with another course of combination antiviral therapy with a good response. Alternatively, repeated infusions of rituximab are effective to control MC vasculitis. However, the dose, safety and continued efficacy of repeated therapy with rituximab in MC deserve further substantiation.

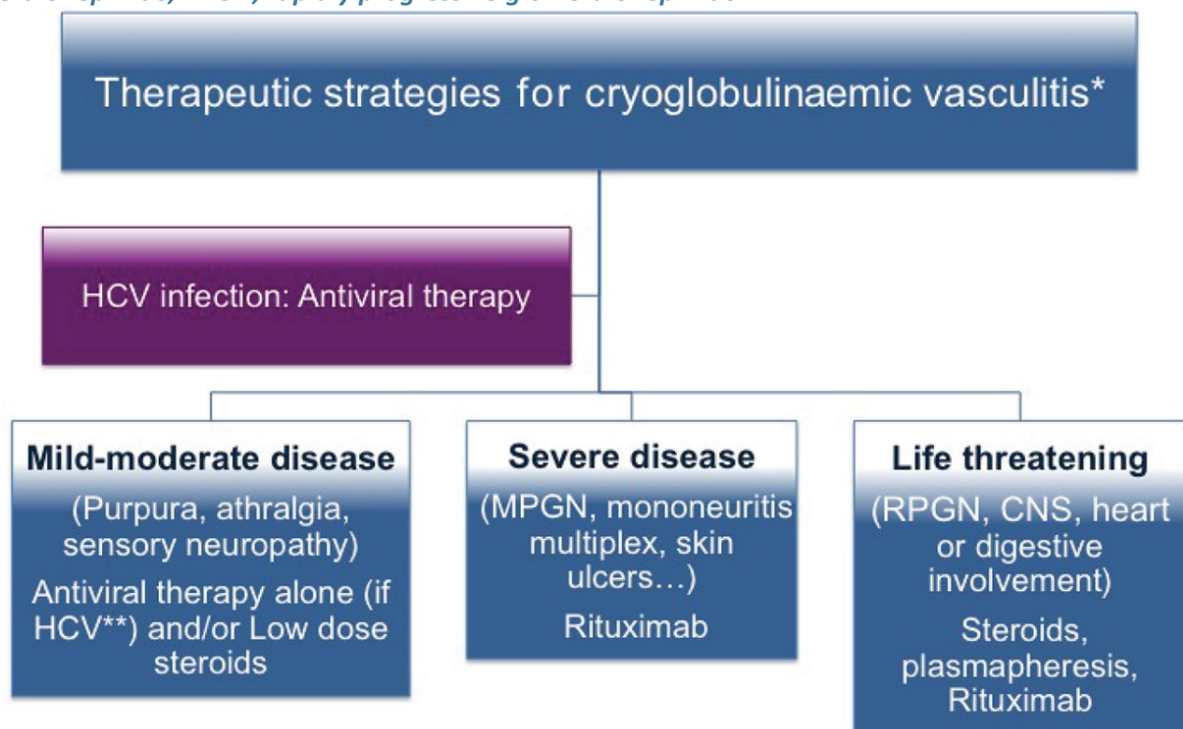
Authors have reported on 8 patients who presented with cryoglobulinemic vasculitis due to chronic active HCV infection with no evidence of underlying malignant disease. After a successful treatment of HCV infection, patients were sustained virological responders as they remained persistently HCV RNA negative. Later on, MC-related symptoms reappeared, with no HCV infection relapse (as demonstrated by numerous negative

viraemia), but a malignant B-NHL was found in two cases. Clinicians should be aware of the possibility of the presence of underlying malignant lymphoma when patients develop a relapse of cryoglobulinemia vasculitis without HCV virological relapse.

4.4 Therapeutic guidelines

The therapeutic strategies of cryoglobulinemia vasculitis are summarized in Figure 15. International therapeutic guidelines for patients with HCV-CV have been published in 2017 in the Autoimmunity Reviews (Zignego AL, 2017).

Figure 15 Therapeutic strategies in patients with cryoglobulinaemia vasculitis. **The treatment of cryoglobulinaemic vasculitis (CV) associated with haematological malignancy is primarily that of the underlying haemopathy. **If failure or contraindication of antiviral therapy or in non-HCV CV, rituximab may be used alone. CNS, central nervous system; HCV, hepatitis C virus; MPGN, membranoproliferative glomerulonephritis; RPGN, rapidly progressive glomerulonephritis.*



- Aggressive optimal antiviral therapy with new antiviral agents (DAA) should be considered as induction therapy for HCV-MC patients with mild to moderate disease severity and activity (i.e. without rapidly progressive nephritis, motor neuropathy or other life threatening complications). The duration of therapy has not yet rigorously been determined but current treatment duration in HCV-MC patients is 48 weeks for all HCV genotypes. With this strategy patients with mild or moderate disease (i.e. arthralgia, purpura, and/or sensory polyneuropathy) may be able to be managed without immunosuppressive agents. Low dose corticosteroids may also help to control minor intermittent inflammatory signs such as arthralgia or purpura.

- In patients presenting with more severe MC disease (i.e. worsening of renal function, mononeuritis multiplex, extensive skin disease including ulcers and distal necrosis), an induction phase with rituximab is often necessary. In HCV-MC, combination therapy with rituximab plus DAA is recommended as it may target both the viral trigger and the downstream B cell arm of autoimmunity. The following therapeutic schedule is recommended: 1) weekly administration of four intravenous infusions of rituximab at 375mg/m² (on days 1, 8, 15 and 22) over a one-month period; 2) antiviral combination starting after the last rituximab infusion for 3 to 6 months duration.

- For patients presenting with the fulminant forms including peripheral necrosis of extremities, rapidly progressive glomerulonephritis, digestive, cardiac, pulmonary and/or central nervous system involvement and or signs and symptoms of hyperviscosity, apheresis can have immediate beneficial effects but must be combined with immunosuppression to avoid post-apheresis rebound of MC. High dose steroids, rituximab, and sometimes cyclophosphamide combination appeared as an effective salvage treatment for refractory MC. In such cases, antiviral therapy should be started soon after the critical phase.

The treatment of cryoglobulinemia vasculitis associated with haematological malignancy is primarily that of the underlying hemopathy. When CG-related symptoms are severe, complete plasmapheresis is indicated, even though no prospective studies have established their efficacy or optimal use. The key point is to adapt treatment modalities to the nature of the underlying gammopathy. If it is plasmacytic (i.e. mainly composed of CD20 negative cells and usually secreting a mIgG), the treatment should be based on anti-myeloma agents including, in selected young patients with severe disease, autologous stem cell transplantation. If the underlying B-cell disorder is lympho-plasmacytic, usually associated with a mIgM, the treatment should be as for Waldenström's disease.

SUMMARY POINTS

- Types II and III mixed cryoglobulinaemia (MC), or cryoglobulinaemic vasculitis, are classified among the small-vessel systemic vasculitides. The disease is a combination of serological findings (mixed cryoglobulins with rheumatoid factor (RF) activity and frequent low C4) and clinico-pathological features (purpura and leukocytoclastic vasculitis with multiple organ involvement).
- There are no diagnostic criteria for MC. The disease can be correctly classified on the basis of typical orthostatic purpura with the histological pattern of leukocytoclastic vasculitis on skin samples taken within the first 24–48 h, detection of serum mixed (IgG-IgM) cryoglobulins, low complement C4 and positive RF.
- MC may be associated with other well-defined immunological, infectious or neoplastic disorders; when isolated, it is a distinct disease, the so-called 'essential' MC. Following the discovery of a striking association between MC and hepatitis C virus (HCV) infection, the term 'essential' is now used to refer to a minority of patients. In over three-quarters of cases, cryoglobulinaemic vasculitis is one of the most important extrahepatic complications of HCV chronic infection.
- The main clinical features of cryoglobulinaemic vasculitis are the typical triad of purpura, arthralgias and weakness. Liver and renal involvement, peripheral neuropathy, skin ulcers and the possible development of malignancies, mainly B cell lymphomas, generally as a late complication, may also be seen
- Liver and/or renal involvement, as well as neoplastic complications, may severely affect the overall prognosis of MC. Such patients, more often women, aged 50–60 years at the time of diagnosis, have a worse prognosis than the general population.
- HCV is both a hepatotropic and a lymphotropic virus; it may exert a chronic stimulus on the immune system with both T and B lymphocyte alterations; 'benign' B cell lymphoproliferation is responsible for different autoantibody production, mainly of RF and cryoglobulins. In addition to cryoglobulinaemic vasculitis, HCV may trigger different immune-mediated extrahepatic disorders (thyroiditis, diabetes type 2, polyarthritis, glomerulonephritis, porphyria cutanea tarda, sicca syndrome, etc.), as well as some malignancies, mainly B cell lymphomas.
- The large geographical heterogeneity in the prevalence of HCV-related extrahepatic manifestations suggests that HCV itself might be insufficient to trigger and maintain these different autoimmune-lymphoproliferative disorders. A variable combination of HCV with other unknown environmental and/or host genetic cofactors may lead to the different clinical phenotypes that characterise HCV syndrome.
- The main targets in the treatment of HCV-related cryoglobulinaemic vasculitis are the clinical (improvement of organ target manifestations), virological (clearance of HCV RNA) and immunological response (serum cryoglobulin and C4 levels).



SUMMARY POINTS

- Treatment of HCV-mixed cryoglobulinaemia (MC) may target either the viral trigger (HCV) or the downstream B cell arm of autoimmunity.
- Antiviral therapy should be considered as induction therapy for HCV-MC with mild to moderate disease severity and activity.
- IFN-free, DAA-based antiviral therapy should be considered a first line therapeutic measure for HCV-MC that does not need urgent/life threatening measures.
- In patients presenting with severe disease (ie, worsening of renal function, mononeuritis multiplex, and extensive skin disease including ulcers and distal necrosis), an immunosuppression induction phase is often necessary while awaiting the generally slow response to antiviral treatments.
- Combination therapy with rituximab and optimal antiviral treatment appears logical as it may target both the viral trigger (HCV) and cryoglobulin producing B cells.
- An early virological response to antiviral therapy is correlated with a complete clinical response in MC.
- Clinical relapses in HCV-related vasculitis are usually associated with relapsing HCV viraemia.
- Recovery of B cell count began 6–9 months after rituximab therapy.
- Low-dose corticosteroids may help to control minor intermittent inflammatory signs such as arthralgia, but are not successful in cases of major organ involvement (ie, neurological, renal) in the long-term control of vasculitis.
- Careful monitoring for adverse effects is mandatory since some manifestations of HCV-related vasculitis, such as peripheral neuropathy or skin ulcers, may worsen under IFN therapy.
- Clinicians should be aware of the possibility of malignant lymphoma when HCV-positive patients experience a relapse in cryoglobulinaemia vasculitis without HCV virological relapse.
- The treatment of cryoglobulinemia vasculitis associated with haematological malignancy is primarily that of the underlying hemopathy.

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EULAR on-line course on Rheumatic Diseases

Cryoglobulinaemia and Hepatitis C Virus

Pauline Baudart, Christian Marcelli, Clodoveo Ferri

A previous version was coauthored by Clodoveo Ferri, Maria Teresa Mascia, David Saadoun, Patrice Cacoub and Marco Sebastiani

IN-DEPTH DISCUSSION I

HCV infection and arthritis

Since its discovery in the last 80s, several extrahepatic manifestations have been reported in association with hepatitis C virus (HCV), including mixed cryoglobulinemia, porphyria cutanea tarda, membranoproliferative glomerulonephritis, sicca syndrome, thyroiditis, and arthritis. Previously, the observation of a pathogenetic link between polyarteritis nodosa and HBV infection prompted an increasing interest about the possible relationship between hepatotropic viruses, liver diseases, and a variety of rheumatic disorders.

Transient articular manifestations are commonly observed during the early stages of acute hepatitis; while patients affected by chronic hepatitis, with or without cirrhosis, frequently refer arthralgias and/or frank arthritis, as well as high incidence of positive tests for rheumatoid factor (RF).

Conversely, clinical researches also uncovered a significant high frequency of hepatic alterations in some rheumatic diseases, including rheumatoid arthritis (RA). The onset of arthritis has been described in about 2-3 percent of HCV infection cases. Clinically, articular manifestations in patients with chronic HCV infection are not uniform; they include musculoskeletal pain and fatigue, fibromyalgia, arthralgias, and/or frank arthritis. While arthralgias are clinically evident in about 40–70% of patients with HCV infection, in a large prospective study of 1,614 patients with chronic HCV infection, 23% of the patients were reported to generically suffer from arthralgia and arthritis.

Several cohort studies have provided conflicting results about the impact of HCV in RA patients; despite a recent large prospective, population-based study in Taiwan, demonstrating a higher incidence of new onset RA in HCV patients, actually HCV cannot be considered as an aetiopathological agent of erosive RA. At present, this HCV-related arthritis is classified as a reactive arthritis, but a real distinction of this form from classical rheumatoid arthritis is often difficult.

In fact, chronic HCV-related polyarthritis may mimic classical RA; arthritis due to HCV infection is frequently described as "rheumatoid-like" or chronic symmetrical polyarthritis. More than 50% may satisfy the ACR criteria for RA classification. Some of the 2010 American College of Rheumatology/European League against Rheumatism criteria for classification of rheumatoid arthritis are common in HCV patients; namely arthritis of three or more joint areas, arthritis of hand joints, symmetric arthritis, alteration of acute-phase reactants, and RF seropositivity.

The clinical picture of HCV-related arthritis could be distinguished in two clinical subsets: symmetrical polyarthritis and intermittent mono-oligoarthritis.

The classical HCV-related polyarthritis usually shows a benign, often fluctuating clinical course. The vast majority of patients develop polyarticular disease, with the small joints (metacarpophalangeal, proximal interphalangeal, wrists and ankles) primarily involved. In some patients, synovitis may also affect shoulders

and knees, and large joint effusions have been described (10-30% of patients have mono- or oligoarthritis involving large joints).

Morning stiffness and positive rheumatoid factor, in 50–80% of cases, are frequent. Rheumatoid nodules are typically absent. Some authors found joint erosions in 20–30% of their subjects. In addition, the erythrocyte sedimentation rate is less commonly increased than in RA.

The oligo-monoarticular arthritis involves medium and large sized joints and rarely shows a chronic course. Symptomatic cryoglobulinaemic syndrome is closely related to this subset of HCV related arthritis. It affects the large joints of the lower limbs, where the purpuric lesions are particularly frequent; furthermore, it is generally asymmetrical, intermittent, non-erosive, and characterized by better prognosis.

These findings cannot be sufficient to formulate a correct diagnosis for individual patients; the presence of other markers of cryoglobulinaemia syndrome such as purpura, Raynaud's phenomenon, glomerulonephritis, peripheral neuropathy, and/or concomitant liver enzyme abnormalities may suggest HCV as a triggering agent of arthritis. In this respect there are some confounding features such as the normal level of liver enzymes in 1/3 of HCV-infected patients and/or the presence of cutaneous lesions that could be classified as rheumatoid vasculitis. Therefore, the search for HCV infection as well as of serum cryoglobulin and anti-cyclic citrullinated peptide antibodies (anti-CCP) should be performed in all patients with chronic arthritis at the first clinical assessment. Serum markers of classical RA may be usefully employed in discriminating HCV patients with true seropositive RA from those with HCV-related arthropathy. Some authors have pointed out the absence of anti-CCP in patients with HCV-related arthritis, while the presence of a rheumatoid factor activity may be confusing as it is positive in both classical RA and MCS.

On the whole, arthralgias and/or rheumatoid-like polyarthritis can be included among HCV-related extrahepatic manifestations. In addition, considering the prevalence of both disorders in the general population, the estimated prevalence of concomitant RA and chronic HCV infection is not negligible. On this basis it is important in clinical practice to clinically differentiate HCV-related arthritis from the simple association between classical RA and concurrent HCV infection.

Patients referred for either symmetrical polyarthritis or mono- oligoarthritis should undergo a careful clinical and laboratory workup, including virological evaluation (See figure). On the basis of different immunological tests, namely rheumatoid factor (RF), anti-cyclic citrullinated peptides antibodies anti-nuclear antibodies (ANA), cryoglobulins, and complement it is possible to correctly classify anti-HCV+ patients into: a) those with simple association RA+HCV infection; b) patients with HCV-related arthritis. This latter condition may include patients with arthritis in the setting of chronic HCV infection and variable degree of liver involvement and patients with HCV-related cryoglobulinaemic syndrome. Symmetrical RA-like polyarthritis is more commonly

found in HCV-positive patients, while HCV-related cryoglobulinaemic syndrome is rather characterized by less severe mono- oligoarthritis (Palazzi C et al. Autoimmunity Rev, 2008; 8: 48-51).

Overall, accurate patient's classification is essential for the therapeutic implications: the management of HCV-related arthritis may include both antiviral, namely interferon α (IFN α) plus ribavirin and/or new antiviral drugs, and immuno-modulating treatments (steroids, conventional or biological DMARDs).

The gold standard treatment of HCV-related arthritis has not yet been established and is largely empirical, since only a few studies have analysed this topic. The coexistence of different diseases is often considered a therapeutic challenge. Generally, treatment with hydroxychloroquine and low doses of steroids is safe and effective in controlling arthritis-related symptoms; moreover, in association with antiviral treatment. However, IFN α treatment should be avoided, owing to the potential 'arthritogenic' effect due to its immunoregulatory properties. Therefore, the eradication of HCV-infection should be considered in all patients with the new antiviral agents as a part of interferon-free eradication regimens. Due to the higher risk of comorbidities-related adverse events, and to the higher risk of developing lymphoproliferative disorders, these patients should be included among those with high treatment priority.

In refractory or severe cases, conventional or biologic DMARDs can be used, according to liver functions. Both in vitro and in vivo studies suggest that cyclosporine A (CyA) also exerts an inhibitory effect on HCV replication at standard therapeutic dose, and some reports also suggest the safety and efficacy of CyA in the treatment of patients with arthritis and concomitant HCV infection. Also methotrexate has been described efficacious and safe in a small group of HCV patients with chronic arthritis. Finally, biological DMARDs (TNF α blockers, abatacept, tocilizumab, and rituximab) have been usefully employed, alone or in combination with conventional DMARDs, in HCV infected patients.

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IN-DEPTH DISCUSSION II

**Current and future therapeutic strategies for treating
mixed cryoglobulinaemia**

With the discovery of HCV as the etiologic agent for most cases of mixed cryoglobulinemia new opportunities and problems for crafting therapy of HCV MC have emerged. A new and major concern was the potential adverse effects that immunosuppressive therapy with glucocorticoids and cytotoxic drugs could have on an underlying chronic viral infection. Alternatively the discovery of HCV provided the opportunity to control HCV-MC with antiviral therapy based on the belief that the underlying infection was driving immune complex formation and resultant vasculitis. While optimum therapy is still unclear a series of recent studies suggest a role for both antiviral as well as targeted immunosuppressive therapy on autoreactive B cells in the treatment of HCV-MC depending on the activity and severity of the underlying vasculitis and the status of the underlying infection. Inducing a sustained virological and clinical response and minimizing the use of immunosuppressive drugs are the main goals in the treatment of patients with HCV-MC vasculitis.

During the last decade, several groups have reported on the efficacy of anti-CD20 monoclonal antibody (rituximab) in patients with MC. Two recent randomized studies reported the results of rituximab compared to conventional immunosuppressive therapy (glucocorticoids, cyclophosphamide, plasma exchanges or methotrexate) for MC patients in whom antiviral therapy had failed to induce remission. Remission was statistically higher in the rituximab group (83% versus 8%, $P < 0.0001$, and 64.3% versus 3.5%, $P < 0.0001$, respectively). The median duration of remission for rituximab-treated patients was 7 months, and the safety profile was good. These findings indicate that rituximab monotherapy is an effective and safe option for severe MC patients. Biologic therapy with B cell directed therapy is promising in the treatment of MC vasculitis but many questions remain regarding the appropriate position of this strategy in treatment. The duration of effect appears finite with response durations typically lasting 6-12 months and its combination with antiviral drugs is necessary. A pilot study reported the efficacy of a lower dosage of rituximab (2 infusions of 250 mg/m² instead of 4 weekly infusions of 375 mg/m²). The safety of repeated therapy in MC needs further investigation. There is no significant difference in the efficacy of rituximab therapy whether patients presented with HCV-induced or essential cryoglobulinemia vasculitis.

Based on the limitations of each therapy (i.e. antiviral and rituximab), and the 30% of MC patients that continue to have active disease while receiving rituximab or antiviral therapy, the combination of rituximab with anti-HCV therapy appeared logical. Two recent clinical trials compared the efficacy and safety profile of Peg-IFN alpha/ribavirin versus rituximab plus Peg-IFN alpha/ribavirin. Rituximab plus Peg-IFN alpha/ribavirin treated patients had a shorter time to clinical remission, better renal response rates, and higher rates of cryoglobulin clearance. Treatment was well tolerated with no worsening of viremia under rituximab. Rituximab synergized the immunological effect of antiviral therapy. In the coming years, new antiviral agents would allow eradication of HCV infection in up to 90% of cases. Recent use of triple therapy with Peg-IFN α , ribavirin, and a specifically targeted antiviral agent (i.e. Boceprevir or Telaprevir) led to significant improve sustained virological response rates and clinical remission in severe and refractory patients with HCV-MC vasculitis. New

antiviral combination (sofosbuvir based therapy), IFN-free regimens have recently proved very high virological response rate and with a very good safety profile in HCV patients. In HCV-MC patient's preliminary data are very promising. Thus, we can therefore expect a significant increase in the proportion of MC remission.

In non-HCV cryoglobulinemia vasculitis, the treatment depends of the severity of the vasculitis, of the associated aetiology (B cell lymphoma, MGUS, myeloma, Sjögren's syndrome..) and of the type of cryoglobulin (type 1 vs type 2 and 3). Low dose corticosteroids may help to control minor intermittent inflammatory signs such arthralgia or purpura, but do not succeed in cases of major organ involvement (i.e. neurologic, renal, cardiac), or in the long-term control of vasculitis. Plasmapheresis is particularly effective for rapidly progressive glomerulonephritis, life threatening organ involvement and/or severe skin necrosis or ulcers.

Type I cryoglobulinemia vasculitis is usually associated with plasma cell hematologic disease. The treatment of type I cryoglobulinemia vasculitis is primarily that of the underlying haematological malignancy. The key point is to adapt treatment modalities to the nature of the underlying gammopathy. If it is plasmacytic (i.e. mainly composed of CD20 negative cells and usually secreting a mIgG), the treatment should be based on anti-myeloma agents including, in selected young patients with severe disease, autologous stem cell transplantation. If the underlying B-cell disorder is lympho-plasmacytic, usually associated with a mIgM, the treatment should be as for Waldenström's disease.

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